SYNTHETIC AND MECHANISTIC INVESTIGATIONS IN THE FORMATION AND FISSION OF CYCLIC ACETALS

A Thesis submitted by

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ABSTRACT

The acid catalysed formation of acetals and ketals has been investigated.

The synthesis of isopropylidene ketals was studied in detail by vapour phase chromatography so as to determine the reaction sequence. The ketals observed in this study have been prepared and further investigated by proton magnetic resonance and mass spectrometry.

The formation of the acetals of D-glucitol and 1-deoxy-D-glucitol were studied previously and shown to exhibit kinetic and thermodynamic control. Similar control had been observed with 2-deoxy-D-glucitol and n-butyraldehyde giving the 1,3-acetal as the kinetically controlled product and the 3,4-acetal(s) as the thermodynamically controlled product.

A detailed study of the mechanism of the formation of the monoacetals of D-glucitol has been attempted. D-Glucitol is known to give the 2,3-acetal(s) as its kinetically controlled product. It would be expected that hemi-acetal formation, which must be the initial step in the reaction sequence, would occur at a primary hydroxyl and in particular at C1, so that initial cyclisation occurs with the formation of the 1,2-acetals or less probably the 1,3-acetal.

Direct hemi-acetal formation has been possible with diols and triols but with hexitols alternative electrophiles have been used, chlorethers and vinylethers. These would seem to indicate hemi-acetal formation is occurring at C1 hydroxyl, but that hemiacetals

undergo intermolecular rearrangement to the subsequent products the 2,3 and 2,4 mono-acetals. This together with hydrolysis studies on the 1,2;3,4;2,4;2,3;5,6 and 4,6 mono-acetals of D-glucitol, shows that it is unlikely that the 1,2 acetal or the others investigated are kinetic intermediates, since their stabilities towards hydrolysis are too high.

Synthetic investigations on equi-molar solutions of n-butyraldehyde and D-glucitol using various substrate concentrations, coupled with a mathematical approach to the reaction mechanism suggest that the overall mechanism involving kinetic and thermodynamic control is governed by both intra and an inter-molecular processes.

CONTENTS

INTRODUCTION

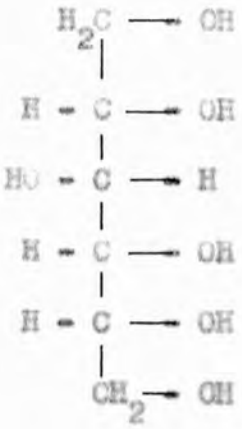
THE FORMATION OF CYCLIC ACETALS

The formation of cyclic acetals and ketals has been studied extensively since ethylidene ethane diol was synthesised by Wurtz in 1861[1].

Much of the subsequent interest in acetal formation has been due to their use as blocking groups in both synthetic and natural product carbohydrate chemistry, i.e. D-glucitol was isolated and characterised as an acetal[2]. Their use as blocking groups was due to the facility of alkylidene and arylidene groups to span specific hydroxyl groups under mild synthetic conditions, and subsequently to be removed under mild conditions; so that the stereochemistry of the original molecule remains unaltered.

The knowledge that specific acetals will be formed under various conditions has been used extensively, but these observations were not correlated until Hann and Hudson[3] drew up empirical rules based upon data available from methylene acetals of D-glucitol, D-mannitol and dulcitol. These rules were developed by Barker and Bourne[4] who introduced a nomenclature for classifying the rings.

If the hydroxyls spanned by the acetal were attached to adjacent carbon atoms the ring was classified as an α ring (1,3 dioxolan) while if the carbon atoms were seperated by one carbon atom the ring was β (1,3 dioxan) and similarly a γ ring (1,3 dioxepan). Further the spacial position was shown by reference to the Fischer projection



I

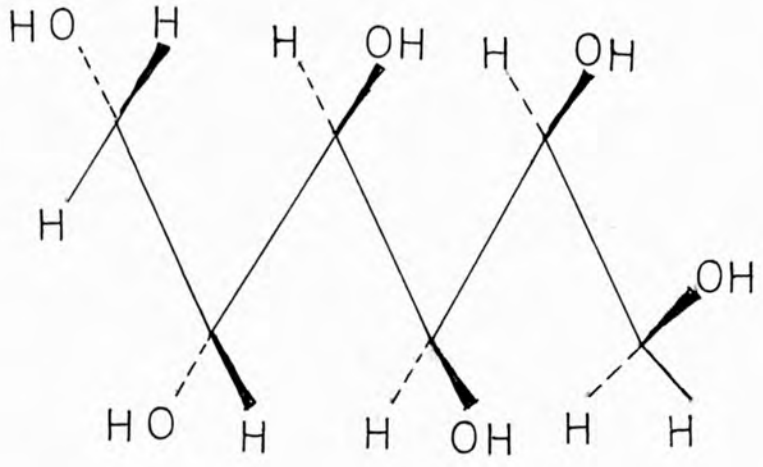
formula (I) for the polyhydric alcohol; so that if the hydroxyls involved in cyclisation were on the same side of the carbon chain the ring is cis (c) and if on the opposite side of the carbon chain, trans (T). This nomenclature is not required when a primary hydroxyl is involved in the ring due to free rotation of the C-C bond. Therefore rings involving a primary hydroxyl are classified as α , β , γ and those involving two secondary hydroxyls as α C, β C, β T and γ T etc.

The Barker and Bourne rules had expanded the Hann and Hudson rules to cover most of the polyhydric alcohols and therefore they were able to draw up a table of prefered rings.

It has been found that a β C ring was the most prefered, then the β ring followed by α , α T, β T or γ T. These were empirical rules which were found to be obeyed except in cases where the parent polyhydroxy compound was already partially substituted and in fact enabled predictions to be made as to the formation and stability of acetals, as then not synthesised. These predictions have subsequently been shown to be valid.

A theoretical basis for the stability of acetals was now sought. This was approached from two directions. Firstly Barker, Bourne and Whiffen[5] considered the parent polyhydric alcohol. They considered it

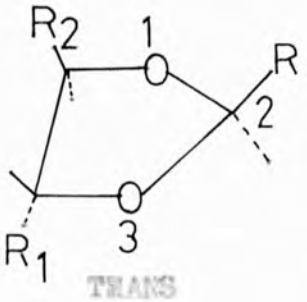
to exist in a planar zig-zag conformation with the substituents on each carbon atom in a fully staggered position relative to substitutuents on adjacent carbon atoms.



These authors stated that this would lead to the minimisation of interaction, as this gives the distance between groups to be just greater than the sum of the van der Waals radii. The seperation of the oxygens in a 1,3-dioxolan (α ring) 1,3-dioxan (β ring) and 1,3-dioxepan (γ ring) can be calculated and by comparing these with the distances in the preferred conformation of the parent polyhydroxy compound it was shown that there was an increase deviation from the ideal for the polyhydroxy compound (i.e. distortion) such that $\beta C < \beta < \alpha$. An increase in distortion will raise the energy of the system thereby lowering its stability. This will decrease the stability of the rings so that the stability decreases $\beta C > \beta > \alpha$ Mills[6] considered ring stabilities by considering the acetals formed. These were classified as 1,3-dioxolan, 1,3-dioxan and 1,3-dioxepans.

Raman spectroscopy has shown the 1,3-dioxolan ring to be slightly puckered[7] so that cis neighbouring substituents define a small dihedral

angle while trans substituents do not, this causes a greater interaction in the cis isomer than the trans isomer and hence destabilisation.



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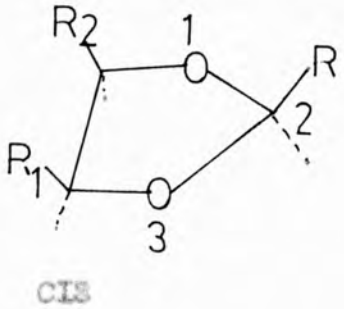
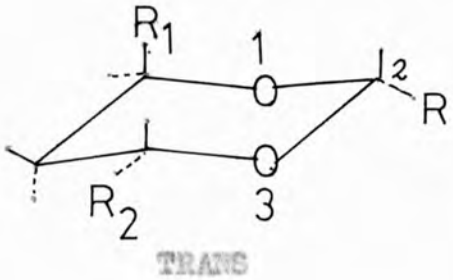


CIS

The α T ring is more stable than the α C ring. In addition assuming $R_1 \neq R_2$ there is the possibility of stereoisomerism at C2.

The 1,3-dioxan is usually accepted as existing in the chair form with the energy of the system minimised by equatorial substituents.



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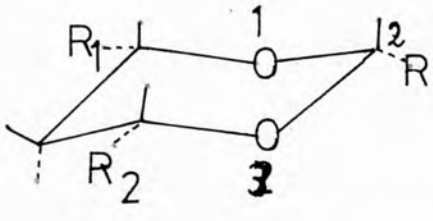


CIS

The β C ring will be more stable than a β T ring. Again there should be the possibility of stereoisomerism at C2 but in the majority of cases the equatorial isomer is far more favoured than the axial so that one isomer predominates. The 1,3-dioxepan ring (γ ring) is very flexible and is said to exist in a twist chair form when all interactions are minimised[8].

Thus by considering the Barker and Bourne rules[4] the type of rings which will be formed may be predicted.

Turning now to a consideration of acetal structure determination; classically ring size may be determined by periodate oxidation[9], with estimation of periodate uptake[10], liberated formaldehyde[11] and formic acid[12], and study of the fragments. Which together with initial methylation[13], followed by removal of the acetal rings and subsequent periodate determinations on the methylated derivative will establish the position and size of the acetal ring. These techniques are still of considerable importance but recently other techniques have rapidly become more important for both structural determination and for studying reactions.

Of these proton magnetic resonance (P.M.R.) is probably the most widely applied. It is very conveniently applied to structural and conformational determinations in the field of acetal chemistry[14,15].

As previously stated acetals may be classified as 1,3-dioxolans, 1,3-dioxans and 1,3-dioxepans and these show a significant downfield shift in the position of resonance of the acetal proton, with the acetal proton resonance moving downfield in the series dioxan, dioxepan, dioxolan, i.e. for butylidene acetals of D-mannitol we observe the acetal protons of dioxolan rings at or below τ 5.10, dioxan rings at or above τ 5.41 with the dioxepan rings intermediate. This is suggested to be due to deshielding of the acetal proton by the unshared electrons adjacent to the oxygen atoms[16]. Further the absolute stereochemistry may be determined by considering the chemical shift and coupling

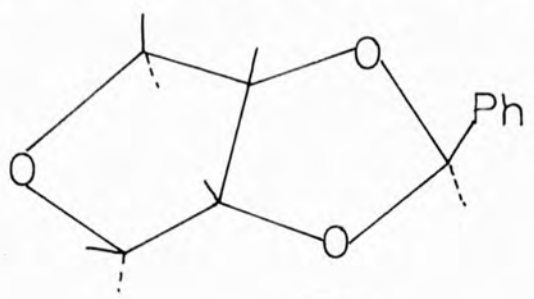
constants. Due to the reasons outlined above the acetal proton appears downfield of most other protons in the spectrum. In the case of the 1,3-dioxan the equatorial or axial position of the acetal proton may be established since the equatorial proton will appear downfield of the axial proton.

With the 1,3-dioxolan the acetal in the more sterically hindered environment will appear downfield, in the case of the 1,3-dioxepan the system is extremely flexible and not enough examples are known to be able to distinguish isomers. So with the proviso that the spectrum of both isomers are known the stereochemistry at C2 of the dioxolans may be determined.

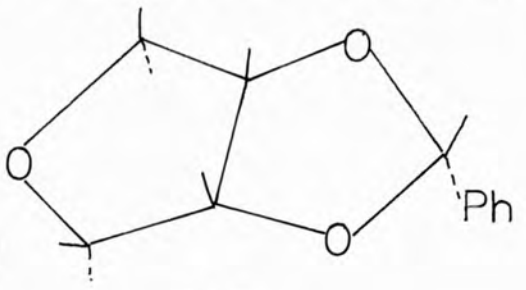
Unlike other methods used for structural and stereochemical determinations, proton magnetic resonance spectroscopy may be used for kinetic studies. Baggett and co-workers[17,18] have demonstrated this in the case of isopropylidene derivatives of D-mannitol when it was used to show that these rings do not migrate during hydrolysis so that graded hydrolysis work is valid for structural determinations of the tri-ketal. They also applied this to synthesis and showed that during the benzylidenation of methyl α - D galactopyranoside the initial products were the diastereoisomers of 3,4 - O - benzylidene α - D galactopyranoxide while at equilibrium the 4,6 acetal was present as the major product. Other acetal migrations have been studied by proton magnetic resonance, Al-Jeboury et al[19] followed the benzylidenation of 1,4 anhydroerythritol in nitroethane at 25-30° in the presence of toluene-p- sulphonic acid and noticed a rapid

development of an acetal proton signal at relatively high field followed by slow appearance of a signal at lower field as the intensity of the high field signal decreased; while at equilibrium the two signals were comparable.

The two signals were attributed to the isomers of the acetal with the phenyl groups in the endo- and exo-positions.respectively.

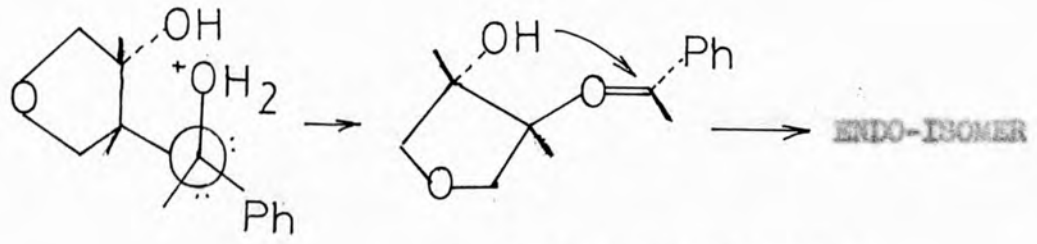


EXO-



ENDO-

This kinetic control may be explained by considering the hemi-acetal or its protenated form.



TRANSOID OXONIUMION

While rotation about the C - $O^{\oplus}$ bond in the oxonium ion would allow attack from the opposite side of the acetal carbon atom to give the exo-isomer. Similarly 1,4-anhydro 3,5 - O benzylidene - L-mannitol in acetic acid has been shown to rearrange to the 2,3-acetals with both isomers.

So far we have considered the ring forms and how we may determine the conformation of cyclic acetals. We must now consider in more detail the synthetic techniques involved. It has already been mentioned that condensation is acid catalysed and in this respect the most common catalysts are the mineral acids and especially concentrated sulphuric acid, hydrochloric acid and hydrogen chloride and a number of organic acids such as toluene p sulphonic acid. Milder catalysts may be obtained by the use of Lewis acids such as anhydrous copper sulphate and zinc chloride. In general variation in catalysis will vary the degree of acetalisation i.e. 1,2 - O - isopropylidene mannitol[21] with acetone and copper sulphate gives the 1,2 ; 5, 6 di O - isopropylidene D-mannitol while concentrated sulphuric acid gives the tri-O-isopropylidene D-mannitol. There are however anomolies so that 1,6 di - O - benzoyl dulicitol[20] when condensed with benzaldehyde in the presence of hydrogen chloride gives a di-acetal MP 119-120° while with zinc chloride a di-acetal MP 147-148° is obtained, which may be converted to the lower melting point isomer by heating the zinc chloride catalysed reaction to 60°.

The course of the acid catalysed acetalisation of polyhydric alcohols has received comparatively little study. Hann and Hudson[2] envisaged that such condensations would entail a succession of reactions, some perhaps in competition, and that a final equilibrium would be attained involving a number of acetals. That equilibrium are involved may be demonstrated by exchange reactions since

ethylidene acetals will exchange to give their analgous methylene acetals in the presence of acidic formaldehyde solution. The kinetic phase of the reaction is controlled by the energies of activation which can be dependant on factors other than the stabilisation of the final products. A consequence of this is the often rapid formation of an intermediate product requiring a low energy of activation, which then slowly passes to the more thermodynamically stable product.

CYCLIC ACETALS OF D-GLUCITOL

+other mono acetals

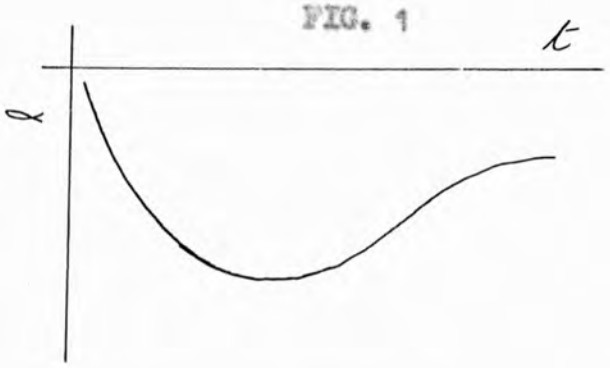
+polyacetals and water

When equimolar quantities of D-glucitol and an aldehyde are dissolved in aqueous sulphuric acid (3N) and allowed to stand at room temperature the main product of the reaction is a 2,4 mono-acetal with a β C ring, as would be predicted by the Barker and Bourne rules[4].

This has been found to be generally applicable to furfuraldehyde[22], crotonaldehyde[23], bensaldehyde[24] and butyraldehyde[25]. The polyacetals may be obtained by increasing the molar quantities of aldehyde. This synthetic method has been applied extensively without further study of the reaction.

Dr. S. R. Harwood[24] studied the reaction in greater detail polarimetrically and obtained a curve (FIG 1) characterised by a minimum when n-butyraldehyde and D-glucitol were mixed in aqueous acid.

FIG. 1

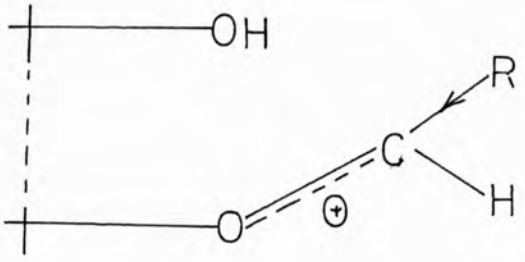


At that time the only butylidene acetal of D-glucitol known to have a large negative rotation was 4,6 - O - butylidene D-glucitol. The curve was therefore interpreted as initial formation of a 4,6 - O - butylidene acetal (β ring) followed by its re-arrangement to a 2,4 - O - butylidene acetal (β T ring). This seemed rational since initial attack at a primary hydroxyl would be expected.

When Dr. P. J. V. Cleare[26] continued the work and analysed the reaction by quenching the reaction at the rotational minimum and analysing the products, a crystalline compound was isolated, which was analysed by proton magnetic resonance as well as the classical techniques, showing it to be the 2,3 O - butylidene - D-glucitol. Therefore we can ascribe kinetic control to the formation of the 2,3 acetals and thermodynamic control to the formation of the 2,4 acetal. This was shown to be independant of catalysis since the same results were obtained with hydrochloric acid, sulphuric acid and 2,5 dichlorobenzenesulphonic acid. The kinetic and thermodynamic control was shown to be a general phenomenon with D-glucitol and occurs with acetaldehyde, benzaldehyde and iso-butyraldehyde as well as n-butyraldehyde. The characteristic curve (FIG 1) was also observed

in non-aqueous media so that kinetic and thermodynamic control can be shown with a large number of aldehydes in both aqueous and non-aqueous media.

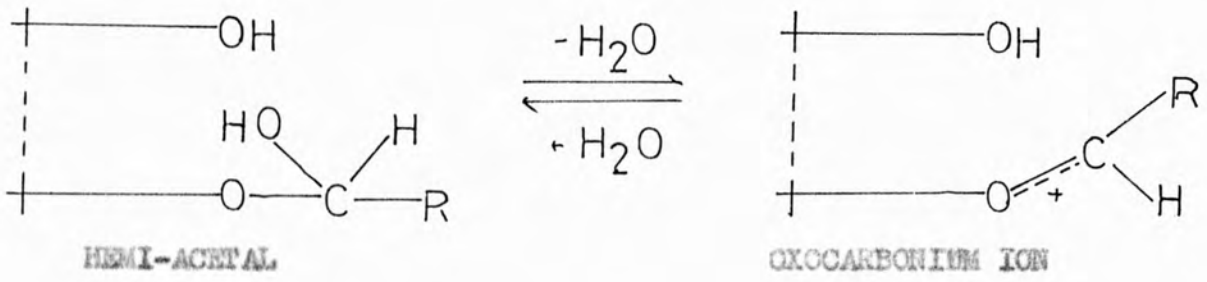
Even with this evidence the exact mechanism of acetal formation is not known. Bell and co-workers[26] suggest, that the rate determining step involves an oxocarbonium ion.



This would be stabilised by the inductive effect of the alkyl groups, hence reaction would be favoured by aldehydes with electron-donating substituents. This explains the vigorous conditions required for the reaction with tri-chloroacetaldehyde, with a strong electron-withdrawing group, and similarly that the 2,4 ethylidene acetal may not be prepared by the general method described previously, which is applicable to n-butyraldehyde etc.

Finally kinetic and thermodynamic control was established with 1-deoxy-D-glucitol[26], the initial uptake of aldehyde being faster than with D-glucitol itself.

The work to be considered carries on from this. The suggestion by Bell and co-workers[27] being considered, the formation of a hemi-acetal must be postulated.



HEMI-ACETAL OXOCARBONIUM ION

If we add to this the suggestion by Baggett and co-workers[29] that the initial hemi-acetal stage must preferentially involve a primary hydroxyl, together with the facts established in the work of Drs. S. E. Harwood and P. J. V. Cleare, we may suggest that initial hemi-acetal formation occurs at the primary hydroxyl C1 of D-glucitol. Initial cyclisation may then take place to a 1,2-acetal, which subsequently rearranges to give further kinetically controlled acetals, which ultimately yield the thermodynamically controlled products. This may be envisaged as either an intermolecular process with liberation of aldehyde or an intramolecular rearrangement.

THE MECHANISM OF CYCLIC ACETAL FORMATION

The courses of study that have been followed have been an attempt to elucidate the mechanism of cyclic acetal formation with D-glucitol. The working hypothesis was that the initial hemi-acetal formation must be at a primary hydroxyl and in particular the hydroxyl at C1. This led to the conclusion that initial cyclisation must be to the 1,2 acetal, as a 2,3-acetal was known as an intermediate.

Cyclic ketal formation gives preferentially a 1,3 dioxolan system containing a primary hydroxyl i.e. 1,2 - O - isopropylidene - D-glucitol and 1,2 ; 5,6 di - O - isopropylidene D-glucitol. This will suggest that the hemi-ketal is formed at a primary hydroxyl.

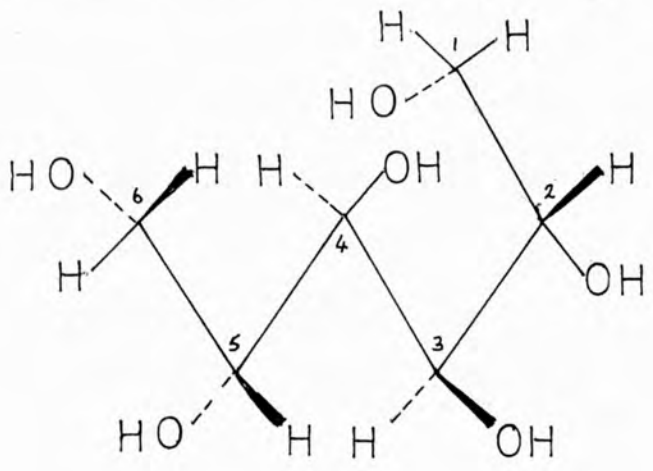
When hemi-acetals are formed there is evidence for the preferential formation at a primary hydroxyl but studies of their subsequent rearrangements have only been possible on related systems. (See Section 2).

The mixed acyclic acetals, formed in the reaction between D-glucitol and either chlorodimethylether or vinylether, were found to be at the C1 - OH, but gave the 2,3-acetals and the 2,4-acetals with no evidence of the intermediate 1,2-acetals. When the rearrangement was studied in more detail using ultra-violet spectroscopy and vapour phase chromatography, free aldehyde and D-glucitol were revealed. This suggests an intermolecular process. This was partially verified by the formation of a trace of di-acetal.

From this it may be concluded that initial attack on D-glucitol

is at C1 - OH but that this is not important in the subsequent reactions. Hydrolysis studies on cyclic acetals have shown that initial hydrolysis is followed by recombination and equilibration of the 2,3-acetals and 2,4-acetal and other monoacetal products, while the stability of the 1,2-acetal is too high for it to be considered as a kinetic intermediate.

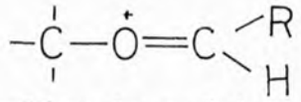
From this it might be concluded that the effective attack for hemi-acetal formation and cyclisation is at C_2 or C_3 - OH.



If D-glucitol is considered to be a bent molecule[28], (in aqueous solution this may not be completely valid), C_2 might be expected to be most susceptible to electrophilic attack, so that steric considerations would favour hemi-acetal formation at C_2 with subsequent cyclisation to the 2,3-acetal.

When vapour phase chromatography of the synthesis of monoacetals has been considered emphasis has been on the build up and decay of the kinetically and thermodynamically controlled products but careful analysis of the chromatographs and comparison with standards shows small but not insignificant amounts of the 3,4-acetals and the 4,6-acetal[29].

Nevertheless it would appear to be valid to consider the main reaction occuring via C1, C2 etc., while others cause the formation of minor products.

Hydrolysis of the 4,6-acetal gives the usual equilibrium mixture, as do all the other acetals. This process must occur via the oxocarbonium ion  . If this ion is formed at C_4 it may cyclise to a 3,4-or 2,4-mono-acetal or it may undergo nucleophilic attack by the aqueous solvent instead of the hydroxyl of D-glucitol with liberation of free aldehyde. Free aldehyde and D-glucitol are indicated by ultra-violet spectroscopy and vapour phase chromatography as in the case of all other acetals. This shows an intermolecular process as well as what might be an intramolecular process. The free aldehyde would then equilibrate in the normal way.

The 2,3 acetal under hydrolysis conditions would go to an oxocarbonium ion at C_2 or C_3. Hydrolysis is never complete and in fact rarely rises above 40% so that it may be that a proportion of the oxocarbonium ion at C_3 cyclises ⟶ 3,4-acetal while that at C_2 cyclises ⟶ the 2,4 acetal or reforms the 2,3-acetal, while the remainder undergoes hydrolysis to give free aldehyde which is seen by ultra-violet spectroscopy.

Rather than the intramolecular process it has been suggested that hydrolysis is complete but that there is then a rapid reformation of the oxocarbonium ion so that kinetically this hydrolysis is not observed.

The main consideration is kinetic and thermodynamic control.

Oxocarbonium ion formation at C_2 must be involved in the formation of the 2,3-acetals. On steric grounds it is reasonable to expect that this cyclisation has a lower free energy of activation although the 2,4-acetal has a lower free energy and must be more stable.

If D-glucitol is a bent molecule, when the 2,3-acetal is formed, to retain the C1 - C4 OH interaction would cause strain within the system. When the stereochemistry changes to minimise this energy, intermolecular hydrogen bonding might be favoured over intramolecular hydrogen bonding, providing a stereochemistry favourable for the formation of the 2,4-acetal.

A totally intermolecular process requires D-glucitol as the common intermediate between 2,3 - O - butylidene D-glucitol and 2,4 - O-butylidene D-glucitol, unless hemi-acetal formation and cyclisation is very rapid there will be reformation of the 2,3 acetal since the stereochemistry would not necessarily remain favourable for 2,4 acetal formation.

With a process which requires intramolecular rearrangement to the 2,4-acetal, the oxocarbonium formed by the opening of the 2,3-acetal at C2 is more likely to be in a favourable conformation for nucleophilic attack by the hydroxyl at C4.

An intramolecular mechanism more easily gives a conformation whereby change from kinetic to thermodynamic control can be attained and seems the more likely mechanism, that is not to say that the process is completely intramolecular. By considering the mathematical approach to the mechanism, the theoretical rotation versus time plot

is not identical to the experimental plot which would suggest that the overall mechanisms involve both an inter-and intramolecular processes.

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SECTION 1

THE ACID CATALYSED FORMATION OF MONO ACETALS

FROM n - BUTYRALDEHYDE AND 2 - DEOXY - D - GLUCITOL

INTRODUCTION

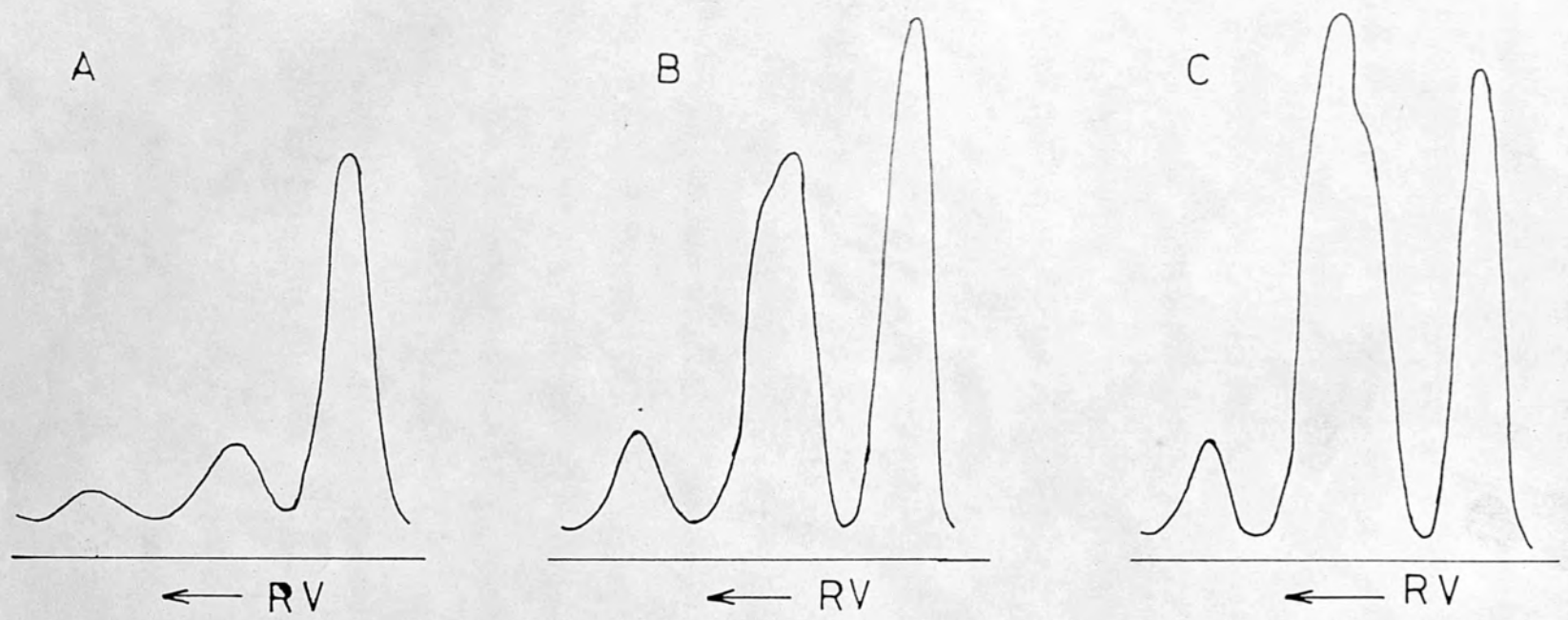
This work is a sequal to the work of Dr. Cleare, published by him in collaberation with Bonner, Bourne and Lewis[1,2,3] and work in his thesis[4]. In that work the reaction of n-butyraldehyde with D-glucitol and 1-deoxy-D-glucitol was studied.

DISCUSSION AND RESULTS

The plot of optical rotation of the reaction with time gave a curve (Fig. 1) which was imitative of the curve for D-glucitol[1] with a pronounced minimum after about 20 mins., the only difference from D-glucitol being that after the maximum had been obtained there was a slight decline in rotation to equilibrium. Following the reaction by ultraviolet absorption of the carbonyl bond at 281 nm showed that the minimum rotation and the equilibrium position corresponded to an uptake of 30 and 35% of aldehyde respectively while vapour phase chromatography proved that there was a main kinetically formed product[4] - the 1,3-acetal, which gave way at equilibrium to a mixture, which though not properly resolved chromatographically was shown to be consistent with being mainly the 3,4-isomers.

Crystalline 1,3-O-butylidene-2-deoxy-D-glucitol was obtained in 3.8% yield by neutralisation of the reaction mixture after 20 minutes and removing the uncharged 2-deoxy-D-glucitol by chromatography on alumina, followed by extraction of the semi-crystalline syrup so obtained with boiling light petroleum or by direct extraction with boiling light petroleum.

Previous work[4] had shown that the periodate oxidation and formaldehyde liberated were indicative of a 1,3-acetal while the proton magnetic resonance spectra showed a triplet at τ 5.4 which was additional evidence for the six-membered ring structure. Further characterisation was gained from the crystalline tribenzoate



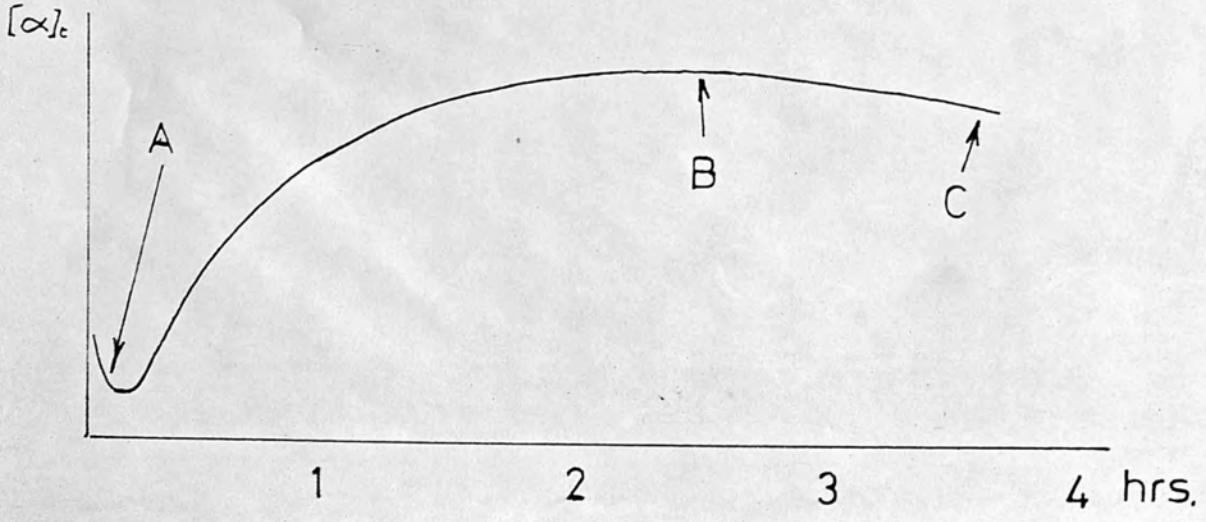


Fig. 1

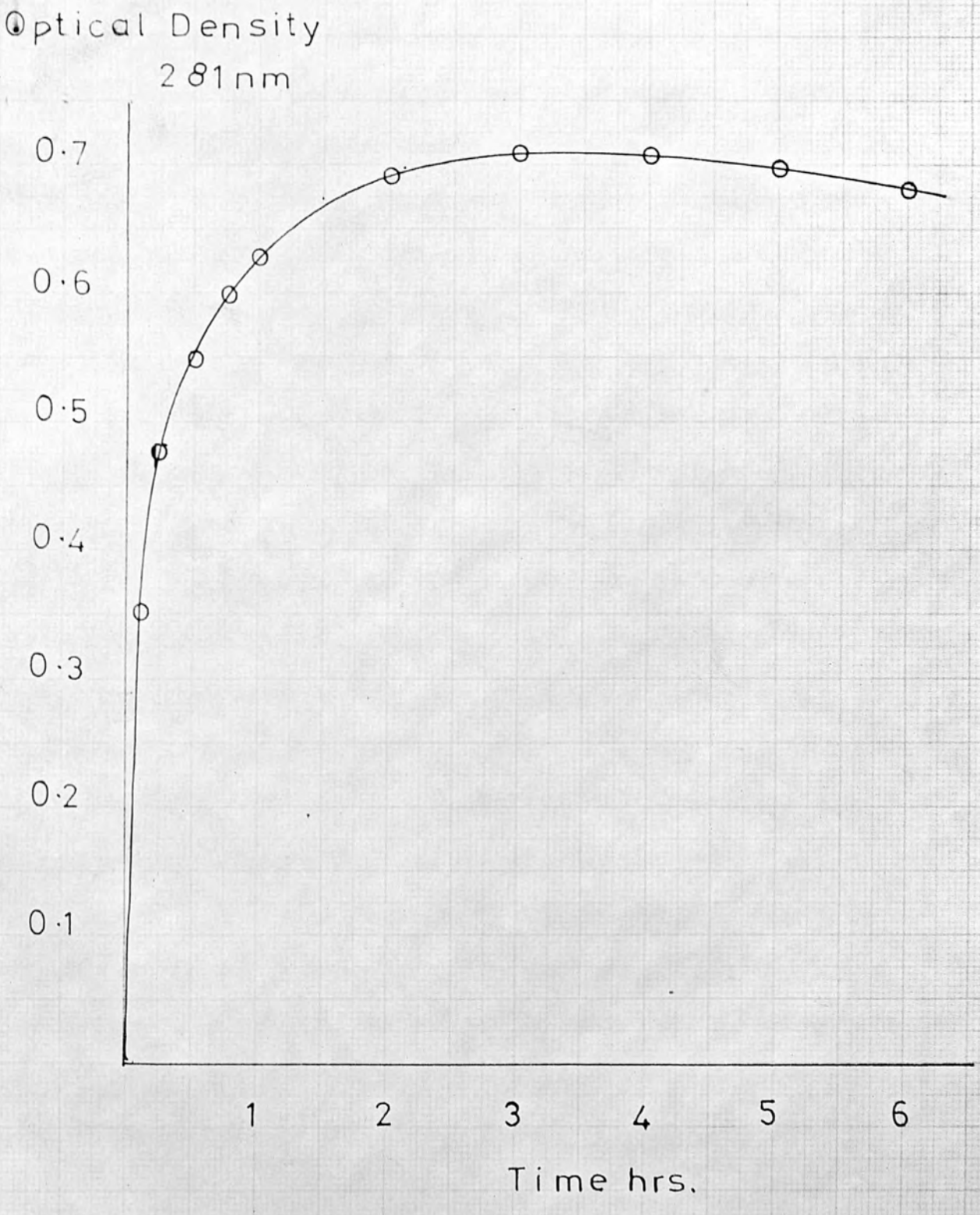
Analysis of the Reaction of n-Butyraldehyde(0·1M) with 2 Deoxy-D-Glucitol(0·1M) in 0·5N Aqueous Hydrochloric Acid at 25°

The aqueous acid hydrolysis of the 1,3-acetal, followed spectropholometrically by carbonyl absorption at 281 nm (Fig. 2) of the liberated aldehyde coupled with analysis by vapour phase chromatography showed that the ascending part of the curve was mainly due to hydrolysis to 2-deoxy-D-glucitol, and the descending part to the gradual establishment of an equilibrium mixture of 2-deoxy-D-glucitol and its various acetals. The rate constant ~ 7.0×10^{-4} sec^{-1}, for the liberation of n-butyraldehyde in an assumed pseudo-first order reaction was derived from the initial slope of the curve (Fig. 2) using a value of 1.5550 $m^2 mol^{-1}$ for the extinction coefficient of n-butyraldehyde in 1M aqueous hydrochloric acid solution at 281 nm[16] and is of the expected magnitude for the hydrolysis of a kinetically controlled product and in good agreement with that seen for the 2,3-O-butylidene-D-glucitol studied in another part of this thesis.

The equilibrium mixture arising from 2-deoxy-D-glucitol and n-butyraldehyde can be readily separated into a syrup mixed monoacetal fraction and uncharged 2-deoxy-D-glucitol by chromatography on alumina[4], but no purification of the syrup was achieved. Periodate oxidation of the syrupy monoacetal fraction involved 1,31 mol. of periodate ion. The simultaneous liberation of 1.0 mols of formaldehyde means that the components of the mixture are free of linkages at C_5 and C_6, so that the syrup would consist only of 1,3 - 3,4 and 1,4-acetals, and the 1,31 mols uptake of periodate ion gives the ratio of 1,3 to (3,4- + 1,4-) isomers as 31:69. Sequential methylation, acid hydrolysis and periodate oxidation of the syrupy monoacetal fraction

Fig 2

Hydrolysis of 1,3-O-Butylidene-2-Deoxy-D-Glucitol in 1·0 M Aqueous Hydrochloric Acid at 25°C



resulted in 0.67 mol. of periodate being reduced, and no formaldehyde was formed. Thus the ratio of (1,3- + 1,4-) to 3,4-isomers is 33:67. This result, together with the above periodate results, means that there is an insignificant amount of 1,4-acetal, and hence the equilibrium monoacetal fraction consists only of 1,3 - and 3,4 - isomers in the ratio 1:2. This conclusion was supported in two ways. Benzoylation of the syrupy monoacetal fraction gave a syrup which did not crystallise. Sequential mild acid hydrolysis[5] to remove the acetal rings, periodate oxidation and catalytic debenzoylation gave a mixture which was subjected to vapour phase chromatography, and by comparison with standards the mixture was shown to give peaks corresponding to 2 deoxy-D-glucitol arising from the 1,3 - monoacetal and glyceraldehyde together with β hydroxy propionaldehyde arising from the 3,4 - isomers.

Secondly, the low field part of the proton magnetic resonance spectrum of the syrupy monoacetal fraction in deuterochloroform showed triplets centred at τ 5.08 and τ 5.50, arising from the protons of the acetal carbons which are characteristic of the five and six membered ring protons respectively. Further discussion of the significance of these synthesis cannot be considered without extensive reference to the work on D-glucitol, 1-deoxy-D-glucitol and 3-O-methyl-D-glucitol[1,2,3,4] as this is a direct continuation as previously stated. It has been shown that D-glucitol[1] 1-deoxy-D-glucitol[4] both show kinetic and thermodynamic control in the formation of monoacetals and that 3-O-methyl-D-glucitol only forms the expected 2,4-monoacetal.

The thermodynamically most stable acetal of 1-deoxy-D-glucitol

would be predicted to be the one with a β C^6 i.e. 2,4-ring, as was found experimentally[4]. For 2-deoxy-D-glucitol (= 2-deoxy-D-mannitol) the predicted most stable acetal would have a β i.e. a 1,3-or 4,6-ring while experimentally, at equilibrium, considerably more 3,4-acetal was present than 1,3- and no 4,6- was indicated. Thus the 2-deoxy compound is behaving neither as a glucitol nor mannitol derivative.

The shape of the rotation time curve (Fig. 1) qualitatively observed fit the predictions considering rotations of the main components present at any time in the reaction. So that for 2-deoxy-D-glucitol $[\alpha]_D$ + 16° should decrease as the 1,3-acetal $[\alpha]_D$ 0.0° forms, but the subsequent formation of the 3,4-isomers should cause an increase since a 3,4-O-butylidene-D-glucitol[7] has a rotation $[\alpha]_D$ + 37 and 3,4 - O-butylidene-D-mannitol[8] has a rotation $[\alpha]_D$ + 28° i.e. both having high positive rotations.

If we consider the effect of replacing D-glucitol by a modified D-glucitol it has been shown[1,2,3,4], that we maintain kinetic and thermodynamic control in the reaction with n-butyraldehyde such that D-glucitol gives 2,3-and 2,4-monoacetals, 1-deoxy-D-glucitol gives the 2,3-and 2,4-monoacetals and 2-deoxy-D-glucitol gives the 1,3-and 3,4-monoacetals as kinetically and thermodynamically controlled products respectively. One factor likely to be effected is the electronegativity of the two oxygens which form the ring. It has been suggested[9] that the primary hydroxyl groups are probably preferentially involved in the initial hemiacetal stage of cyclic acetal formation. One reason

could be that the inductive effect in simple polyhydric alcohols is such that the primary alcohol group tends, in general, to be more susceptible to electrophilic attack. However, no evidence has been found for acetals involving the primary hydroxyl positions (neither C_1 nor C_6) in either D-glucitol or its 3-O-methyl ether. Thus formation of the 2,4-acetals of these two compounds either does not involve a prior formation of an acetal at a primary hydroxyl group, or if an acetal formation is necessary, then its rate of formation and subsequent opening, leading to intramolecular migration (or intramolecular migration and hydrolysis) is large, and the concentration of the acetal involving the primary hydroxyl group is too small to detect.

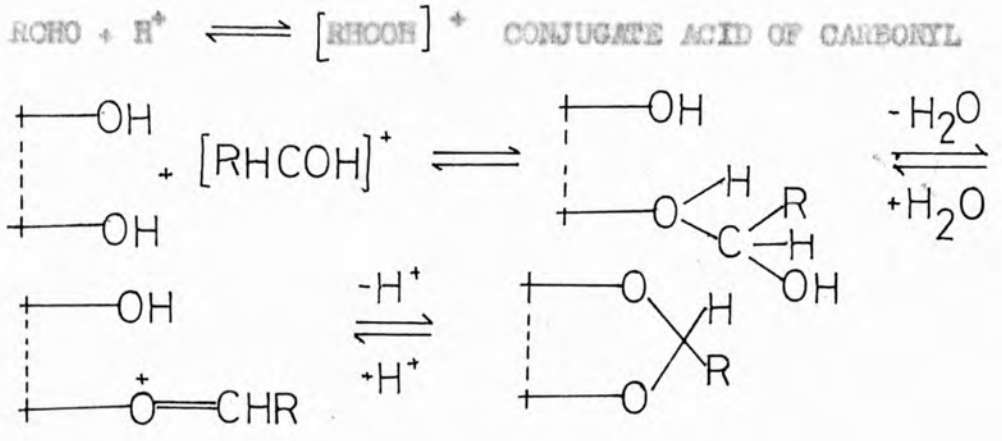
Attack at a primary hydroxyl group may also be preferred on steric consideration because it is more accessible to the aldehyde; however this also makes solvation at this position easier and negates this proposition to a certain extent.

A superficial comparison of the similarity of the reaction course of D-glucitol and the substituted D-glucitols suggests C_1 is not involved in acetal formation. However, replacement of a hydroxyl by a deoxy or methoxy may cause different hydrogen bonding patterns and alter the nucleophilicity of adjacent hydroxyls so that direct comparisons cannot be correctly made.

We do see however that the initial rates of uptake of n-butyraldehyde vary (initially 0.1 M) with D-glucitol, 2-deoxy and 1-deoxy-D-glucitol (each initially 0.1 M) in 0.5 m aqueous hydrochloric acid at 25° were 3×10^{-5}, 5×10^{-5} and 7×10^{-5} m l^{-1} sec^{-1} respectively,

as measured by the change in optical density at 281 nm of the reaction. This gives pseudo second order rate constants for initial acetal formation of 3×10^{-3}, 5×10^{-3} and 7×10^{-3} $l.m^{-1}$ sec^{-1} respectively.

The mechanistic sequence for acetal formation is normally considered to be



In aqueous acid the aldehyde is substantially hydrate (n-butyraldehyde ~ 40%[13]) so that the conjugate acid is formed either from the free aldehyde or less effectively from the hydrated form when water has to be eliminated to form the conjugate acid. This is again substantiated by the fact that in aqueous solution formaldehyde is 99.95% hydrated[10] and reacts similarly to n-butyraldehyde with D-glucitol but much more slowly.

EXPERIMENTAL

EXPERIMENT 1

Preparation of 2-deoxy-D-glucitol from fructose

Toluene-p-sulphoryl hydrazine (19.0 g) was dissolved in warm ethanol (150 ml) and fructose (18 g) in 50% acetic acid (40 ml) was added and the mixture allowed to stand at room temperature for four days. The solution was then evaporated to a syrup which was freeze dried giving a white hydroscopic solid.

MP 46-47°

This proved to contain a small trace of fructose as impurity which could not be removed by recrystallisation.

Paper chromatography showed two spots using butanol/ethanol/ water (40/11/19) Rf. 0.16 fructose and Rf. 0.57 the phenyl hydrazone of fructose. The above compound (5 g) was dissolved in dry methanol (50 ml) and potassium borohydride (6 g) were slowly added keeping the temperature below 50°. When the effervescence had ceased the solution was heated on a water bath at 50° for twelve hours. The solution was allowed to cool, the potassium ions were removed by the addition of Amberite IR 120H* resin and successively evaporated with methanol to remove the borate as volatile methyl borate.

Paper chromatography butanol/ethanol/ water (40/11/19) showed two significant spots Rf. 0.13 D-glucitol and Rf. 0.23 2-deoxy-D-glucitol. The mixture from the borohydride reduction which also contained the

pheryl hydrazone was separated on a cellulose column using butan-1-ol saturated with water as eluent. This yielded a white amorphous compound which was recrystallised from ethanol.

MP 104-105°

LIT MP 104-106° [14]

The formation of 2-deoxy-D-glucitol from fructose has been observed by ionophoresis[12] but has not been sited as being used preparatively.

YIELD = 0.5 g = 10%

EXPERIMENT 2

The preparation of 2-Deoxy-D-Glucitol from commercially available 2-Deoxy-D-Glucose (α and β)

2-Deoxy-D-glucitol (α and β) (2.0 g) and sodium borohydride (0.4 g) were dissolved in water (20 ml) and the solution was allowed to stand at room temperature for 24 hours. The excess borohydride was then destroyed and the sodium ions removed by the addition of Amberlite IR 120H$^+$ resin. The resin was filtered, the solution evaporated to a syrup and successively evaporated with methanol to remove borate as volatile methyl borate. The colourless syrup so obtained was crystallised and recrystallised from ethanol.

MP 105-106°

LIT MP 104-106° [14]

EXPERIMENT 3

Preparation of 1,3-O-Butylidene 2-Deoxy-D-Glucitol[4]

n-Butyraldehyde (4.4 g) and 2-deoxy-D-glucitol (10 g) were dissolved in water (60 ml) and the reaction started by the addition of 5 N hydrochloric acid (50 ml). The solution was left for 20 mins and then exactly neutralised with sodium hydroxide. This mixture was evaporated to dryness under reduced pressure and extracted exhaustively with boiling petroleum ether (BP 40-60°) giving feathery crystals. It was found that initial column chromatography[4] was unnecessary.

MP 62-64°

YIELD = 0.51 g = 3.82%

$[\alpha]_D^{25} = 0$ [c = 0.88 g in H_2O]

EXPERIMENT 4

Reaction between n-Butyraldehyde and 2-Deoxy-D-Glucitol

n-Butyraldehyde (0.044 g) and 2-deoxy-D-glucitol (0.1 g) were dissolved in water (6 ml) and the reaction started by the addition of 5 N hydrochloric acid (0.5 ml). The solution was allowed to stand at room temperature for 48 hrs and then exactly neutralised with sodium hydroxide. The neutralised solution was evaporated to dryness and reduced pressure and extracted with boiling ethanol. The ethanol extract was evaporated to a syrup which was analysed by vapour phase chromatography as its trimethyl silyl ether. (5% P.E.S. at 198°)

This showed peaks at RV = 0.94, 2.04, 2.55 and 2.87 relative to D-glucitol.

By comparison with standards the following results were obtained

RV 0.94 = 2-deoxy-D-glucitol

RV 2.04 = 1,3-n-butylidene-2-deoxy-D-glucitol

Paper chromatography and then layer chromatography using various eluents were unable to effect the same separation.

EXPERIMENT 5

Preparation of the 4,5,6-Tri-O-benzoyl-1,3-O-butylidene 2-deoxy-D-glucitol

1,3-O-Butylidene-2-deoxy-D-glucitol (80 mg) was dissolved in pyridine (3 ml) and benzoyl chloride (1 ml) was slowly added. The solution was left for 3 days at room temperature and then poured into ice water. A syrup was deposited, this was extracted with chloroform. The extract washed with water and dried over magnesium sulphate. The chloroform was evaporated off leaving a syrup which was crystallised from ethanol.

MP 103-104°

YIELD = 0.18 g

Analysis found	C%69.85%	H 5.9%	O 24.2%
$C_{31}H_{32}O_8$ requires	C%69.9%	H 6.0%	O 24.0%

EXPERIMENT 6

Investigation of the Mixed Monoacetal Fraction Obtained at Equilibrium from the Acid Catalysed Condensation of 2-deoxy-D-glucitol (1 mol) and n-Butyraldehyde (1 mol)

The syrup obtained as in experiment 4 was subjected to column chromatography using silica gel eluting with toluene 1.5% methanol or alumina eluting successively with ethanol and ethanol water mixture (9:1 v/v).

In both cases the initial fractions were shown by vapour phase chromatography to contain the 1,3-O-butylidene-D-glucitol and the unknown monoacetal(s).

(a) Periodate Oxidation of Monoacetals

The syrup was freeze dried and subjected to periodate oxidation in the normal way, (see experiment Chapter), and the formaldehyde determination was carried out as normal (see Section 4, Chapter 1, Experiment 6).

Weight of compound	Formaldehyde liberated	Periodate uptake
0.0120 g	1.01 mol	1.3 mol/mol syrup
0.0181 g	1.1 mol	1.25 mol/mol syrup
0.0113 g	0.99 mol	1.35 mol/mol syrup

Periodate uptake is 1.3 mols/mol of syrup

(b) Sequential Methylation, Hydrolysis and Periodate Oxidation of the Mixed 2-Deoxy-D-glucitol monoacetals

The syrup (0.5 g) in N N-dimethyl formamide (15 ml) was shaken with dry silver oxide (8 g) and methyl iodide (12 ml) for 24 hrs. The mixture was filtered and the filtrate evaporated. The semi-solid extract was extracted with chloroform (20 ml) and the solution was washed with water and dried over sodium sulphate and evaporated to a yellow syrup. The methylation and work up were repeated twice. The syrup was shown to free from hydroxyl absorption by infrared spectroscopy. It was treated with Amberlite 1R 120H$^+$ resin for 3 hours at 100° .

The hydrolysate yielded a syrup. Part (0.005 g) of the syrup was treated with periodate ion and reduced 0.67 mol of oxidant, no formaldehyde being liberated. (Periodate oxidation and determination of liberated formaldehyde being determined in the usual way.)

(c) Sequential Benzoylation, Hydrolysis, Periodate Oxidation and Debenzoylation of the Mixed 2-Deoxy-D-glucitol Monoacetals

The syrup (1 g) dissolved in pyridine, was treated with benzoyl chloride (4 ml). The syrup perbenzoylated product was treated[5] with a mixture trifluoroacetic acid (9 ml) and water (1 ml) at room temperature, to selectively remove the acetal rings. The product was then periodate oxidised in the usual way, freeze dried, and extracted with boiling toluene. The extract was evaporated, and the syrupy residue catalytically debenzoylated with sodium methoxide in methonol. After neutralisation with carbon dioxide, the methanolic solution was evaporated to a semi solid. A sample of the residue (trimethyl silyl

ether on 5% Apreson K firstly at 185° and secondly at 130°) showed the presence of 2-deoxy-D-glucitol RV = 0.94 and glyceraldehyde by comparison with a standard, and indicated a compound which had the same R.V. as a product from periodate oxidation of 2-deoxy-D-glucitol. (β hydroxy propionaldehyde or its dimer).

(d) Borate electrophoresis of the Mixed 2-Deoxy-D-glucitol Monoacetals

Using borate buffer (pH 10) all the components of the syrup migrated to $R_{GLUCOSE}$ 0.36. Suggesting either adjacent or 1,3-diol system[15].

(e) Nuclear Magnetic Resonance Spectroscopy

The syrupy mixture, so far inseparable had been shown by vapour phase chromatography to contain two components. The proton magnetic spectrum obtained in deuterochloroform showed two triplets τ 5.50 and τ 5.08. The absence of two triplets at τ 5.08 cannot be explained (this would be expected from the two conformers of a five membered ring).

By a double resonance technique it was shown that these features belonged to the acetal proton.

EXPERIMENT 7

Hydrolysis of 1,3-O-Butylidene 2-Deoxy-D-glucitol

1,3 O-Butylidene-2-deoxy-D-glucitol (0.0242 g) were dissolved in 1 N hydrochloric acid (1 ml) previously equilibrated at 25° in a thermostat and liberation of n-butyraldehyde was followed spectropholametrically by carbonyl absorption at 281 nm. From the calibration curve (see Section 3, Chapter 1) the initial rate of liberation of n-butyraldehyde could be calculated.

$$\left[\frac{d\,OD}{dt}\right]_{INITIAL} = \frac{0.435}{6 \times 60}$$

$$\text{Acetal}_1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{hemi-acetal} \underset{k_3}{\overset{k}{\rightleftharpoons}} \text{aldehyde} + \text{glucitol} \left[\rightarrow \text{eventually to equal mixture of acetal + glucitol + aldehyde}\right]$$

$$\text{hemi-acetal} \xrightarrow{k_4} \text{acetal}_2$$

We observe the rate (k) of hydrolysis of hemi-acetal where a first order reaction is assumed.

$$\text{at } t = 0 \quad -\frac{d[\text{ACETAL}]}{dt} = \frac{d[\text{CARBONYL}]}{dt} = \frac{0.435}{6 \times 60} \qquad \left(\text{factor relating O.D. to g mol/litre } C{=}O\right)$$

$$-\frac{d[\text{ACETAL}]}{dt} = k\,[\text{ACETAL}]$$

$$k = \frac{0.32}{6 \times 60} \times \frac{0.61}{0.11} = 7 \times 10^{-4}\ \text{sec}^{-1}$$

Vapour phase chromatography, by sampling the reaction at intervals

shows that there is initial hydrolysis followed by recombination with the formation of an equilibrium mixture of monoacetals, as stated by previously postulated reaction sequence so that $k_4 \sim 0$.

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SECTION 2

The role of Hemi-acetal formation in the Mechanism of Cyclic Acetal Formation

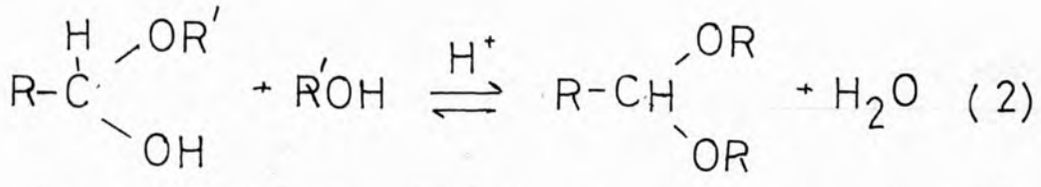
INTRODUCTION

Acetal formation may simply be expressed as a two step process.[1] The first step being hemi-acetal formation

(1)

This reaction is analagous to hydration of an aldehyde which occurs very rapidly, with catalytic constants very similar to hemi-acetal formation.

The second step, the formation of the acetal may be expressed as:



(2)

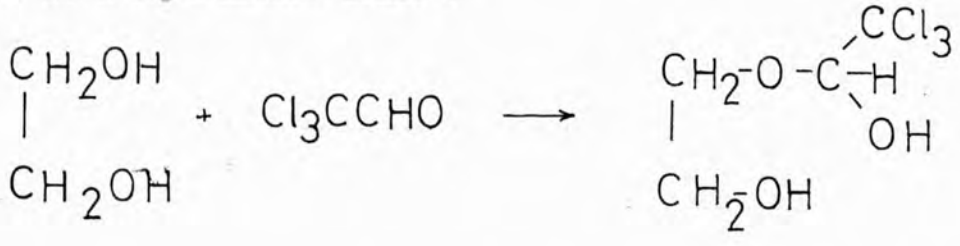
and requires acid catalysis, which is not necessary for the initial step (1).

The formation of an acetal may be considered as a two step process, step (1) being spontaneous and requiring very mild or no catalysis while step (2) is much slower requiring specific acid catalysis. Much work has been directed towards showing that hemi-acetals are formed with methanol and ethanol and various simple aldehydes[2,3]. That the first step is very rapid is nearly unanimously accepted and has only been questioned in one case, Bell and co-workers concluded that the overall equilibrium in acetal formation must be controlled by the nucleophilic addition of alcohol to the carbonyl group and not the esterification stage. They do however find from acid catalysed acetal formation that

there is some validity for the conclusion that hemi-acetal conversion does not control the overall equilibrium. The weight of evidence must be for the theory that hemi-acetal formation is the fast step.

When however hemi-acetal formation of the polyhydroxy compounds is considered there is very little direct evidence.

The hemi-acetal of ethane diol and anhydrous chloral has been isolated as a crystalline solid[4].

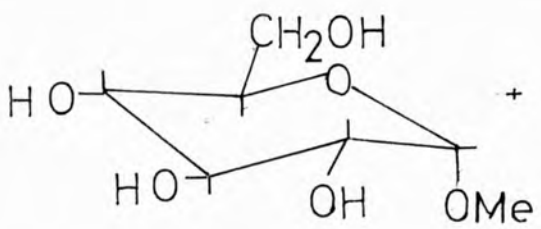


Mineral acid catalysis will induce ring closure to form the cyclic acetal. With glycerol there is evidence of a reaction with anhydrous chloral[4] but no product has been isolated in the absence of catalysis and with tetritols, pentitols and hexitols we can only assume hemi-acetal formation. With the hexitols it is a question of where the equilibrium lies in the uncatalysed reaction and also the position of formation of the hemi-acetal on the hexitol chain. The data available for acyclic acetals shows that for an isomeric series primary, secondary and tertiary the order of preference of hemi-acetal formation is primary > secondary > tertiary. This has been ascertained by observation of the deviation from additivity of the refractive indices for a binary mixture of alcohol and aldehyde, with the magnitude of deviation decreasing in the order, primary > secondary > tertiary. Showing the highest concentration of hemi-acetal for the

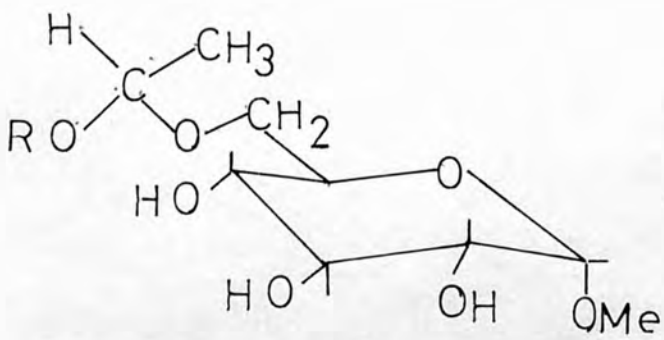
primary alcohol system. This is to be expected when considering hemi-acetal formation as electrophilic attack of the carbonyl carbon atom on the alcohol, as the acidity of the alcohols decrease primary > secondary > tertiary.

If the direct electrophilic attack by the carbonyl carbon atom of an aldehyde cannot be studied in the case of hexitols, we can consider other electrophiles which may give an analogous reaction giving a product similar to a hemi-acetal.

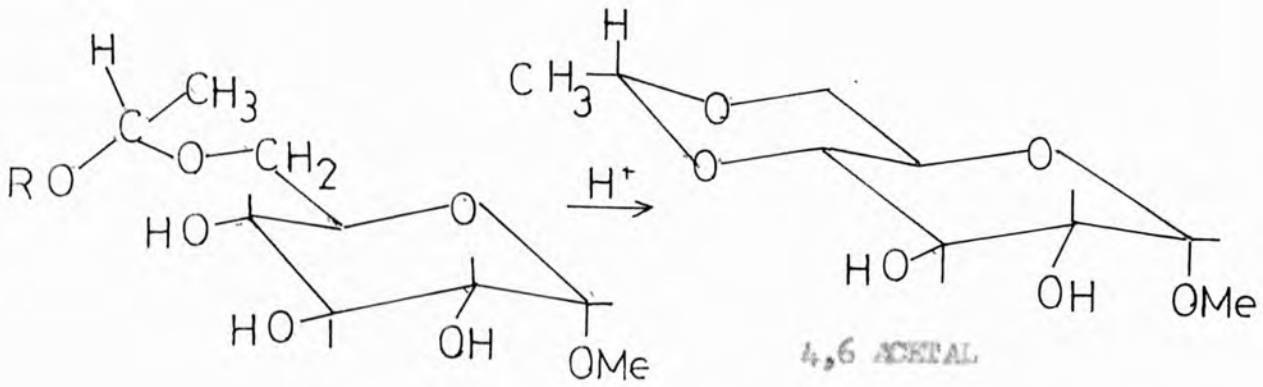
It has been shown that alkyl halogenomethyl ethers react with carbohydrates to give alkyloxymethyl ethers ($-\overset{|}{C}-O-CH_2-O-R$) i.e. a mixed acyclic formal[6], while alkyl vinyl ethers have been shown to react with methyl α-D-glucopyranoxide in a two step process.



+ $CH_2=CH-O-R \longrightarrow$

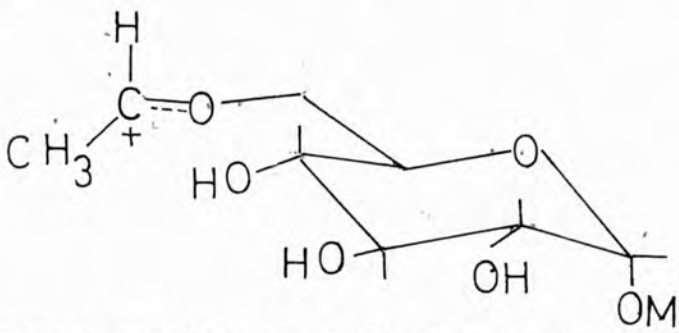


— (1)

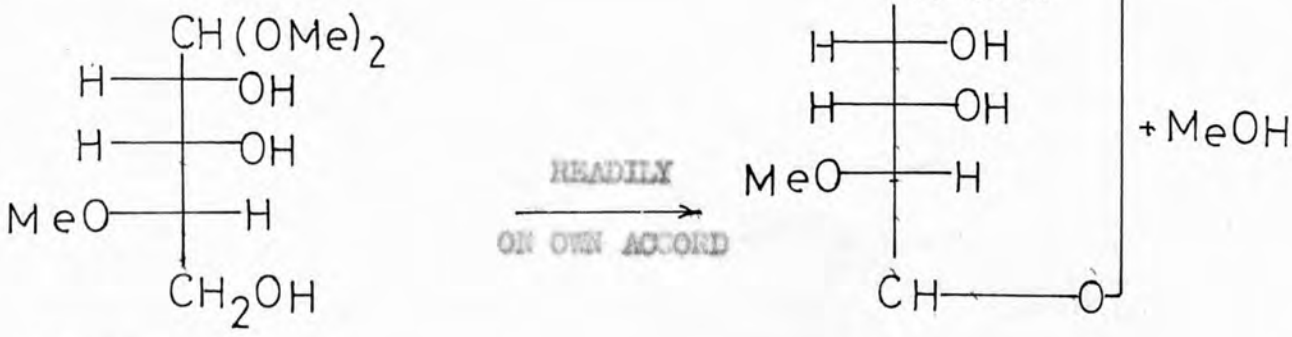


4,6 ACETAL

In this second case the intermediate in step (2) would be the oxycarbonium ion.



Under the correct conditions we find an analogous situation with the mixed acyclic acetal from the chloromethyl alkyl ethers, the same oxycarbonium ion should be involved, and an analogous reaction has been shown to occur[8].



DIMETHYL ACETAL OF
4 METHYL LYXOSE

The acyclic mixed acetal $-\overset{\alpha}{C}-O-\overset{\alpha}{CH_2}-OMe$ places $-\overset{\alpha}{CH_2}-$ in the same environment as C_1 in the lyxose derivative, which should give cyclisation to the acetal. It has also been shown that hydrogenation of a

mixture of aldehyde and alcohol yields an ether. The mechanism that was suggested involved a hemi-acetal[9]

$$RCHO + R'CH_2OH \rightleftharpoons \underset{\text{HEMI-ACETAL}}{R-\overset{OH}{\overset{|}{C}}H-O-CH_2-R'}$$

$$\xrightarrow[-H_2O]{H^+} \underset{\text{ETHER}}{R-CH_2-O-CH_2-R'}$$

This has not been applied to carbohydrates.

We therefore have evidence that hemi-acetal formation occurs with some electrophiles.

DISCUSSION

Direct studies using the carbonyl carbon atom as the electrophile in hemi-acetal formation is the obvious approach to hemi-acetal formation.

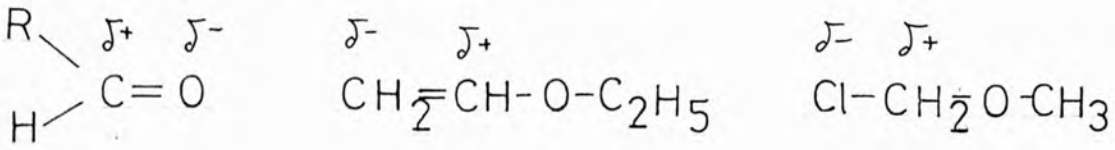
Ethane diol, propane 1,3-diol and glycerol were considered with a number of aldehydes, trichloroacetaldehyde, acetaldehyde and butyraldehyde. Trichloroacetaldehyde is the best electrophile and n-butyraldehyde the least effective electrophile.

$$R\,CHO + R'OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R-C(H)(OH)-OR'$$

So that as we proceed from trichloroacetaldehyde through acetaldehyde to n-butyraldehyde the equilibrium should be displaced to the left. Experimentally with ethane diol we can isolate the trichloro ethylidene hemi-acetal as a crystalline solid[4]. Infra-red measurements show that acetaldehyde forms approximately 17% hemi-acetal while with n-butyraldehyde the hemi-acetal is negligible. The same was seen with propane 1,3-diol. Glycerol again gave directly analogous results, but there are primary and secondary hydroxyls present. The trichloro-ethylidene hemi-acetal in this case was shown to be at a primary hydroxyl which has been suggested by Baggett et al[10]. Hexitols require forcing conditions for acetal formation with trichloroacetaldehyde[23] and therefore as expected no hemi-acetal was detected.

We therefore turned to an indirect route to hemi-acetal formation

by varying the conditions and electrophiles.



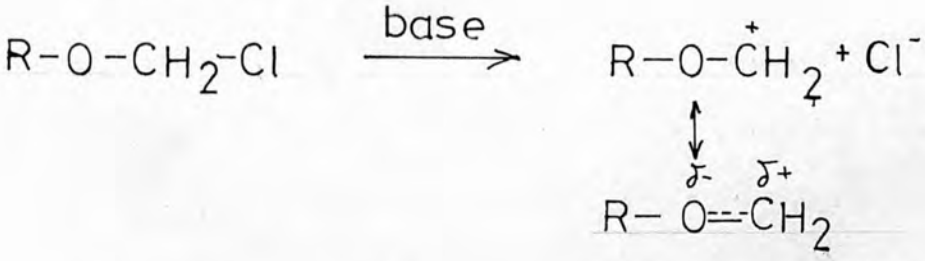
I II III

The compounds I, II and III should act as electrophiles in very similar way, with II and III reacting under milder conditions.

It is obvious from direct studies with aldehydes that the energy barrier for the reaction with hexitols for the non-catalysed reaction inhibits any reaction occuring, while acid catalysis lowers this barrier causing the reaction to go to completion with cyclic acetal formation.

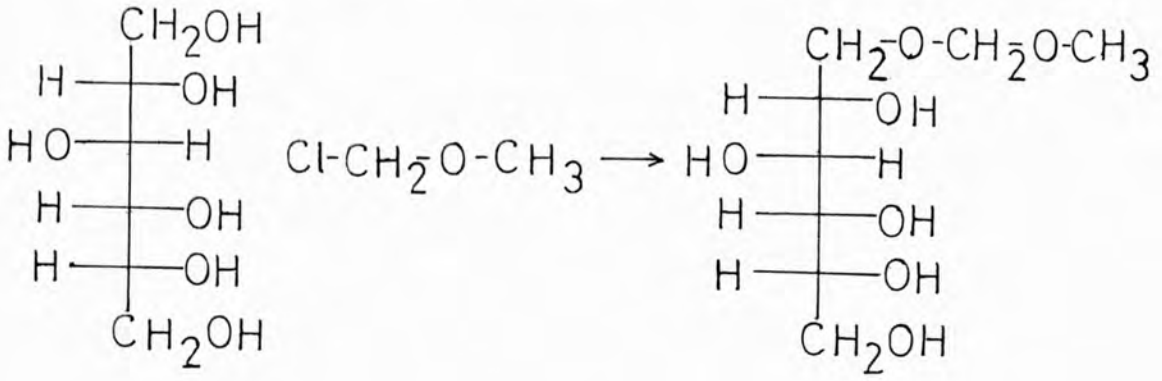
The chloroethers are seen to react to give the same product, the acyclic mixed acetal in the presence of catalysts, i.e. mineral acid, iodine and bases such as silver oxide and pyridine. Bases undergo an initial exothermic reaction with the catalyst, silver oxide or pyridine, forming silver chloride or pyridinium chloride respectively.

This may be explained



It was noticed that the subsequent reaction was faster than the acid catalysed reaction due to the initial formation of the

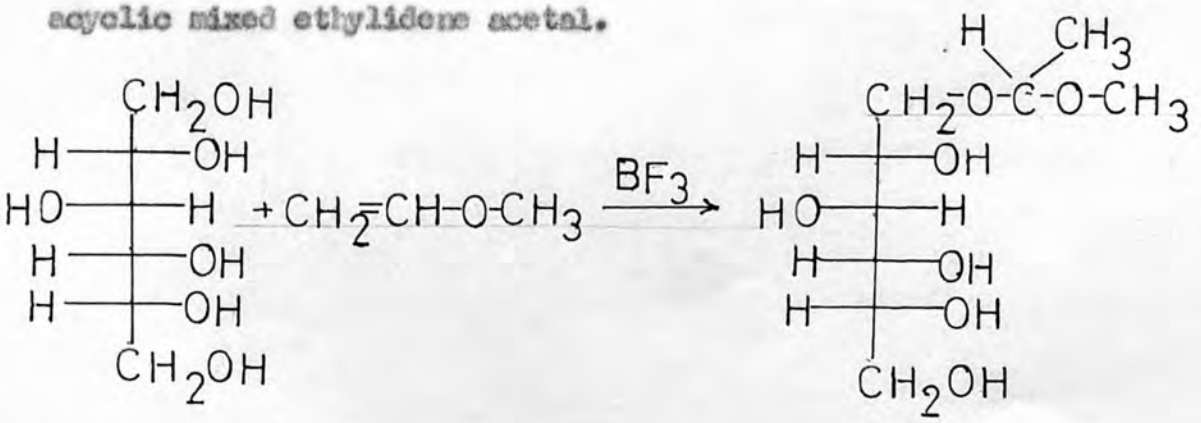
oxycarbonium ion. Using equi-molar proportions of hydroxyl compound and chloro ether it was found that a mono-acyclic acetal was formed and that this was in fact at a primary hydroxyl, the main product by far involving C1 of D-glucitol. (Experiments 4 and 5).



This product gives a methylene acetal, the 2,4-acetal, with initial liberation of formaldehyde so that the comparison to the lyxose derivative is not relevant in this case. This may be substantiated since the pure mono-acyclic acetal gives a small amount of cyclic di-acetal.

Very little further data could be obtained since we are dealing with methylene acetals and their analogues which have been shown to be unfavourable for kinetic studies[22].

Vinyl ethers on the other hand yield ethylidene acetals and their precursors. In this case D-glucitol was studied with two modes of catalysis. Boron trifluoride gave the major product as the acyclic mixed ethylidene acetal.



which subsequently re-arranged to give a mixture of 2,3-O-ethylidene and 2,4-O-ethylidene D-glucitols, showing the usual kinetic and thermodynamic control.

Catalysis with toluene-p-sulphonic acid showed that the initial product was the acyclic mixed acetal which then rearranged to the 2,3-O-ethylidene D-glucitol and finally the 2,4-O-ethylidene D-glucitol. With the alternative electrophiles the initial position has been the primary hydroxyl at C1, this suggests that hemi-acetal formation must be at C1. With hydrogenolysis however although difficulties in reaction procedure were encountered, we can more definitely suggest that the hemi-acetal is formed at the primary hydroxyl, since 1,3-2,4-di-O methylene D-glucitol gave its 6-O-methyl ether.

What we may conclude therefore is that hemi-acetals must be an intermediate step, the acyclic mixed acetal is unstable in the presence of $-\overset{|}{\underset{|}{C}}H-\overset{+}{O}H_2$ acting as a catalyst for a rearrangement, but that there is no evidence for an initial acetal ring involving a primary hydroxyl.

We should expect that the primary hydroxyl should be more susceptible to electrophilic attack on both electronic and steric considerations. The above studies have shown this to be the case, nevertheless while this is undoubtedly the case, the next obvious conclusion is that the carbonyl compound should act in the same way in its reaction with a hexitol, so that the subsequent ring closure should give at 1,2-or 1,3-acetal which should then rearrange. Since the 2,3-acetal is shown to be the kinetically controlled acetal product[23], the initial product should be considered to be the 1,2-acetal.

At this stage we may say that if the hemi-acetal is initially formed at a primary hydroxyl it is formed in a transient equilibrium which removes the carbonyl compound as a substrate from the kinetically and thermodynamically important reactions.

EXPERIMENTAL

EXPERIMENT 1

Reaction between D-Glucitol and Chlorodimethyl Ether

(a) Concentrated sulphuric acid catalysis:-

D-glucitol (1 g) was dissolved in anhydrous dimethyl-formamide (10 ml) and chlorodimethyl ether (0.473 g) was added followed by concentrated sulphuric acid (0.05 ml). The solution was shaken for three hours and then neutralised with barium hydroxide. The mixture was filtered and the filtrate evaporated to a syrup under reduced pressure, which was spotted on silica gel thin layer plates and also paper chromatograms.

(i) Thin layer chromatography using methyl ethyl ketone saturated with water as developing agent.

One spot Rf = 0.47

(ii) Paper chromatography using Butanol/Ethanol/water (40:11:19) as eluent.

Two spots Rf = 0.193 = D-glucitol

Rf = 0.34

(iii) When the syrup was subjected to vapour phase chromatographic analysis as its trimethylsilylether (10% ppe at 195°C) the following results were obtained, all retention volumes being measured relative to the trimethyl silyl ether of D-glucitol.

RV = 1=D-glucitol

RV = 1.71

(iv) The syrup was therefore subjected to column chromatography using a cellulose column and n-butanol saturated with water as the eluent. Fractions 20-30 contained the material Rf = 0.36 (Butanol/Ethanol/water 40/11/19). This syrup was taken up in ethanol from which crystals were deposited (Compound A).

Mixed MP with 2,4 Q Methylene D-Glucitol = 159-160°

MP with 2,4 Q Methylene D-Glucitol = 163-164°

MP Compound A = 158-159.5°

$C_7H_{14}O_6$ requires C 43.33% H 7.27% O 49.40%

Analysis C 43.28% H 7.26% O 49.48%

$[\alpha]^{25°}_{Hg}$ = -11.9 $[\alpha]^{25°}_{D}$ = -10.1 c 3.2 in $CHCl_3$

Lit. $[\alpha]^{25°}_{D}$ = -9.8

(b) Iodine catalysis:-

D-glucitol (10 g) was dissolved in anhydrous dimethylformamide and one crystal of iodine was added (i.e. a catalytic amount) followed by chlorodimethyl ether (4.73 g) with cooling in a salt ice bath to avoid the violent reaction which otherwise occurred. This was then allowed to stand at room temperature for three hours. The iodine was then destroyed using saturated aqueous sodium thiosulphate (1.0 mls). The solution was evaporated to a syrup and extracted with ethanol when a white solid was again deposited (Compound A). The violence of the reaction in the presence of iodine was considered further. The chlorodimethyl ether (4.73 mls) was dissolved in anhydrous dimethylformamide and the catalytic amount of iodine was added, a great deal of heat was liberated so that the temperature, without cooling, rose to 65°. On addition of D-glucitol (10 g) no further heat was evolved but vapour phase chromatography of samples removed over a period of half an hour showed the reaction to be complete within 25 minutes.

EXPERIMENT 2

Analysis of Compound A

(i) Determination of free hydroxyls by formation of the acetate in the presence of excess acetic anhydride:-

A standard solution was prepared by dissolving acetic anhydride (1 ml) in anhydrous pyridene (20 mls). (This will be referred to as Ac).

A sample of compound A (approx. 0.04 g) was weighed out accurately and dissolved in Ac (2 mls) in a stoppered test tube and the mixture heated on a boiling water bath for two hours, similarly Ac (2 mls) was boiled for five minutes to be used as a blank. After their periods of heating both the blank and the reactions were cooled and poured into water (40 mls) and titrated using 0.1 M sodium hydroxide.

Results:-

Weight of compound A	0.1 M Sodium hydroxide	Uptake equivalent of acetic acid
0.0416 g	7.35 ml	0.0441 g
0.0332 g	5.87 ml	0.0353 g

2 mls of standard solution contains 0.1198 g acetic acid.

Initial assumption

D-GLUCITOL + $Cl \cdot CH_2$-O-Me $\longrightarrow$ O-O-CH_2-O-Me +

On the assumption that we have a linear mixed acetal these results cannot be rationalised. Assuming that we have had cyclisation, the above results agree with there being four free hydroxyls.

Number of free hydroxyls = 4.005/molecule.

(ii) Periodate oxidation and determination of liberated formaldehyde for compound A. This was carried out in the normal way.

Molar uptake of periodate ion = 1.13 mols/mol compound A

Mols of formaldehyde liberated = 1.97 mols/mol compound A

This could correspond to the 2,4-methylene-D-glucitol.

(iii) Comparison of the initial syrup with compound A.

By paper chromotograph; butanol/Ethanol/water (40/11/19)

Compound A	Rf	= 0.51
2,4-Methylene-D-glucitol	Rf	= 0.51
Syrup	Rf	= 0.36

Vapour phase chromatography (10% ppe 195°C)

Syrup RV	= 1.71
2,4-Methylene D-glucitol	= 4.3
Compound A RV	= 4.3

The syrup and Compound A are different and in ethanol there must have been a rearrangement.

EXPERIMENT 3

Analysis of the reaction between D-Glucitol and Chlorodimethyl ether by following the Optical Rotation

D-Glucitol (5 g) was dissolved in 0.5 M dimethylformamide/ hydrogen chloride (25 ml) and equilibrated at 25°. Similarly a solution of chlorodimethyl ether (2.47 g) in anhydrous dimethyl-formamide (25 ml) was prepared and equilibrated. The two were then rapidly mixed and their reaction followed polarimetrically at 25. The reaction was between 0.109 M substrates in 0.25 M DMF/HCl.

The optical rotation of the reaction followed a smooth downward curve and analysis by vapour phase chromatography showed a gradual build up of a material RV = 1.71 (ppe 195°).

This syrupy mixture obtained from work up of the above reaction mixture was separated on a cellulose column as previously (Experiment 1) giving (Compound B).

EXPERIMENT 4

Analysis of Compound B

(a) Sequential periodate oxidation and hydrolysis.

The syrup (0.05 g) was dissolved in sodium metaperiodate solution (30 ml 0.15 M) and left in the dark for four hours. The solution was then saturated with sodium chloride and extracted with chloroform. The chloroform extract was evaporated to a syrup, taken up in aqueous ethanol and heated on a boiling water bath with 1R 120H$^+$ resin (0.1 g) for two hours. The resin was then filtered off and the filtrate evaporated to a semi-solid.

(i) Borate electrophoresis:-

This gave three spots $R_{GLUCOSE}$ = 0.52 0.76 and 1.2 which was identical to glycolaldehyde.

(ii) Test for glycolaldehyde using diphenylamine reagent[11a].

The reagent was prepared as follows:- trichloroacetic acid (100 g) was made up to 100 ml with water and 1% solution of recrystallised diphenylamine in glacial acetic acid was prepared.

Analysis of the syrup:-

The syrup (0.001 g) was dissolved in water (1 ml) and the trichloroacetic acid solution (0.2 ml) was added followed by the diphenylamine solution (2.4 ml) and the mixture was heated for half an hour. A similar solution using water (1 ml) was prepared as a blank. The ultra violet spectrum of the above solution was run showing λ max 660nm which is characteristic of the glycolaldehyde colour

reaction with the above reagent.

(b) Determination of Free hydroxyls in Compound B

The reagent AC was prepared as before (Experiment 2)

	Wt. of Compound B	0.1 M sodium hydroxide	Blank 0.1 M NaOH
a)	0.0448 g	12.8 ml	22.975
b)	0.0449 g	12.8 ml	22.975

Uptake for the sample = 10.175 ml 0.1 M Na OH

Therefore molar uptake = 5.11 mols assuming a linear mixed acetal.

The glycolaldehyde and hydroxyl determination fit in with a linear mixed acetal at C_1 or C_6.

EXPERIMENT 5

Sequential acetylation, hydrolysis, and methylation

The compound B (1 g) was dissolved in dry pyridene (10 ml) and acetic anhydride (6 ml) were added with cooling. The mixture was left at room temperature for twenty four hours and then poured into ice water, a syrup was deposited, this was extracted with chloroform, washed twice with water and dried over sodium sulphate. The chloroform solution was evaporated to a syrup which was taken up in aqueous ethanol and warmed with 1R 120H+ resin (0.5 g) for one hour. The resin was then filtered off and the filtrate was evaporated to a syrup. This syrup (0.6 g) was dissolved in anhydrous dimethyl formamide (5 ml) and methyl iodide (1 ml) was added, followed by dry silver oxide (0.5 g). The mixture was shaken for twenty four hours, evaporated to a semi-solid, extracted with chloroform and the chloroform extract washed with water and dried over sodium sulphate. The chloroform was evaporated giving a semi-solid. This was repeated twice finally giving a solid material. This was recrystallised from ethanol/petroleum ether (BP 40-60°), mp 65-67°.

Analysis	Calculated for methyl penta-acetyl D-glucitol	C% 50.24	H% 6.45	O% 43.31
	Found	C% 50.43	H% 6.43	O% 43.14

EXPERIMENT 6

Preparation of authentic 1-O-methyl D-glucitol Penta-acetate

(a) Preparation of Glucose diethyl mercaptal[12,13,14]

D-glucose (1 g) was dissolved in concentrated hydrochloric acid (1 ml) and ethane thiol (1 ml) was added to the mixture cooled to 0°. The mixture was then allowed to warm to room temperature and shaken for 30 mins, left to stand for ten minutes and cooled again to 0°. Water (2 ml) was then added when the mixture went solid. The solid mass was broken up, filtered and washed with ice cold water and recrystallised from boiling water.

mp 127-127.5

Lit mp 127-127.5

Yield 1.4 g

(b) Preparation of D-Glucose diethyl mercaptal penta acetate[3]

The D-glucose diethyl mercaptal (3.01 g) was dissolved in pyridine (16 ml) and acetic anhydride (10 ml) was added with cooling, after 16 hours the mixture was poured into ice water and the syrup so formed extracted with chloroform. The chloroform solution was washed with water five times, dried over sodium sulphate and evaporated to a syrup which crystallised after starting at -5° for 8 days.

This was recrystallised from aqueous methanol and nucleated when crystals were deposited.

mp 46-47°

Lit mp 45-47°

Yield 3.16 g

(c) Preparation of 1-Bromo-1-methyl mercapto-al-glucose-penta-acetate

D-glucose mercaptal penta acetate (4.69 g) were dissolved in ether (50 ml) and bromine solution in ether (0.55 ml in 10 ml ether) was added dropwise with rapid stirring. After stirring for a further 30 mins with cooling in an ice/salt bath the excess bromine was destroyed using cyclohexene and the solution evaporated under vacuum to a syrup which would not crystallise.

(d) Preparation of 1-O-Methyl-ethyl mercapto-al D-glucose-penta acetate

The compound from (c) (4.96 g) was dissolved in dry methanol and dry silver carbonate (8 g) was slowly added and the suspension was stirred for 24 hours at room temperature. The silver salts were then filtered off and water was added to the filtrate until turbidity was obtained. The solution was then set aside at -5° until crystals were deposited. These crystals were recrystallised from aqueous methanol.

mp = 72-73°

Lit mp = 71-73°

Yield = 2.1 g

(e) Preparation of 1-O-Methyl-D-glucitol penta acetate[15]

The D-glucose-diethyl-mercapto-penta acetate (3.0 g) was dissolved in dry ether (200 ml) and Raney nickel[20] (30 g) was added under nitrogen. The mixture was heated under reflux for twenty four hours, then filtered under nitrogen. The ether solution was evaporated to a syrup which was taken up in ethanol/Petroleum ether (BP 40-60°) from which crystals were deposited.

mp = 65-67°

Lit mp = 65-67°

Yield = 2.1 gr

Mixed melting point with the suspected 1-O-methyl D-glucitol penta acetate showed the two samples to be identical.

EXPERIMENT 7

Reaction between D-Glucitol and Chlorodimethyl ether under Base catalysis

D-glucitol (6) was dissolved in anhydrous dimethylformamide (10 ml) and dry silver oxide (4.5 g) was added to the solution cooled in acetone/card ice and the chlorodimethyl ether (2.47 g) was slowly added with swirling, the reaction was very vigorous, even though cooled to -78°. When the violent reaction had ceased the reaction was shaken at room temperature for six hours. After this period the silver salts were filtered off and the filtrate evaporated to a syrup which was again separated on a cellulose column yielding a syrup. Rf = 0.36 (Butanol/ethanol/water 40/11/19). This is compound B.

It was found that in the absence of D-glucitol there was a very violent reaction between chlorodimethyl ether in dimethylformamide and dry silver oxide.

EXPERIMENT 8

Determination of vicinal hydroxyls and liberated formaldehyde by sodium metaperiodate oxidation for compound B

This was carried out as normal.

Molar uptake of periodate ion = 4.09 mols/mol of compound

Mols of liberated formaldehyde = 1.93 mols/mol of compound

EXPERIMENT 9

Rearrangement of compound B to compound A

Compound B (0.3096 g) was dissolved in dimethylformamide and the reaction followed polarimetrically, no change was observed, but on the addition of 1 drop of dimethylformamide/hydrogen chloride (1.0 M) a smooth downward transition occurred.

Analysis of the same reaction spectrophotometrically 280 nm. showed the first step to be liberation of formaldehyde, with subsequent recondensation.

EXPERIMENT 10

Preparation of 1 chloroethylmethyl Ether[17,18,19]

Acetaldehyde (100 ml) and anhydrous methanol (150 mls) were mixed and cooled to 0°C in an ice bath and dry hydrogen chloride was bubbled through until no more was absorbed and two layers could be seen. The lower layer was then blown out and the upper layer dried over calcium chloride for one hour (after two hours decomposition occurs). The liquid was decanted from the calcium chloride and distilled.

BP	72-75°	D	= 0.996
LIT BP	72-75°	LIT D	= 0.997
YIELD	90 gr.		

EXPERIMENT 11

Reaction of Chloroethyl-methyl Ether with D-Glucitol

The reaction was repeated as for experiment 1 using D-glucitol (1 g) and chloroethyl-methyl ether (0.521 mls).

This gave a syrup by column chromatography. Rf = 0.41 Butanol/Ethanol/water (40/11/19) (Compound C).

EXPERIMENT 12

Analysis of Compound C

Sequential acetylation, hydrolysis and methylation

Experiment 5 was repeated exactly as before except that Compound C (1.g) was used. This again yielded 1-O methyl D-glucitol penta acetate.

MIXED MP and MP 65-67°

LIT MP 65-67°

EXPERIMENT 13

Rearrangement of compound C

This was studied both polarimetrically and spectrophotometrically (280 nm) and it was again shown that the first step was liberation of aldehyde. No intermediate was established but the final product was shown to be 2,4 ethylidene D-glucitol by MP and MIXED MP.

MP 146-147°

MIXED MP 145-146°

EXPERIMENT 14

Preparation of 1,3-2,4-Di-O-Methylene D-Glucitol[16]

D-Glucitol (200 g) was added to 37% aqueous formaldehyde (300 ml) and concentrated hydrochloric acid (200 ml) was added, the mixture was heated on a water bath for two hours when the mixture went solid due to the formation of crystals. The mixture was cooled and filtered and the filtrate evaporated to a syrup which was extracted twice with boiling ethanol, on cooling crystals were deposited.

MP = 174-175°

LIT MP = 174-175°

The solid formed in the reaction was recrystallised from 50% aqueous ethanol.

EXPERIMENT 15

(a) Preparation of 1,3;2,4 di-O-methylene 5,6 dimethyl D-Glucitol[16]

1,3;2,4-Di-O-Methylene-D glucitol (1 g) was dissolved in dimethyl formamide (10 ml and dry silver oxide (1 g) was added followed by methyl iodide (2 ml) and the mixture shaken for 24 hours. The mixture was filtered and the filtrate evaporated to a semi-solid which was extracted with chloroform, washed four times with water and dried over sodium sulphate. The chloroform was evaporated off under reduced pressure leaving a syrup. The methylation was repeated twice leaving a syrup which was crystallised from ethanol.

MP 193-194°C

LIT MP 193-194°C

(b) Preparation of 1,3;2,4 Di-O-methylene-6-O-methyl D-glucitol

(i) 1,3;2,4 Dimethylene D-glucitol (5 g) was dissolved in ice cold hydridine (50 ml) and toluene-p-sulphonyl chloride (4.6 g) in pyridene (10 ml) was slowly added and the mixture allowed to stand at room temperature overnight. The mixture was then poured into ice water and extracted with chloroform. The chloroform solution was dried over sodium sulphate and evaporated giving a solid which was re-crystallised from ethanol.

MP 160-161°C

(ii) The toluene-p-sulphonate (1 g) was dissolved in 0.5 M methanolic sodium methoxide (30 mls) and refluxed on a water bath for 16 hours. The mixture was then evaporated to a semi-solid which was separated

on a silica column using Ethyl Methyl ketone saturated with water as eluent. Fractions 5-10 gave a solid which was recrystallised from ethanol.

MP 180-181°

LIT MP 180-181°

Thin layer chromatography of the semi-solid, silica gel using Ethyl Methyl ketone as developing agent gave

Rf = 0.7 - the methyl ether

Rf = 0.91 - compound (B)

(c) Attempted Tosylation of Compound 1,3;2,4-Di-O-Methylene 6-O-Methyl D-Glucitol

The compound (1 g) was dissolved in cold pyridine and p-toluene sulphonyl chloride (1 g) in pyridene was added and the solution left at room temperature for 16 hours. This mixture was then poured into water when a solid was precipitated. This was recrystallised from ethanol.

MP 180-181°

Mixed melting point proved it to be identical to the starting material.

(d) Attempted Tritylation of compound 1,3;2,4-Di-O-Methylene 6-O Methyl D-Glucitol

Compound (c) (1 g) was dissolved in pyridene and trityl chloride (1 g) was added and the solution allowed to stand at room temperature for two days. The mixture was then poured into ice water, when crystals were deposited. These were recrystallised from ethanol.

MP 180-181°

Mixed melting point proved it to be identical to the starting material.

Tosylation and tritylation failed. Thus the free hydroxyl in above compound shown by infrared spectroscopy nujol mull 3540 cm^{-1} must be a secondary hydroxyl.

EXPERIMENT 16

Reaction between 1,3;2,4 Di-O-Methylene D-glucitol and Methylal under conditions of Hydrogenation ($Pd/BaSO_4/H_2$)

The title compound (4 g) was dissolved in glacial acetic acid (5 ml) and methylal (30 ml) was added followed by 5% $Pd/BaSO_4$ catalyst (2 g), and the mixture was hydrogenated at 4-6 atmospheres. After 12 hours hydrogenation the catalyst was filtered off and the filtrate evaporated to a syrup.

Thin layer chromatography on silica gel developing with Ethyl Methyl ketone saturated with water showed three stops

Rf = 0.49

Rf = 0.7

Rf = 0.83

The mixture was separated by column chromatography on silical gel eluting with Ethyl Methyl ketone saturated with water.

This gave fractions 3-8 compound Rf on tlc (as above) Rf = 0.83

10-14 compound Rf = 0.7

20-25 compound Rf = 0.49

These were evaporated yielding solids which were recrystallised from ethanol giving melting points of:

fraction giving	Rf = 0.49	174-175°	LIT MP 176-175°
	Rf = 0.7	180-181°	180-181°
	Rf = 0.83	193-194°	193-194°

By comparison with standards by mixed melting points these were shown

to be 1,3-2,4-di-O-methylene-D-glucitol and its 6-O methyl and 5,6 di-O-methyl ethers respectively.

EXPERIMENT 17

Condensation of Ethyl Vinyl Ether and D-Glucitol

Boron trifluoride catalysis:

D-Glucitol (20 g) was dissolved in anhydrous dimethyl formamide in the presence of anhydrous calcium sulphate (1 g) followed by Ethyl vinyl ether (10 ml). The reaction was started by breaking a capillary containing boron trifluoride etherate (0.005 ml) below the surface of the reaction mixture by shaking and the mixture shaken vigorously for two hours, after which the suspension was neutralised with anhydrous sodium carbonate. The mixture was filtered and the filtrate evaporated under reduced pressure yielding a syrup. Thin lay chromatography, silica gel, developed with Methanol/diethyl ether (1/6) showed five spots

Rf = 0.0 Rf 0.21 Rf = 0.29 Rf = 0.46 Rf = 0.76

The mixture was separated by column chromatography using a silica gel column eluting with ether gradually increasing the percentage of ethanol to 20%.

Compound Rf = 0.21 yielded a solid which was recrystallised from ethanol/ether MP 145-146° LIT MP 146-147° YIELD 0.21 g

Rf = 0.29 yielded a solid which was recrystallised from chloroform MP 115-117° LIT MP 116-118° YIELD 0.34 g

These were shown to be 2,4 and 2,3-O-Ethylidene D-glucitol respectively. The compound Rf = 0.46 yielded a syrup Compound D. The compound Rf = 0.76 was not obtained pure and was not analysed.

EXPERIMENT 18

Analysis of compound D

Analysis was carried out as for compound B experiments 4, 5 and 8.

Periodate oxidation showed

= 4.1 mols uptake of periodate ion

1.05 mols of formaldehyde liberated

sequential acetylation, hydrolysis and methylation again yielded

1-O-Methyl-D-glucitol penta acetate

EXPERIMENT 19

Analysis of the reaction between D-glucitol and Ethyl Vinyl Ether by following the Optical Rotation

This was considered using two catalysts:

(a) Boron trifluoride etherate

(b) Anhydrous p-toluene sulphonic acid

D-Glucitol (9.1 g) was dissolved in anhydrous dimethylformamide (50 ml) and the solution equilibrated at 25° similarly ethyl vinyl ether (5 ml) was dissolved in anhydrous dimethyl formamide (50 ml) and equilibrated at 25° .

Aliquots (10 mls) of each solution were removed, mixed rapidly and

(a) 3 drops of boron trifluoride etherate were added and the reaction followed polarmetrically;

(b) Anhydrous p-toluene sulphonic acid (80 mg) (prepared by azeotropic distillation) were added and the reaction followed polarmetrically.

The polarimetric curves FIG show appreciable differences in the mode of reaction. Analysis was carried out by thin layer chromatography silica gel methanol/ether (1/6).

(i) Boron trifluoride catalysis:

This showed the major product at 2 hours to be the syrup (Compound D).

(ii)Toluene p-sulphonic acid catalysis

a) Half an hour Rf = 0.46

b) One hour Rf = 0.21 and 0.46

c) Two hours Rf = 0.21, 0.29 and 0.46

d) Three hours Rf = 0.2, 0.29 and 0.46

At one hour compound 0.46 predominated while at two hours there is only a small amount of compounds, Rf = 0.29 and 0.46 and compound Rf = 21 predominated while after the elapse of a further hour compound Rf = 0.29 predominated.

EXPERIMENT 20

Rearrangement of Compound D

This was carried out as for experiment 9 with exactly the same results except that the polarmetric curve exhibited a minimum characteristic of the reaction between free acetaldehyde and D-glucitol.

EXPERIMENT 21

Reaction between Various Aldehydes and Diols

(a) Ethylene Glycol:

(i) Chloral:

Ethylene glycol (15.5 g) was mixed with anhydrous chloral (41.5 g), a great deal of heat was evolved and the temperature rose to 73°C, on cooling a very viscous liquid was formed which on cooling to -5° for three weeks yielded a crystalline solid, the mono-chloral hemi acetal of ethane diol.

MP 42°C

LIT MP 42°C

Infrared analysis of the syrup and the solid showed complete absence of carbonyl absorption 1750 cm^{-1} which is present in the aldehyde.

(ii) Acetaldehyde:

Ethylene glycol (14.08 g) was mixed with acetaldehyde (10 g), the solution became warm yielding a colourless liquid which on distillation gave only the starting material.

Infrared analysis of the mixture showed the presence of a peak at 1710 cm^{-1} which was present in pure acetaldehyde.

(10 g) in n-Pentane (20.277 g) (i.e. giving the same dilution as in ethane diol.

From the infrared spectrum of this solution it would seem

that the absorption band in the ethylene glycol was approximately 17% smaller than the n-pentane solution.

(iii) n-Butyraldehyde:

Ethylene glycol (6.61 g) and n-butyraldehyde (10 g) were mixed giving complete solution.

Infrared spectroscopy compared to a n-pentane solution of n-butyraldehyde of the same concentration showed no diminution in carbonyl absorption 1760^{-1} even after five hours.

(b) Propane-1,3-diol

(i) Chloral

Propane 1,3 diol (10 g) and anhydrous chloral (10.4 g) were mixed, the temperature rose to 58° and a viscous liquid was formed. This would not crystallise even after three weeks at -5° and distillation gave complete recovery of the starting materials.

Infrared spectroscopy of the mixture showed the complete absence of carbonyl absorption at ~ 1750 cm^{-1} while hydroxyl absorption at ~3600 cm^{-1} remained.

(ii) n-Butyraldehyde

Propane 1,3-diol (10.6 g) and n-butyraldehyde (10 g) were mixed giving complete solution.

Infrared spectroscopy comparing a n-pentane solution of n-butyraldehyde of the same concentration showed no dimunition in carbonyl absorption.

(c) Glycerol:

(i) The above reactions i.e. with anhydrous chloral[4] and secondly n-butyraldehyde were repeated with glycerol giving directly analogous results.

(ii) The Methylation of the Glycerol Hemi-Acetal:

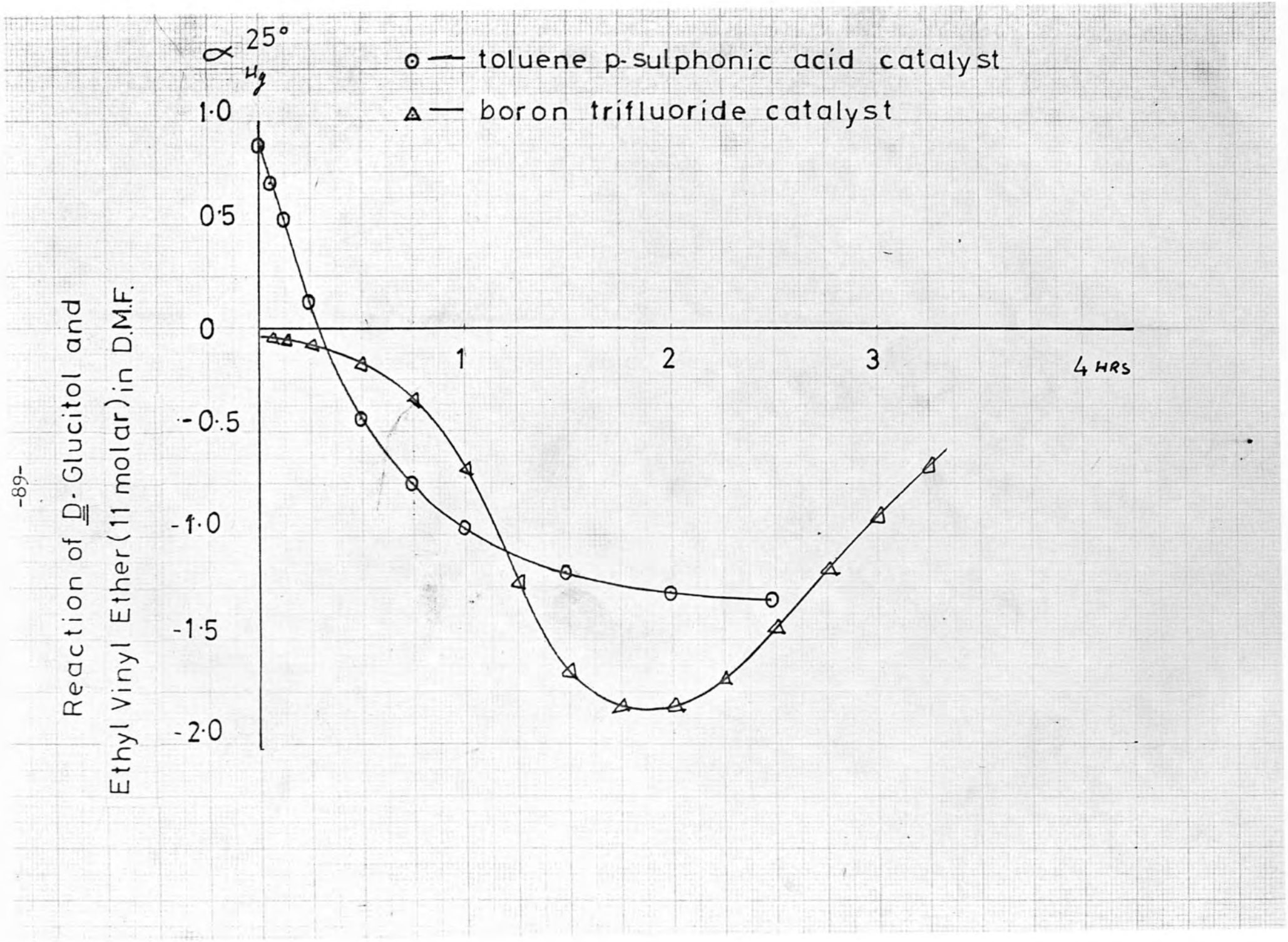
The syrup hemi-acetal (from (i)) (1 g) was dissolved in anhydrous dimethylformamide (10 ml) and dry silver oxide (3 g) was added followed by methyl iodide (5 ml). The mixture was shaken for 24 hours, then filtered and evaporated to a semi-solid which was extracted with chloroform, the chloroform extract washed three times with water and dried over sodium sulphate. The chloroform was then removed under vacuum. The methylation was repeated twice leaving a yellow syrup which was dissolved in ethanol and heated on a water bath with 1R 120H$^+$ resin (0.5 g) for two hours. The resin was then filtered off and the filtrate evaporated to a syrup which was distilled (47°C 1.0 mm).

BP 180° 760 mm

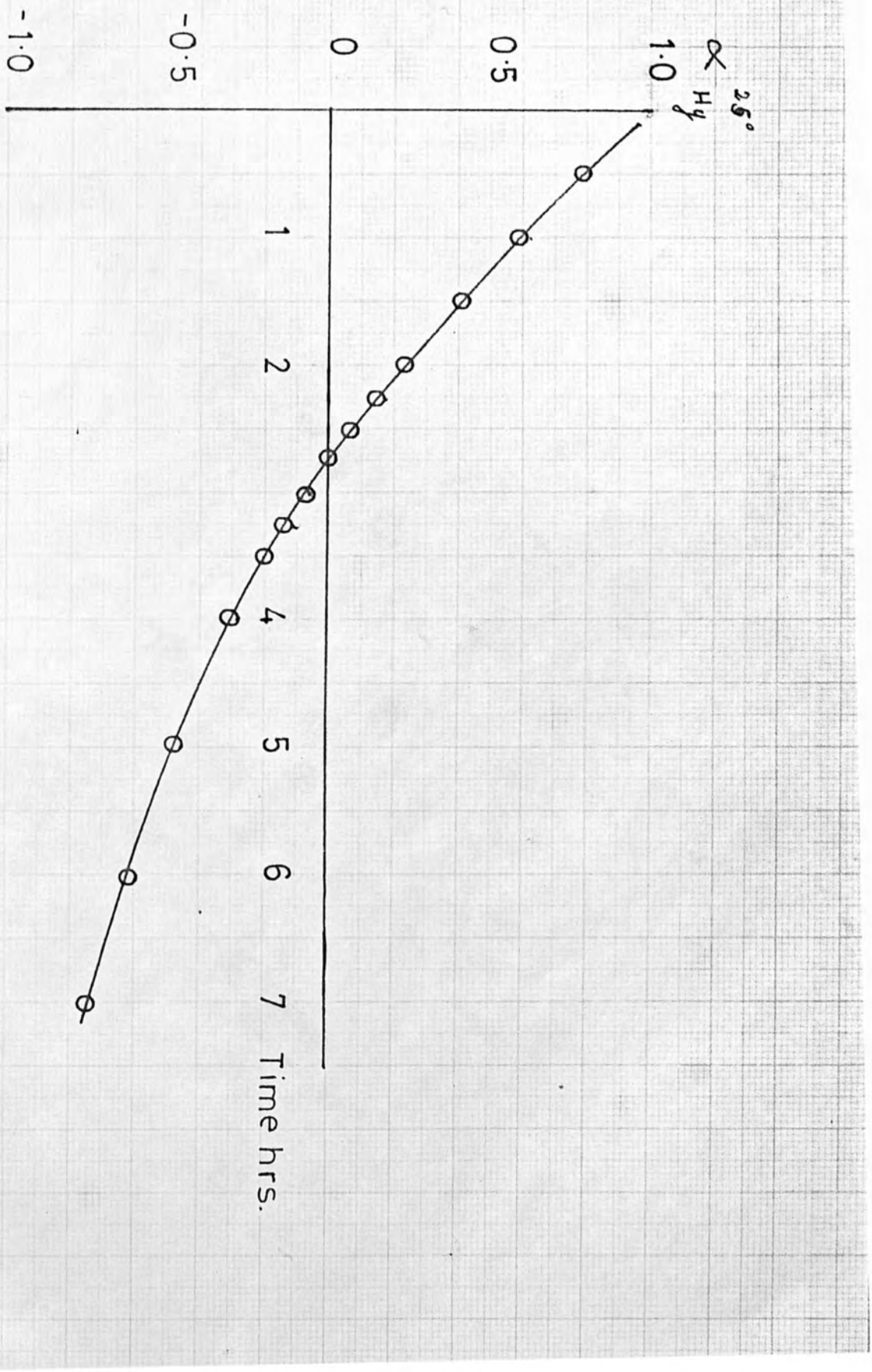
LIT BP 180° 760 mm[21]

YIELD 0.2 g

This was shown to be identical to 1,2-di-O-methyl glycerol.


Reaction of D-Glucitol and
Ethyl Vinyl Ether (11 molar) in D.M.F.
$\alpha^{25°}_{Hg}$
⊙ — toluene p-sulphonic acid catalyst
△ — boron trifluoride catalyst
1·0
0·5
0
-0·5
-1·0
-1·5
-2·0
1
2
3
4 HRS

Hydrogen Chloride Catalysed Reaction of D-Glucitol and Methyl chloromethyl Ether (1:1 molar) in DMF



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SECTION 3

Kinetic Studies related to the Mechanism of Acetal Formation

CHAPTER 1

The Hydrolysis of Mono-acetals of D-Glucitol

INTRODUCTION

Acetal formation may be considered as a two step process, hemi-acetal formation and cyclisation. This may be written as

$$\text{POLYOL} + \text{ALDEHYDE} \overset{\text{FAST}}{\rightleftharpoons} \text{HEMI-ACETAL} \overset{\text{SLOW}}{\rightleftharpoons} \text{CYCLIC ACETAL}$$

This is a very simple representation but is generally considered to be correct with the overall equilibrium being controlled by the cyclisation, this has very rarely been questioned[4] and even then without complete certainty.

Firstly in the kinetic studies the hydrolysis of cyclic acetals will be considered. For acyclic acetals and oliphatic acetals it is now beyond doubt[6] that hydrolysis occurs by an A-1 mechanism (Ingold's terminology[5]). Acetal hydrolysis may be represented as:

$A + H_3O^+ \overset{k_1}{\underset{k-1}{\rightleftharpoons}} AH^+$ EQUILIBRIUM

$AH^+ \xrightarrow{k_2} X^+$ RATE DETERMINING

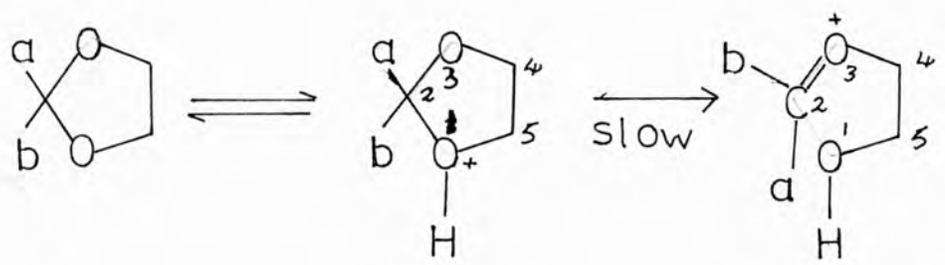
$X^+ + H_2O \longrightarrow$ PRODUCTS V FAST

If $k_2 \ll k_{-1}$ K_a = basic dissociation constant of A

$K_a = \frac{k_{-1}}{k_1}$ $k_{H_3O^+} = \frac{k_2}{K_a}$

OVERALL RATE COEFFICIENT

Therefore the initial step characterised by the equilibrium constant Ka is dependant upon the pKa of the acetal. pKa is seen to vary very little for a series of 1,3-dioxolans[3] so that the differences in observed rate coefficients must be due to the partial reaction in which the 1,3-dioxolan ring is cleaved. Other factors than the pKa of the original acetal must be important. Hydrolysis may be written[6]:



A $\quad$ AH^+ $\quad$ X^+

$\xrightarrow{FAST}$ PRODUCTS

The intermediate X^+ from the conjugate and AH^+ must be a resonance structure giving $C_2 - O_3$ a partial double band character. The alkyl groups attached to C_2 should increase the rate due to their inductive effect, as should substituents at C_4- and C_5- although to a much smaller extent.

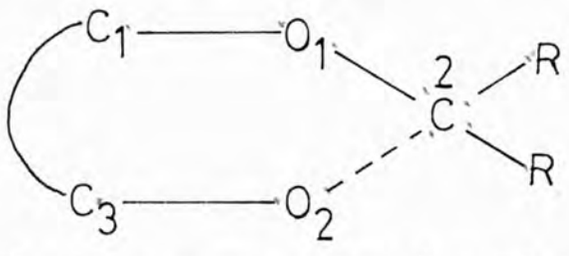
Owing to the partial double band character in X^+ the nuclei joined by 2,3 -; 3,4-and a and b bonds tend to be in the same plane, but to attain the transition start the bonds 'a' and 'b' must be bent to some extent towards the plane of the dioxolan ring, increasing

the steric strain. This will vary with the substituents on the ring, but a cis interaction between substituents at C_2 and C_4 or C_5 would increase the strain more than a trans interaction.

The 1,3-dioxan exists preferentially in a chair conformation. Here again it is suggested that steric factors involved in attaining the transition are important.

Normally 1,3 - dioxans are more basic than their analogous 1,3 dioxolans due to the increased inductive effect of the increased polymethylene chain interacting with the ring oxygens. Hence Ka for the dioxan should be smaller thereby increasing the overall rate. This is not usually the case and therefore steric factors must be considered It is suggested that the transition state requires a mutually perpendicular arrangement[7].

FIG 1

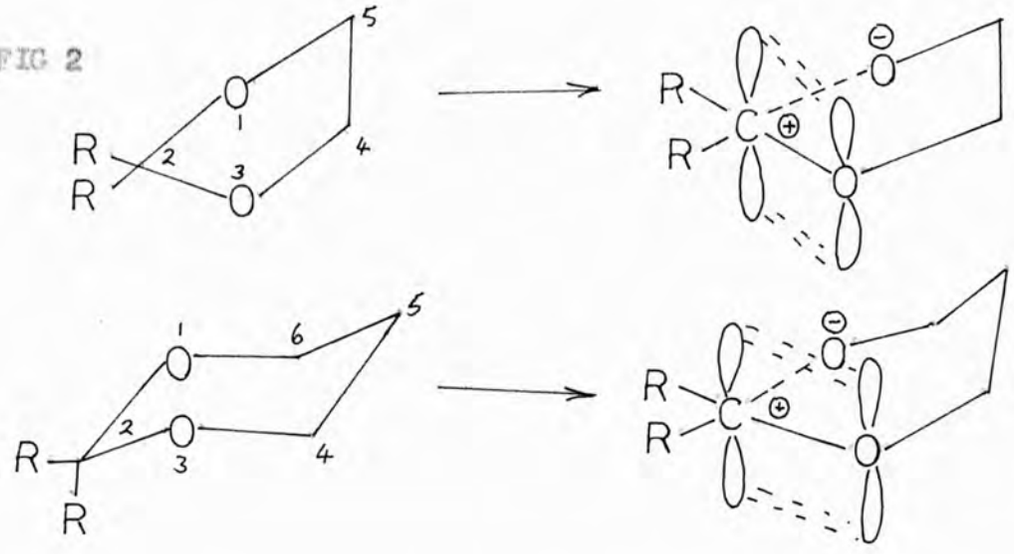


so that C(1) - O(1) - C(2) of the cyclic acetal (FIG 1) is in a plane essentially perpendicular to the C(3) - O(2) - C(2) plane in order to maximise electronic assistance of oxygen 1 in the breaking of the bond between O_2 and C_2. This is easily attained for a six membered ring but a five membered ring has some difficulty in meeting this requirement. Hence the transition state of the five membered ring is of higher energy than that of the six membered ring.

This is in variance with Leggetter and co-workers[9] who have considered $LiAlH_4/AlCl_3$ hydrogenolysis of acetals which may be

considered analogous to hydrolysis, and again considered the distortion required to form the intermediate oxocarbonium ion transition state.

FIG 2



The oxo-carbonium ion formation requires the atoms of the $O_1C_2 - O_3 - C_4$ group to attain coplanarity for optimum stabilisation (FIG 2). This is initially more easily attained in a five membered ring because it is initially more nearly coplanar while a six membered ring requires substantial deformation to a half chair to allow orbital overlap. This greater distortion would retard oxo-carbonium ion formation. If this is directly applicable to hydrolysis it is difficult to see that it is correct while that propounded by Watts[7] seems to be substantiated by Baggett and co-workers[10] since their synthetic work shows a direct correllation to the results found during studies on acid catalysed migrations. In both cases the oxo-carbonium ion must be postulated, with steric factors being of importance at this stage.

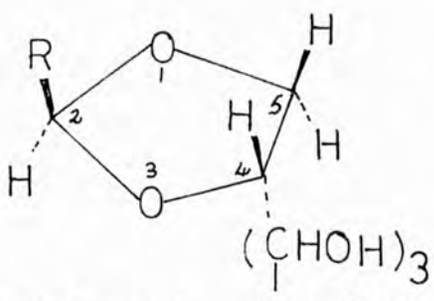
Although the hydrolysis of acetals is in itself of interest, the

main interest is in the kinetics of acetal formation. If the theory of macroscopic reversibility is envoked, hydrolysis is seen to be directly applicable to formation since the same intermediates are involved. The same factors important for hydrolysis would be important in synthesis, i.e. electronic and steric. There is only one dissenting opinion[4] which is seen to be only partially valid, even by the authors, and therefore it is valid to envoke the theory of macro - reversibility for the study of the factors involved in acetal hydrolysis and apply them to acetal formation.

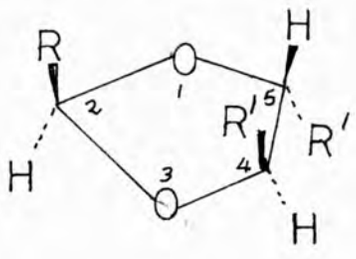
RESULTS AND DISCUSSION

The initial studies show that it is legitimate to use ultra-violet spectroscopy to study the formation and hydrolysis of acetals by observing the aldehyde carbonyl. In the case of the simple cyclic acetals dioxolans and dioxans it has been shown that steric factors are more important than the basicity of the acetal.

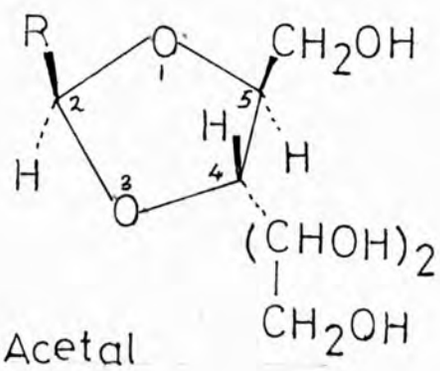
Considering the acetals of D-glucitol we see:



5,6-Acetal
1,2- "(L-Form)



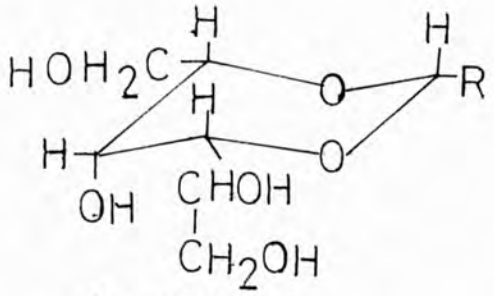
3,4-Acetal
R' = -CHOH
CH$_2$OH



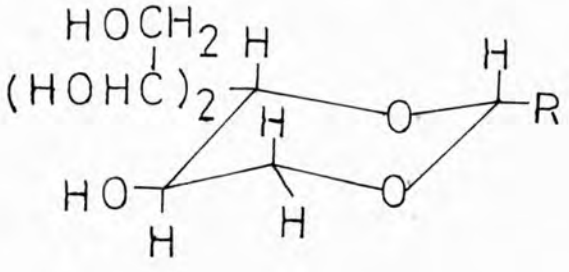
2,3-Acetal

In all these cases the other isomer at C_2 is possible. In the 1,2- and 5,6- mono-acetals there need not be a cis interaction between C_2 alkyl groups and ring substituents at C_4 and C_5 while in the 3,4 and 2,3- mono-acetals this cannot be avoided. On these considerations the

1,2-and 5,6-mono-acetals should be more stable to hydrolysis than the 3,4-or 2,3-mono-acetal. On the other hand the terminal acetal rings should be more susceptible to protonation. It has been stated previously that the pKa of the acetal is not the controlling factor in acetal hydrolysis. The results predicted for the 1,3-dioxolan ring acetals of D-glucitol are born out by the experimental results which show the rates of hydrolysis to be in the order 1,2< 5,6 < 3,4 ≪ 2,3.



2,4-Acetal



4,6-Acetal

The factors involved in the transition state have been discussed in the introduction. In dioxan rings substituents in an equatorial position are favoured, therefore in the ground states of the molecules there can be very little difference. Ease of protonation must be important in this case in determining the difference in rates of hydrolysis of the two dioxans, although the overall difference between the dioxolans and dioxans must be determined by steric requirements of the transition states. For dioxans we would expect a ring involving a primary hydroxyl to be more rapidly protonated and therefore hydrolysed. Experimental results again bear this out with the 4,6-hydrolysed more rapidly than the 2,4-acetal.

When the hydrolysis of the series of mono-acetals is considered

i.e. 2,4; 4,6; 1,2; 5,6; 3,4 and 2,3 we see that hydrolysis is proportional to hydrogen ion concentration raised to unity, since log k obs V-Ho gives a straight line whose slope is unity, which is again to be expected, although it is in variance with results for some glycoside acetals, where hydrolysis was found to be proportional to the acidity squared[11]. The pseudo first order rates (in sec^{-1}) for hydrolysis, (obtained in the initial stages when it is legitimate to consider aldehyde liberation to be due to hydrolysis and not affected by other reactions), are 7.78×10^{-6}; 2.22×10^{-5}; 3.85×10^{-5}; 2.31×10^{-5}; 5.01×10^{-5} and 3.90×10^{-4} for the 2,3; 4,6; 1,2; 5,6; 3,4 and 2,3 respectively at 25°C. By varying the temperature the pseudo first order rate constants at 30° and 35° were obtained and from these $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated. In all cases $\Delta S^{\ddagger}$ was 0.0 Kcal mol^{-1} deg^{-1} which is in agreement with an A - 1 mechanism[13], suggesting in addition that there is virtually no change in entropy in the transition state. The process considered is the ring cleavage of the protonated acetal. The zero entropy of activation must mean that the solvent interaction counteracts the increase in entropy due to ring cleavage. The other reaction parameters give a clearer insight into the factors important for acetal formation since these are of primary importance. From this we see that $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ follow the same trend; they both decrease in the series 2,4 > 4,6 > 1,2 > 5,6 > 3,4 > 2,3- which on theoretical grounds is to be expected. If we look at our original postulate that the 1,2-mono-acetal must be involved in initial cyclisation with a subsequent very rapid rearrangement we see

that this cannot be the case since the 1,2-acetal is relatively stable when compared to the 2,3-acetal which is known as a kinetic intermediate. This being the case we would expect to see it in a reaction sequence since it has a characteristic RV on vapour phase chromatogram. The same may be said for the 5,6-acetal which might be considered as an intermediate. Indeed the known intermediate only, the 2,3-mono-acetal, has the correct stability for a kinetic intermediate.

The hydrolysis may be considered in more detail and from a slightly different point of view. At all temperatures the optical density versus time plots are similar for each compound.

At 25° the 2,4 - O - butylidene D-glucitol is only hydrolysed to a maximum of 8.0% after 4 hours, the 4,6-acetal to 15%; the 1,2-acetal to 25%; the 5,6-acetal to 25%; the 3,4-acetal to 35% while the 2,3-acetal hydrolyses to over 40% in 1½ hours. The 2,3-acetal again shows the characteristic curve with a well defined maximum. In this case there is a rapid equilibration to the mixture of kinetically and thermodynamically controlled products, this is observed but occurs much more slowly with all the others. This observation shows that the initial step involves some hydrolysis to D-glucitol and n-butyraldehyde followed by recombination, i.e. an intermolecular process.

We must now consider what happens in a non-aqueous media. The reactions were repeated using anhydrous dimethyl formamide containing hydrogen chloride (1.0 M).

With the 2,4 - O - butylidene D-glucitol and 4,6 - O - butylidene D-glucitol both rotation measurements and vapour phase chromatography showed no change. With the 1,2 - O - butylidene D-glucitol a steady change with time was observed with a plane curve gradually becoming more negative. Analysis of this by vapour phase chromatography showed a gradual build up of 2,3-and 2,4-acetals with free D-glucitol. Similarly the 2,3-acetals showed a gradual decrease in rotation with vapour phase chromatography showing some D-glucitol and 2,4-acetal. In these cases we cannot have free aldehyde.

The work up procedure in the presence of dimethyl formamide requires fairly vigorous conditions which would cause cleavage of the oxo-carbonium ion to give D-glucitol, so that inter or intramolecular rearrangement cannot be determined.

A similar P.M.R. study on the 1,2-acetal in a non aqueous system again shows rearrangement but no free aldehyde.

Under anhydrous conditions we may be seeing an intramolecular rearrangement but there is no definite evidence from this work.

EXPERIMENTAL

EXPERIMENT 1

Determination of change of optical density with time of an n-Butyraldehyde solution (0.1 M) in hydrochloric acid

The experiment was carried out using a jacketed cell, temperature control ($\pm$ 0.05°) at the temperatures studied, to determine whether there was appreciable change during the proposed time of subsequent reactions (4 hours) as n-butyraldehyde was known to undergo an acid catalysed aldol condensation[1].

The n-butyraldehyde solution was prepared by rapid addition of n-butyraldehyde (7.211 g) to M hydrochloric acid (1 l) thermostatted at 25°, 30° and 35°, respectively, and a sample transferred to the thermostatted cell, and the O.D. studied at 281 nm.

RESULTS

TIME	OD^{25}	OD^{30}	OD^{35}
2 mins	1.45	1.45	1.45
10 mins	1.45	1.45	1.45
15 mins	1.45	1.45	1.45
30 mins	1.45	1.45	1.445
60 mins	1.45	1.445	1.44
2 hrs	1.445	1.44	1.435
3 hrs	1.44	1.435	1.43
4 hrs	1.44	1.435	1.43

No appreciable change during the reaction time

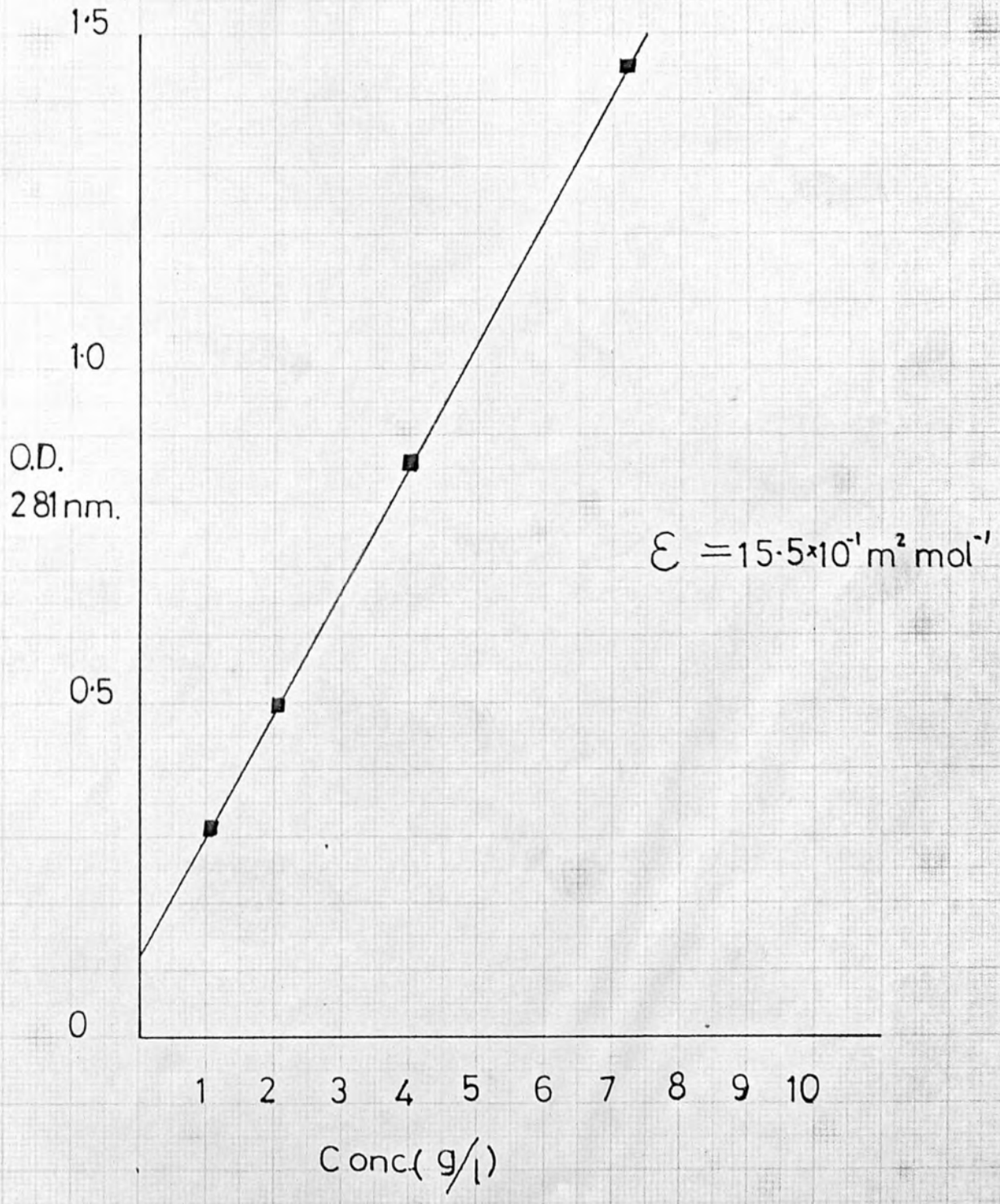
EXPERIMENT 2

Rate of change of Optical Density with time of an Equimolar solution (0.1 M) of D-glucitol and n-Butyraldehyde at 25°

D-glucitol (1.827 g) was dissolved in water (50 mls) and n-butyraldehyde (0.7211 g) was added and the volume made up to 100 mls. The optical density was then studied as in Experiment 1 at 281 nm.

The O.D. was found to be unchanged after 4 hours.

Beer's Law plot for n-Butyraldehyde in Aqueous Hydrochloric Acid (1·0 M)



EXPERIMENT 3

Beer's Law plot for n-Butyraldehyde in 1.0 M Hydrochloric acid

Solutions of n-butyraldehyde were prepared by dissolving n-butyraldehyde in hydrochloric acid (1.0 M) at the three temperatures used for the hydrolytic experiments and the optical densities measured. Within the limits of the instrument the optical densities did not change between 25° and 35°.

CONCENTRATION g/l	O.D. at 281 nm.
7.211	1.45
4.0	0.86
2.0	0.5
1.0	0.315

Extension coefficient E = 1.55 m^2 mol^{-1}

EXPERIMENT 4

Determination of the pKa of a number of simple cyclic n-butylidene acetals[2,3]

It has been noticed that organic bases influence the stretching frequency of the bond to the acidic hydrogen in deuteromethanol[8], and that the shift was proportional to the pKa's of the organic base. Linear relationships were also shown between the shift produced by the different bases on the various hydrogen bond donors proving that the effect was self-consistent.

This method was therfore applied to the cyclic acetals. The infrared spectrum of the mono-deuteromethanol was measured in the range 2000-3000 cm^{-1} on a Pye Unicorn SP 100 using the polystyrene 2850.7 cm^{-1} bond as standard and mono-deuteromethanol in carbon tetra chloride as reference.

All the ethers were sodium dried and then distilled 4 times taking the middle fraction each time. Methanol d_1 (10 μl) was then added to 0.5 ml of the acetal producing approximately 0.5 M solution. The reference cell was filled with the solvent. Each spectrum was repeated 10 times to minimise the error.

Calibrations were obtained using, tetrahydrofuran, 1,4 dioxan, diethyl ether, ethoxy benzene, methoxy benzene and di-butyl ether whose pKa's are well documented.

	-pKa	O-D BAND ν^{SN} cm^{-1} 25°	BAND SHIFT cm^{-1} $\Delta\nu$
T.HF.	2.08	2579.0	112
1,4-DIOXAN	3.22	2592.9	98.1
DIETHYL ETHER	3.59	2594.3	96.7
ETHOXY BENZENE	6.44	2630.2	60.8
METHOXY BENZENE	6.54	2633.7	57.3
DI-BUTYL ETHER	3.05	2591.9	99.1
CARBON TETRACHLORIDE		2691.0 ± 0.25	

These results agree with those of A. Kaukampera[2,3], and therefore the result of their line fitting by method of least squares can be applied.

$$pKa = (0.0789 \pm 0.0042)\ \Delta\nu - (10.91 \pm 0.34)$$

RESULTS

	O-D BAND (cm^{-1})	$\Delta\nu$ (cm^{-1})	pKa
1,3-DIOXOLAN	2600.9	90.1	-3.8
2-PROPYL-4-METHYL DIOXOLAN	2603.1	87.9	-4.0
4-METHYL DIOXOLAN	2602.15	88.85	-3.9
2-PROPYL 1,3-DIOXAN	2590.0	101.0	-2.94
1,3-DIOXAN	2607.5	83	-4.4

EXPERIMENT 5

Determination of acid dependance of the hydrolysis of cyclic acetals

The mode of hydrolysis of all the mono-acetals of D-glucitol are assumed to be identical and therefore the 2,4 acetal and 3,4 were used in this study as representative of the 1,3 dioxan and 1,3 dioxolan ring.

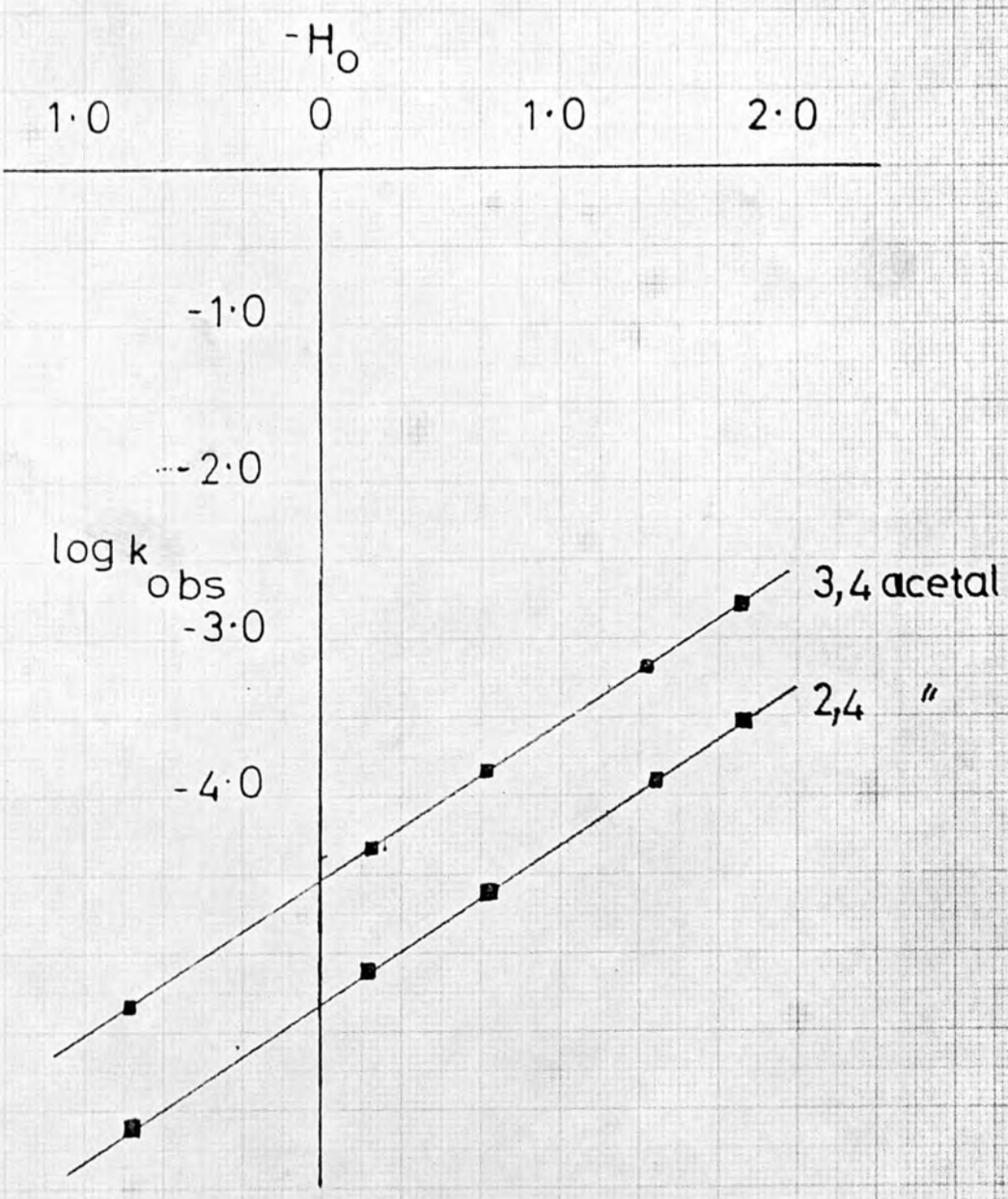
Kinetic experiments were carried out as in Experiment 4 but using 1.0 M, 0.5 M, 0.25 M and 0.1 M hydrochloric acid.

RESULTS

MOLARITY OF HCl at 25°	$k^{2,4}$ ACETAL (sec^{-1})	$k^{3,4}$ ACETAL (sec^{-1})	-Ho[13]
0.1	5.140×10^{-7}	3.31×10^{-6}	-0.98
1.0	7.78×10^{-6}	5.01×10^{-5}	+0.20
2.0	2.41×10^{-5}	1.55×10^{-4}	+0.69
4.0	1.23×10^{-4}	7.94×10^{-4}	+1.40
5.0	2.83×10^{-4}	1.82×10^{-3}	+1.76

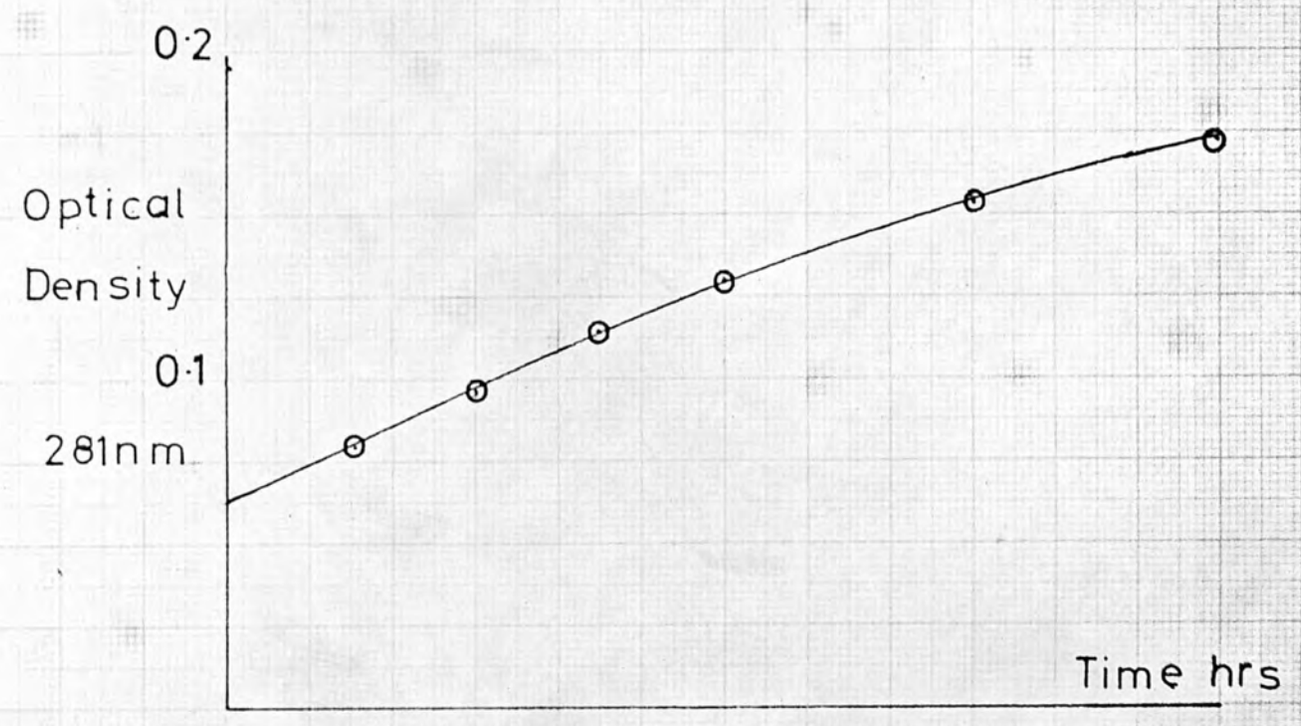
These results show a linear dependance log k V-Ho, slope = 1.
Therefore acid catalysis is dependant on $[H^+]^{+1}$

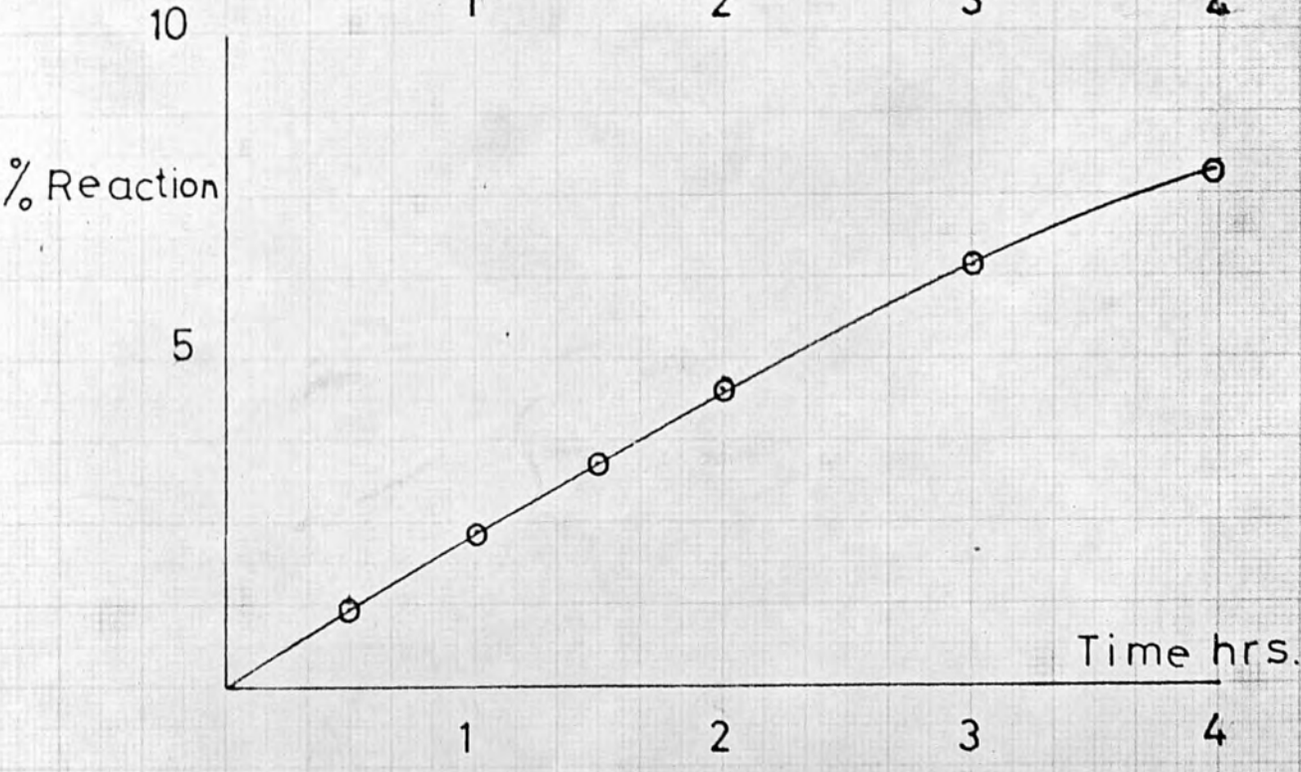
Plot $\log k_{obs}$ against $-H_o$ for Hydrolysis of Mono-O-Butylidene-D-Glucitols in Hydrochloric at 25°



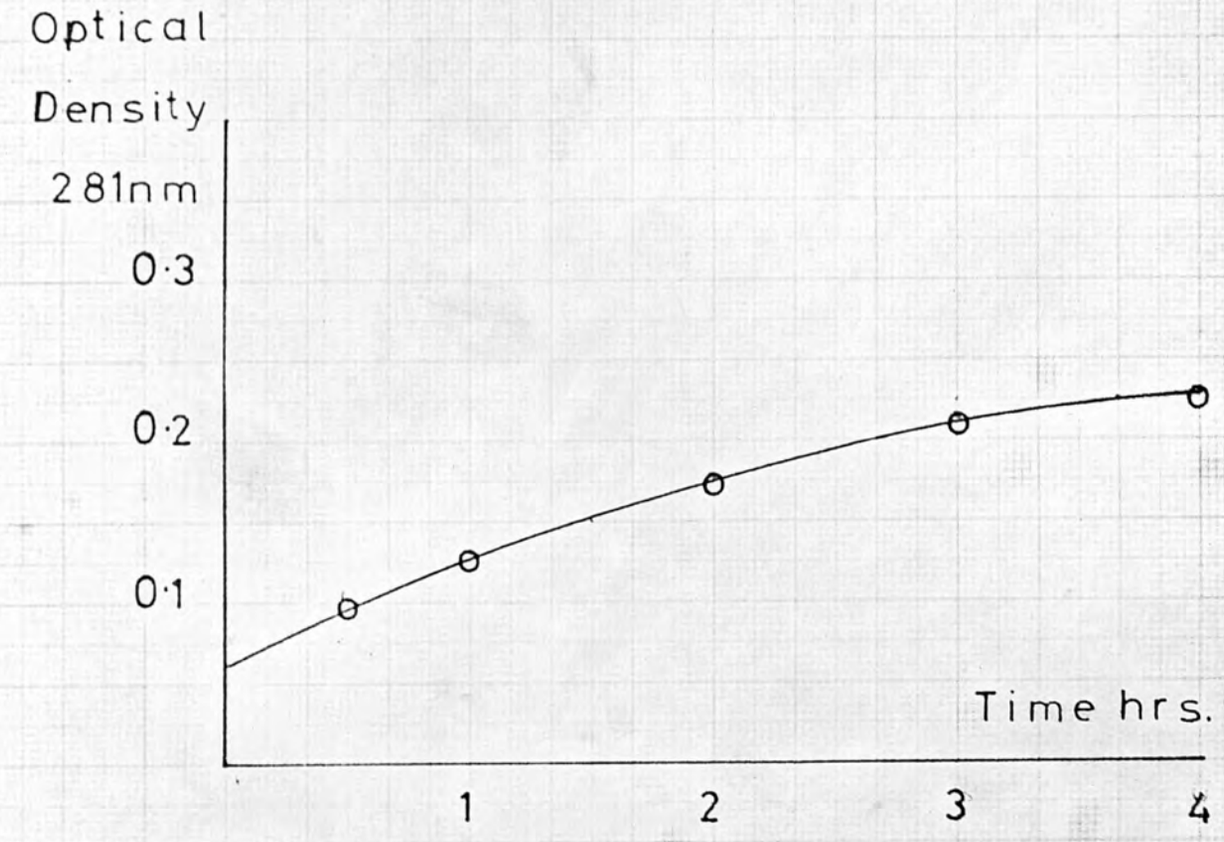
Slope = 1·0

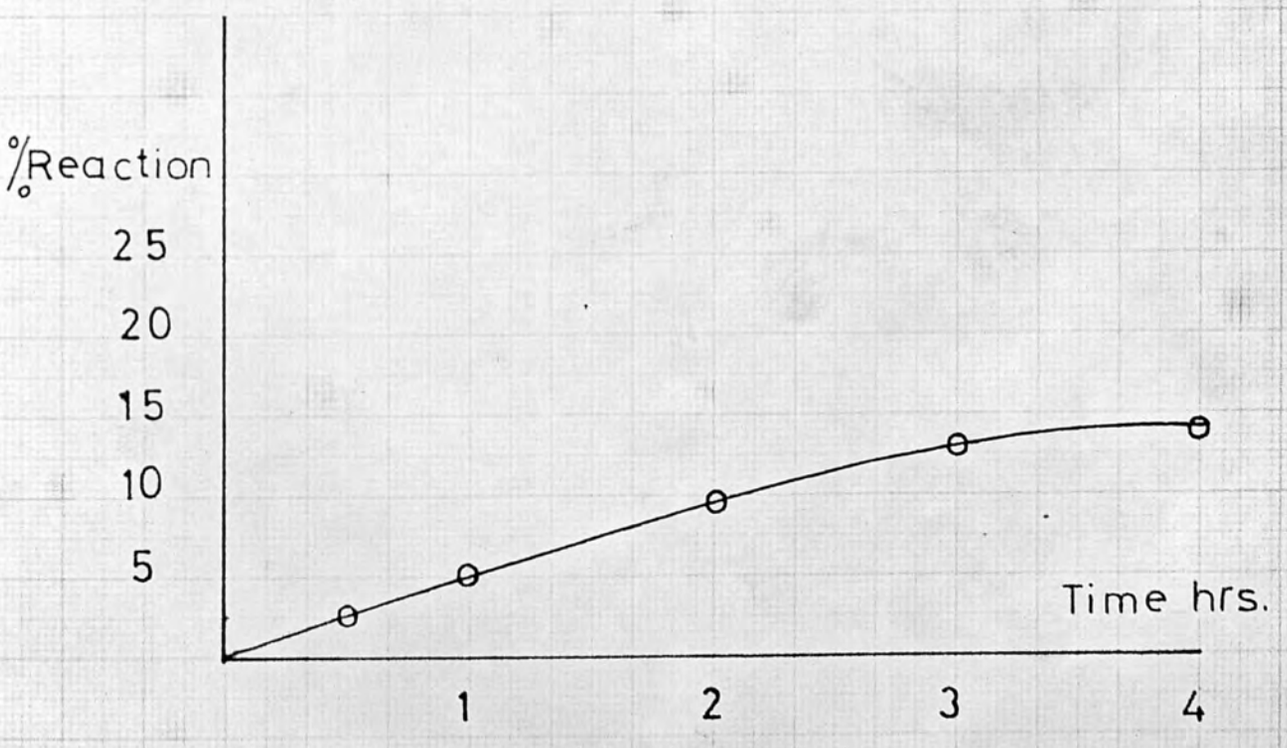
Hydrolysis of 2,4-O-Butylidene-D-Glucitol in 1·0 M Aqueous Hydrochloric Acid at 25°



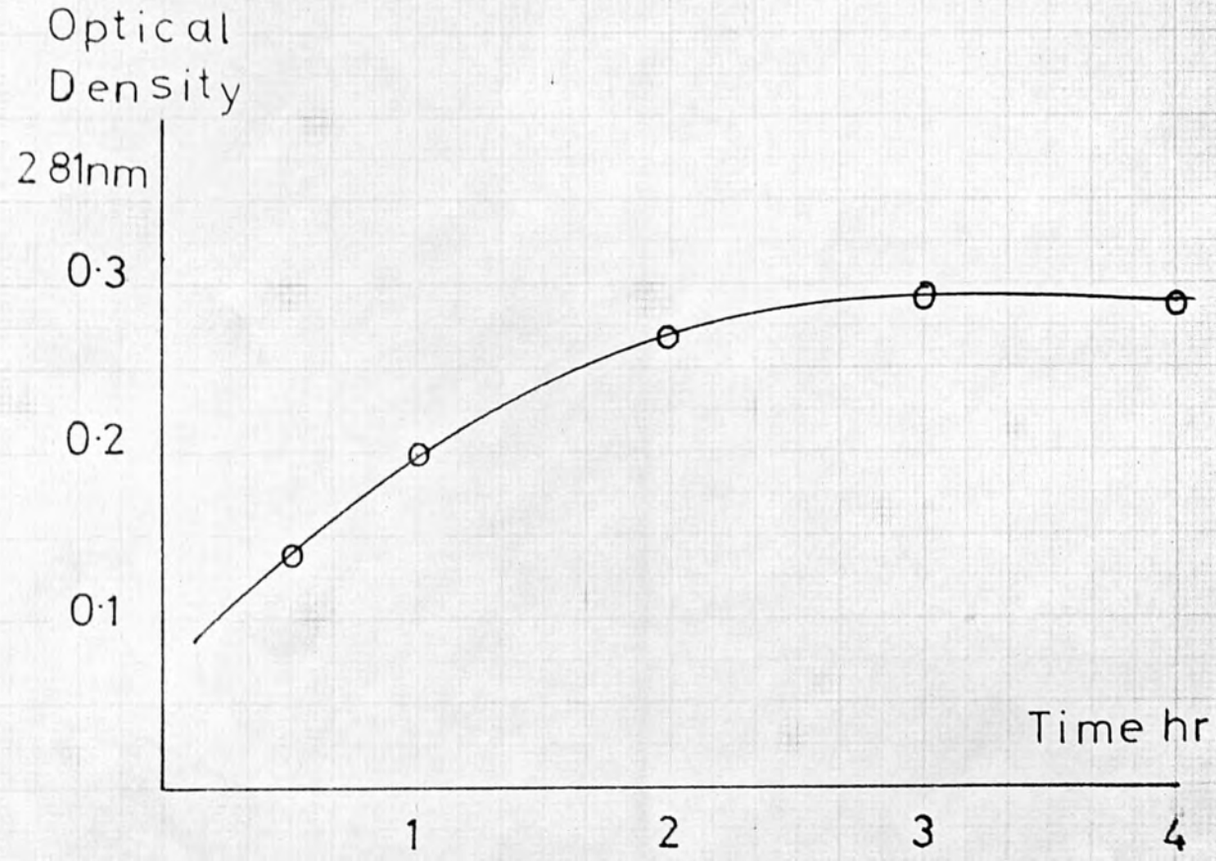


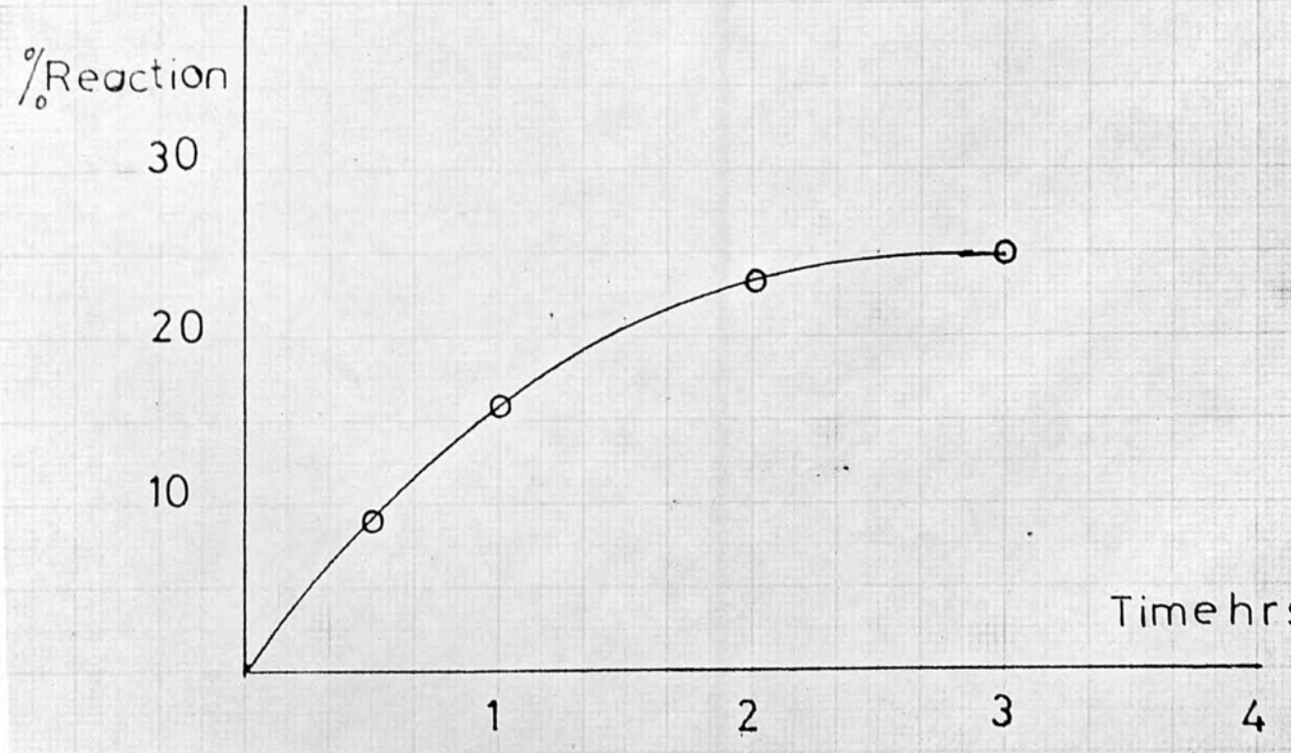
Hydrolysis of 4,6-O-Butylidene-D-Glucitol in 1·0 M Aqueous Hydrochloric Acid at 25°



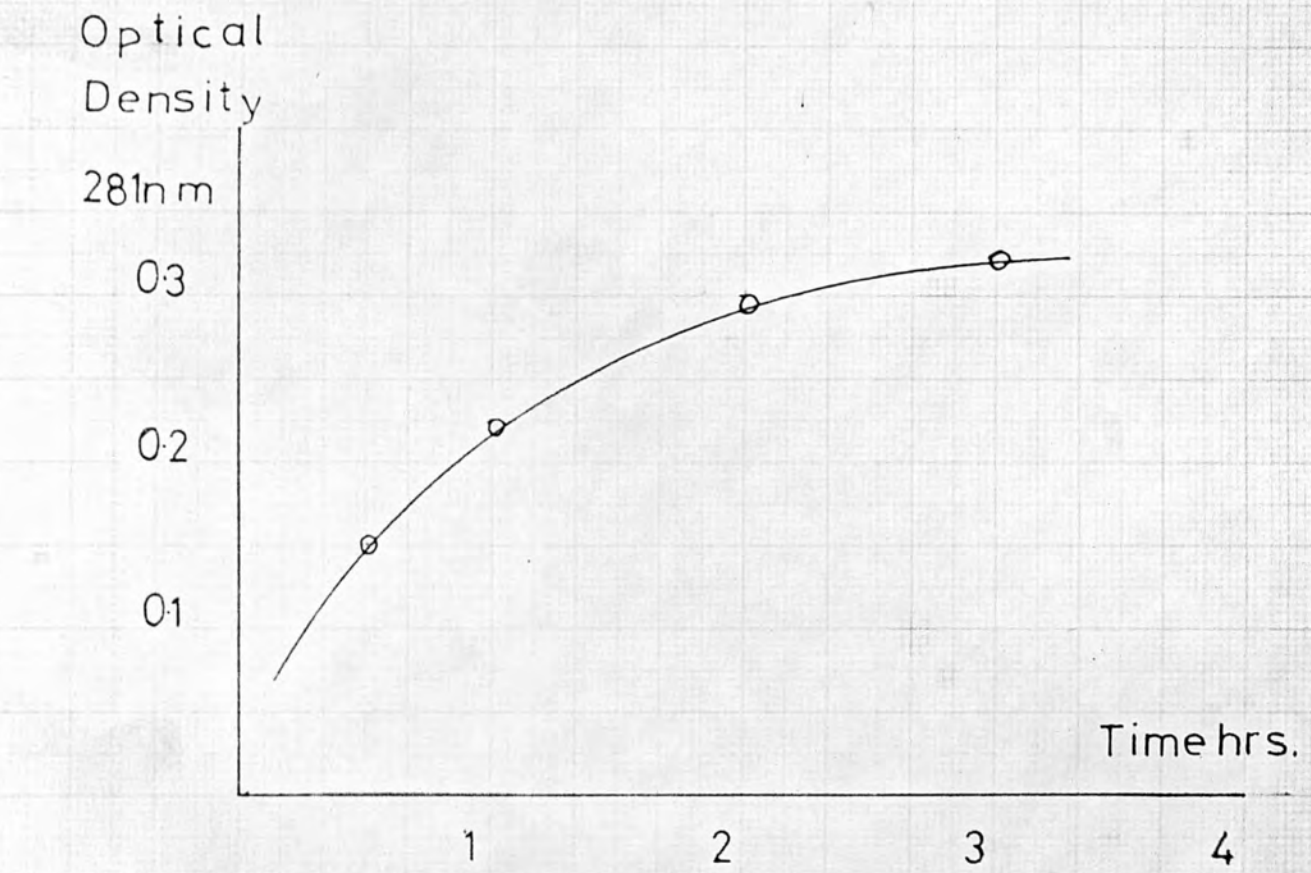


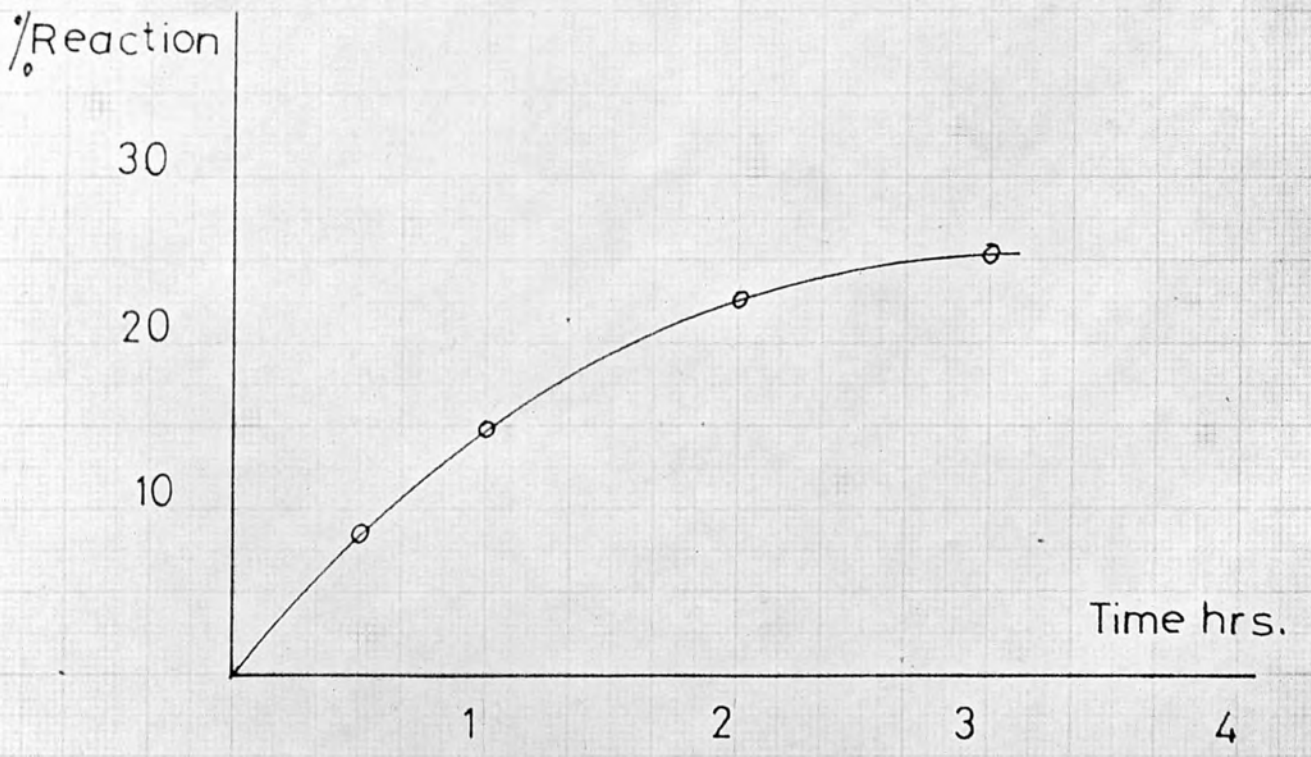
Hydrolysis of 1,2-O-Butylidene-D-Glucitol
in 1·0M Hydrochloric Acid at 25°C



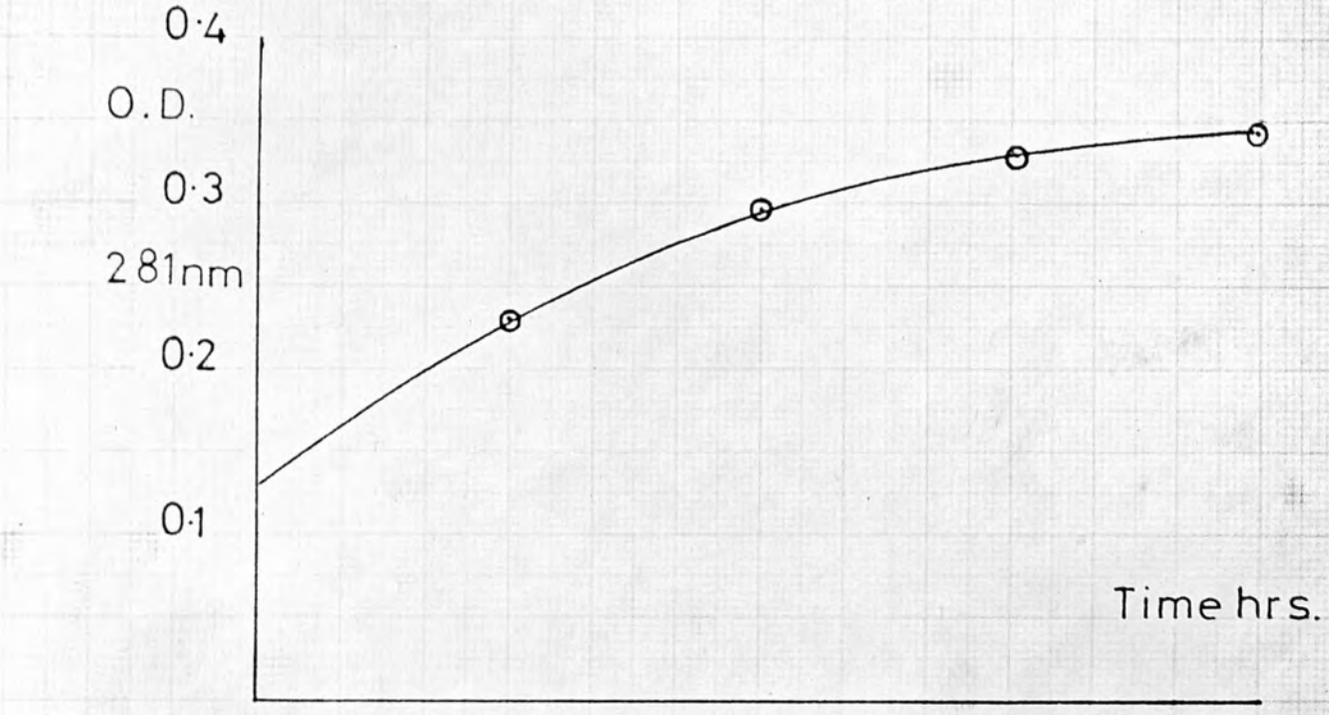


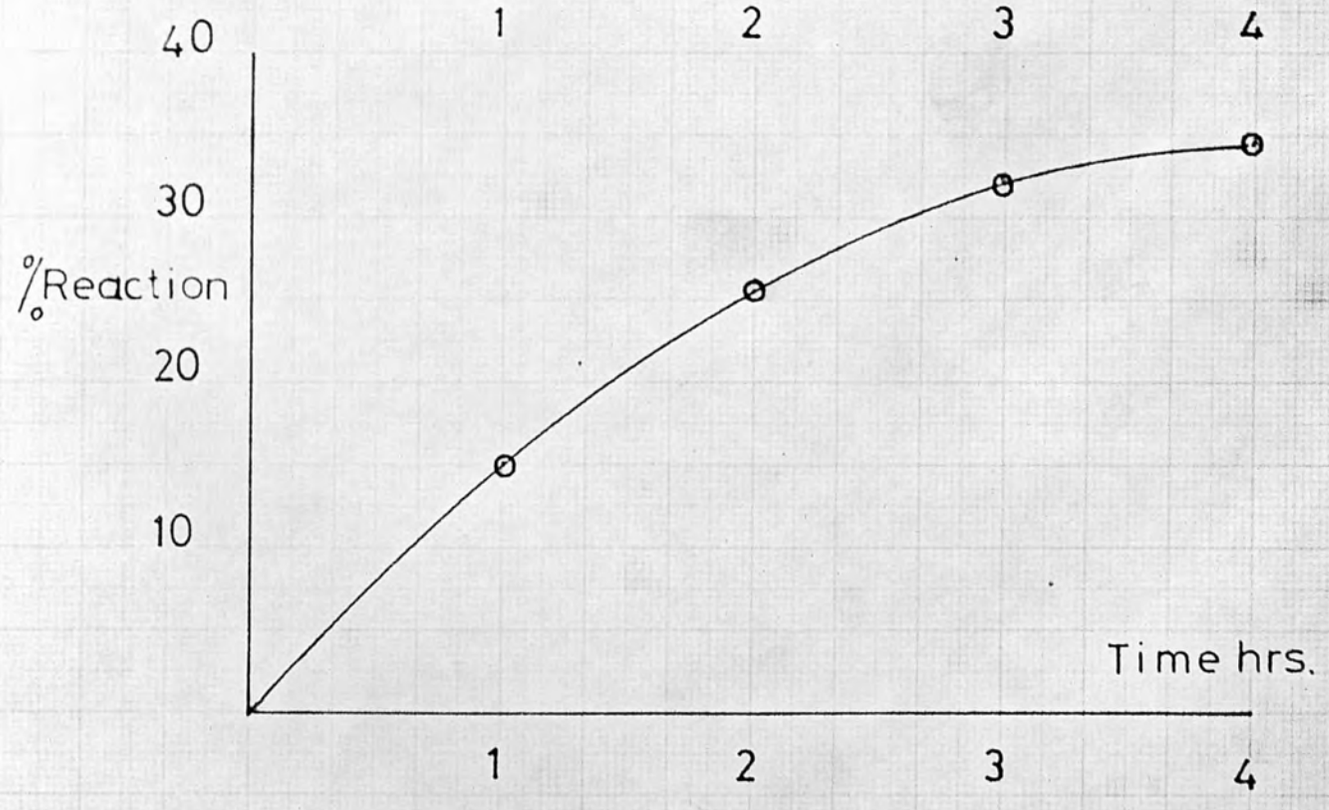
Hydrolysis of 5,6-O-Butylidene-D-Glucitol
in 1·0 M Aqueous Hydrochloric Acid at 25°C



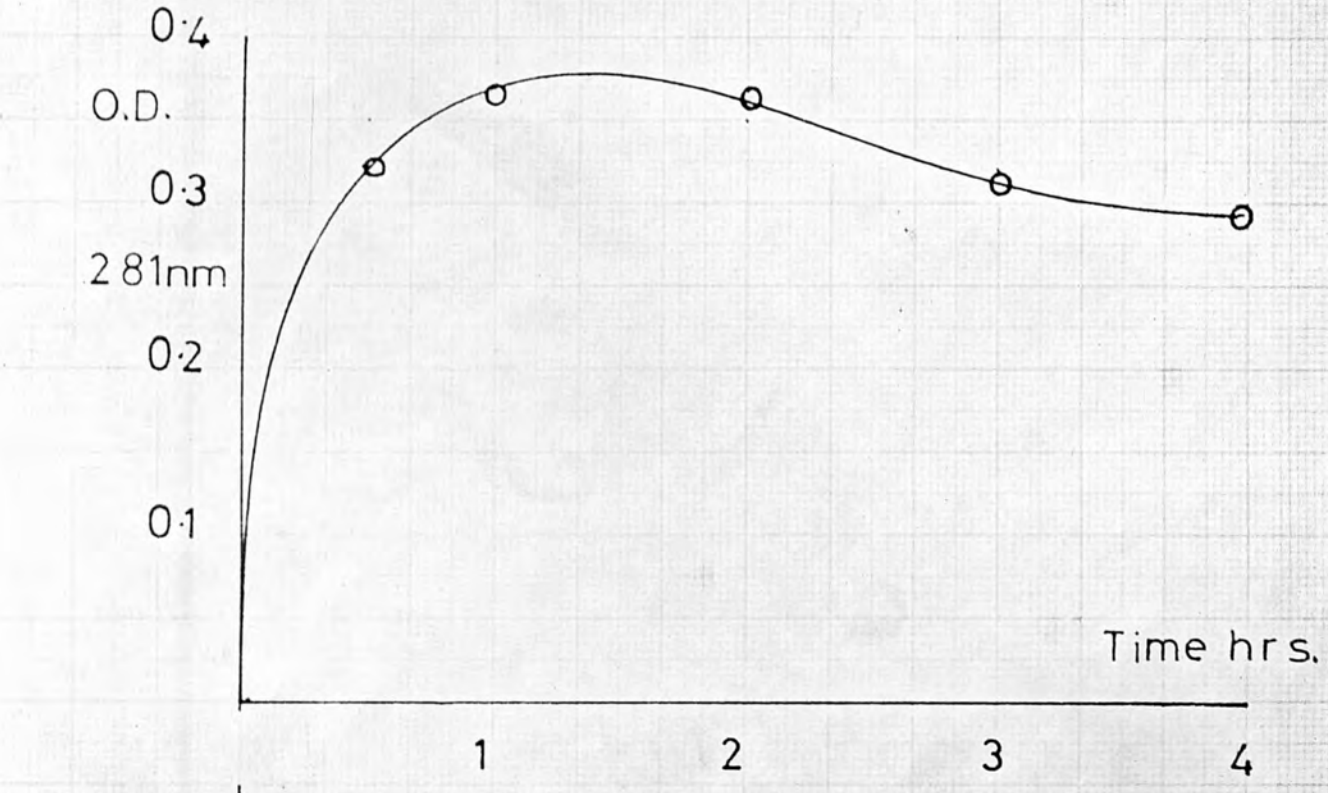


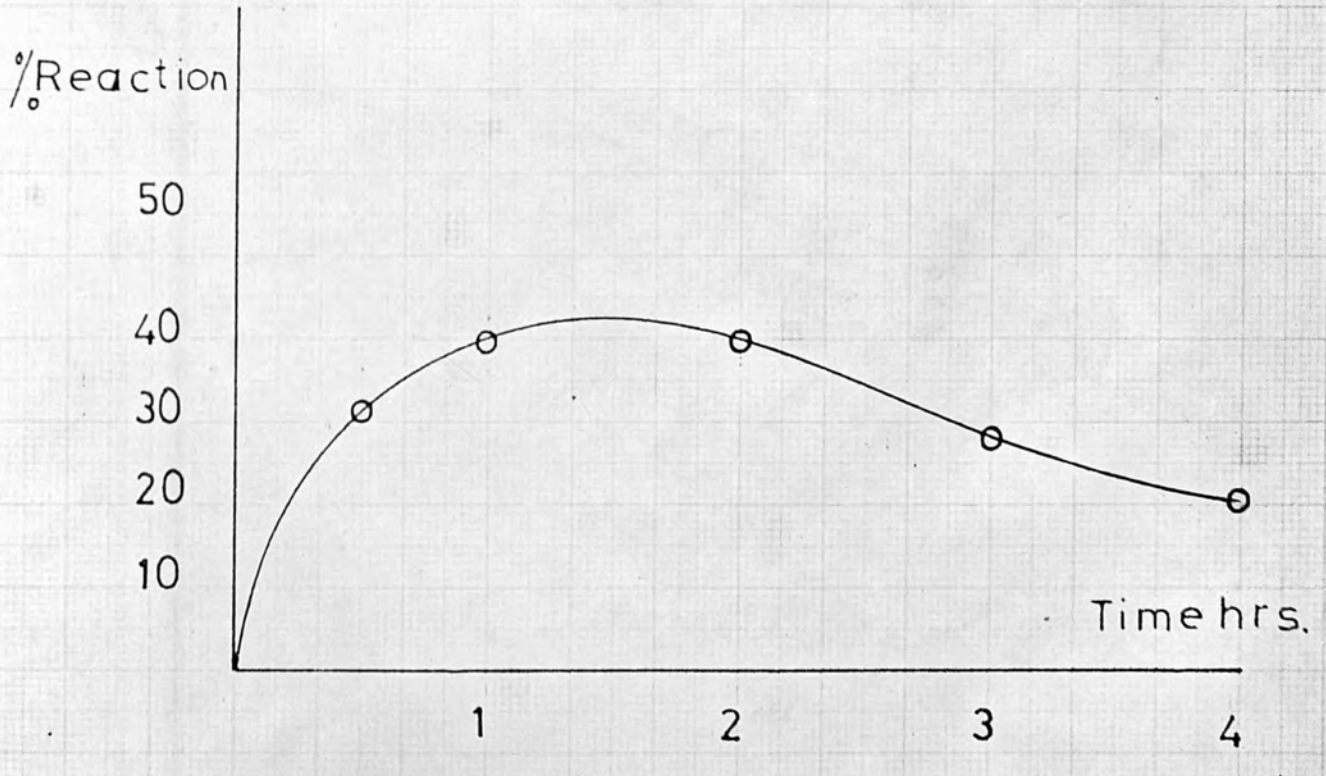
Hydrolysis of 3,4-O-Butylidene-D- Glucitol in 1·0 M Aqueous Hydrochloric Acid at 25°



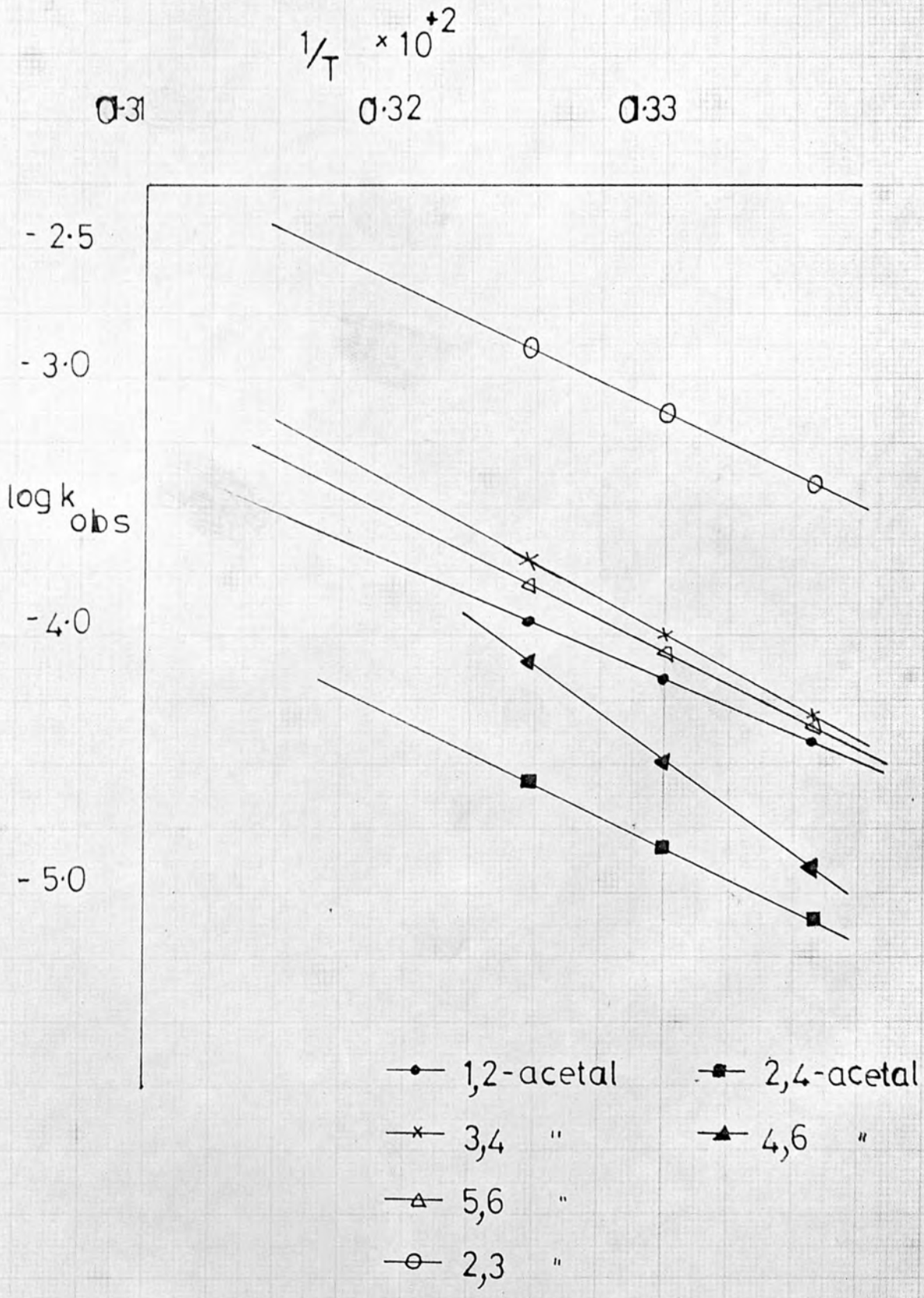


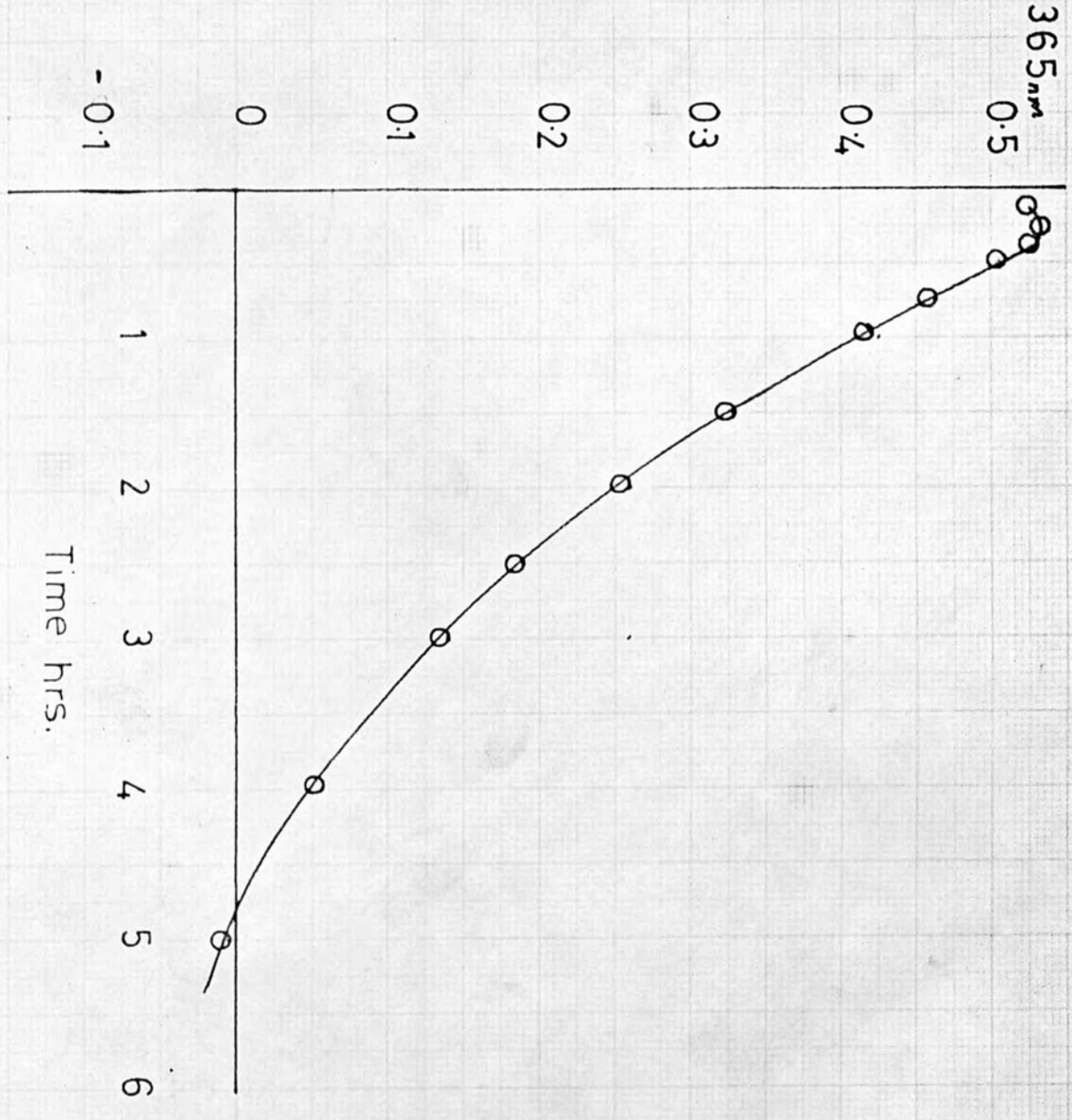
Hydrolysis of 2,3-O-Butylidene-D-Glucitol in 1·0 M Aqueous Hydrochloric Acid at 25°



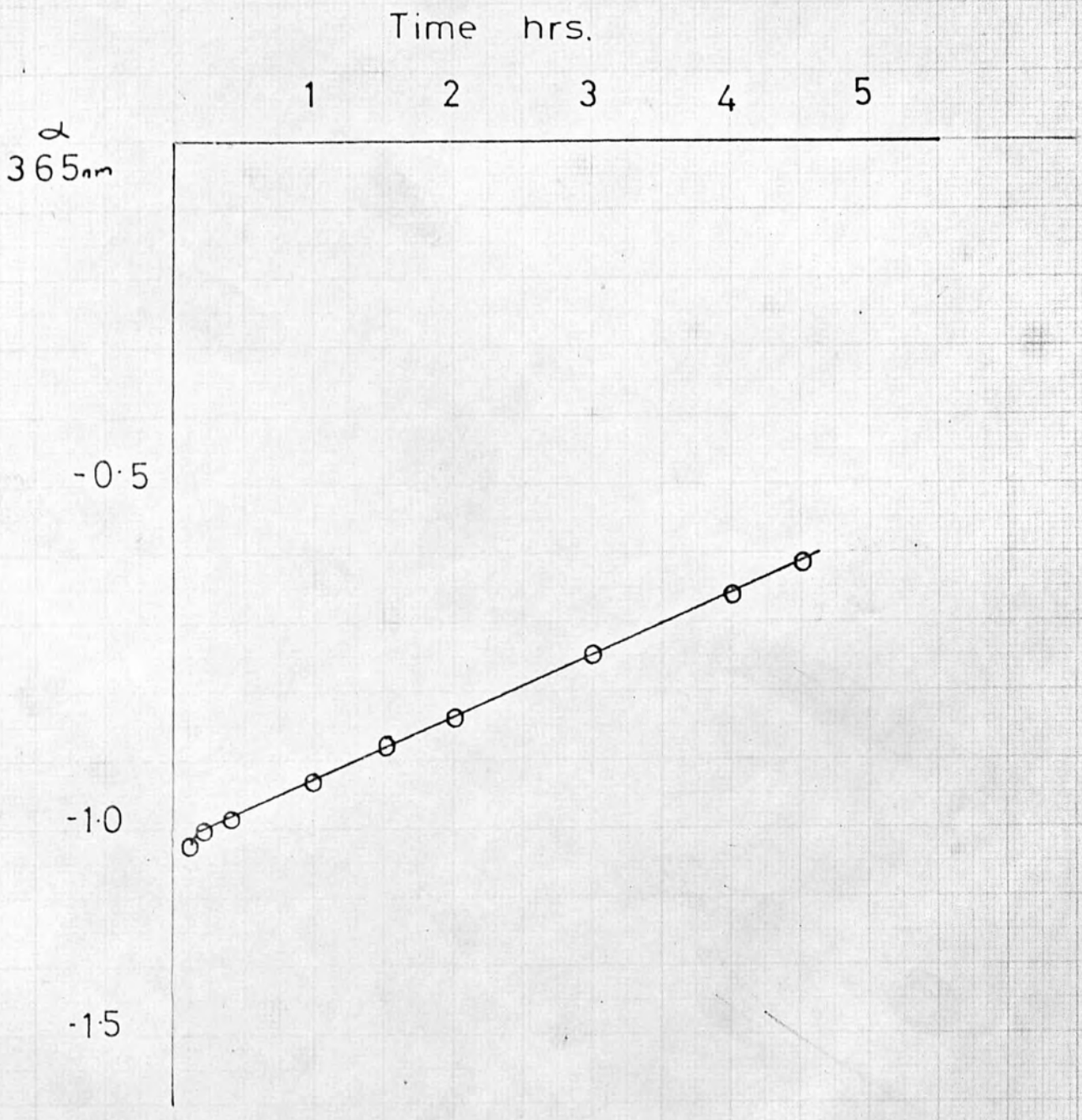


Plot of log k for the acid (1·0M HCl) hydrolysis of mono-n-butylidene-D-glucitols against 1/temp



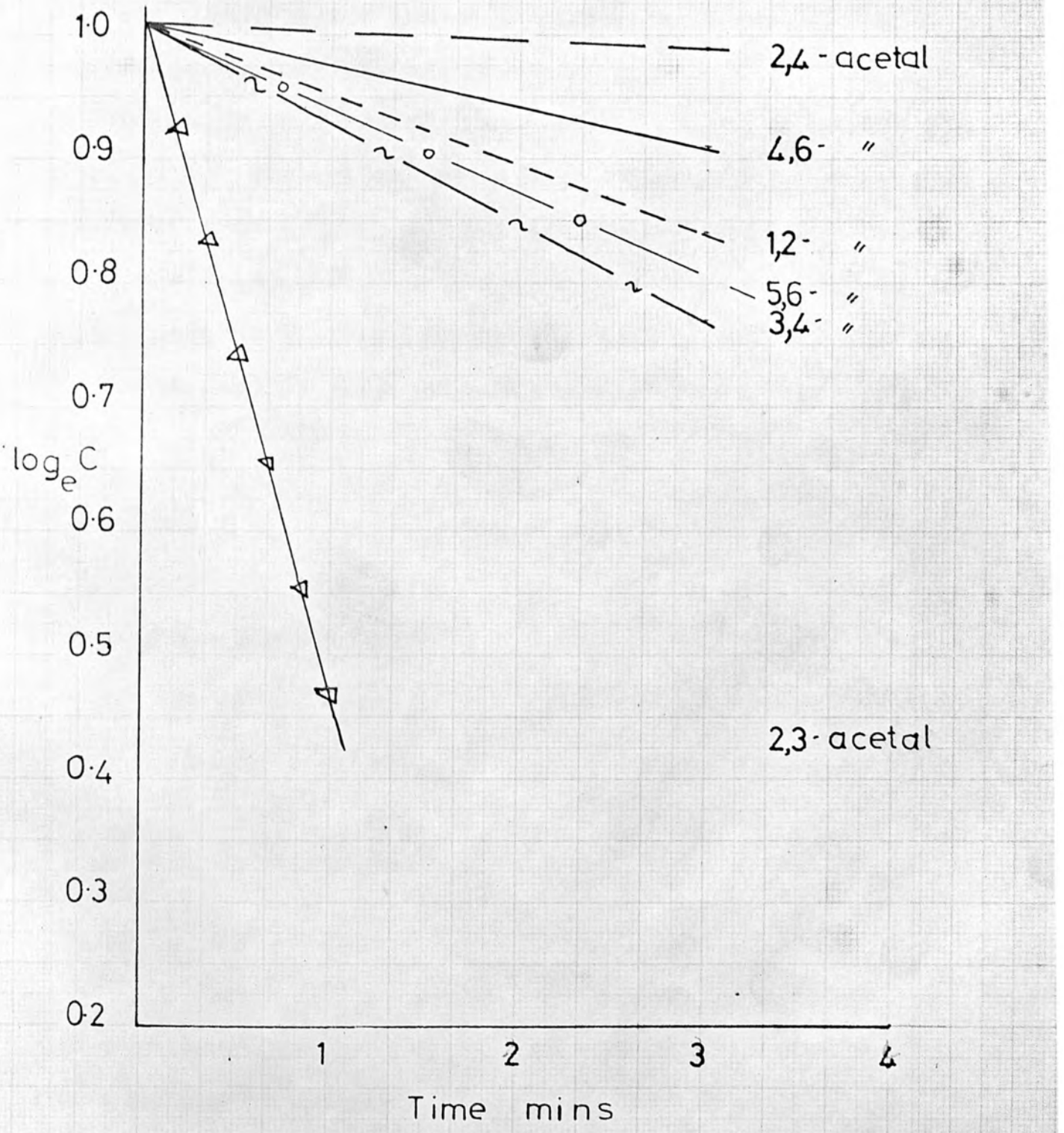


Reaction of 1,2-O-Butylidene-D-Glucitol with 1·0 M Hydrogen Choride gas in anhydrous D.M.F.



Reaction of 2,3-O-Butylidene-D-Glucitol with 1·0 M Hydrogen Chloride gas in anhydrous D.M.F.

Plot of $\log_e C$(acetal) for the acid(1·0 M HCl) hydrolysis of mono-n-butylidene-D-glucitols against time.



EXPERIMENT 6

Hydrolysis of the Mono-acetals of D-glucitol

The hydrolyses were studied at constant temperature ($\pm$ 0.5°) using a thermostatted U.V. cell at 281 nm.

The sample of the acetal, was checked for purity (V.PC 188° 5% Apeizon K) the sample was then weighed accurately ($\sim$ 30 mg) and made up to solution (3 ml) with hydrochloric acid (1.0 m) at the appropriate temperature. A sample was then transferred to the cell and the variation in optical density with time was studied. This was repeated at least six times for each acetal, at each temperature (25°, 30° and 35°)

$$\frac{d(c=O)}{dt} = k(ACETAL) = \frac{-d(ACETAL)}{dt} \qquad (1)$$

Theory of slow reaction rates

$$k = \frac{KT}{h} e^{-\frac{\Delta G^{\neq}}{RT}} = \frac{KT}{h} e^{-\frac{\Delta H^{\neq}}{RT} + \frac{\Delta S^{\neq}}{R}} \qquad (2)$$

$$H^{\neq} = \frac{RT_1T_2}{T_2-T_1} \quad \frac{k_1T_2}{k_2T_1} \qquad (3)$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \qquad (4)$$

$\Delta G^{\neq}$ = Activation Energy

$\Delta H^{\neq}$ = Enthalpy of activation

$\Delta S^{\neq}$ = Entropy of activation

K = Boltzmann constant

h = Planks Constant

R = Universal gas constant

RESULTS

From - (1) pseudo first order rate constants for hydrolysis

	$k^{25}_{sec^{-1}}$	$k^{30}_{sec^{-1}}$	$k^{35}_{sec^{-1}}$
2,4 acetal	7.78×10^{-6}	1.56×10^{-5}	3.06×10^{-5}
4,6 acetal	2.22×10^{-5}	4.38×10^{-5}	8.45×10^{-5}
1,2 acetal	3.85×10^{-5}	7.53×10^{-5}	1.44×10^{-4}
5,6 acetal	4.31×10^{-5}	8.41×10^{-5}	1.61×10^{-4}
3,4 acetal	5.10×10^{-5}	9.75×10^{-5}	1.86×10^{-4}
2,3 acetal	3.90×10^{-4}	7.34×10^{-4}	1.35×10^{-3}

Using the various forms of the equation for slow reaction rates (2) - (4) in programme (1) the data were processed to obtain the reaction parameters;

ACETAL	$\Delta G^{\neq}$(Kcals/mol)	$\Delta H^{\neq}$(Kcals/mol)	$\Delta S^{\neq}$(Kcal/mol/deg)
2,4 ring	24.42	27.42	-0.012
4,6 ring	23.80	27.02	-0.011
1,2 ring	23.47	26.58	-0.010
5,6 ring	23.40	26.50	-0.010
3,4 ring	23.32	26.42	-0.010
2,3 ring	22.10	25.56	-0.012

EXPERIMENT 7

Reaction of 1,2-O-Butylidene D-Glucitol in anhydrous DMF/Hydrogen chloride (1.0 M)

1,2-O-Butylidene D-glucitol (29.9 mg) was dissolved in anhydrous DMF/HCl and made up to 1 ml; and the change of optical rotation with time was observed at 365 nm. After the system had settled down it was observed that there was a steady decrease.

EXPERIMENT 8

Reaction of 2,3-O-Butylidene D-Glucitol in anhydrous DMF/Hydrogen Chloride (1.0 M)

2,3-O-Butylidene D-glucitol (0.1109 g) was dissolved in anhydrous DMF/HCl and made up to 5 ml; and the change in optical rotation with time observed at 365 nm. The system showed a steady increase.

EXPERIMENT 9

Proton Magnetic Resonance Studies on 1,2-O-Butylidene D-Glucitol

(a) The compound was dissolved in anhydrous dimethyl sulphoxide d^6.

The spectrum exhibited a triplet at τ 5.44 J = 5Hz

(b) The compound was dissolved in anhydrous dimethyl sulphoxide d^6 made acid with anhydrous hydrogen chloride.

The spectra was considered at various time intervals.

(i) 10 MINUTES:-

The spectrum was unaltered with the significant feature at 5.44.

(ii) 30 MINUTES:-

The spectrum still appeared unchanged.

(iii) 60 MINUTES

Additional features had appeared at 6.1 and 7.925.

(iv) 24 HOURS

The features at τ 6.1 and τ 7.925 had increased while that at τ 5.44 decreased, and there was no peak in the aldehydic proton region (τ 0-2).

EXPERIMENT 10

Using 4,6-O-butylidene D-glucitol (0.4985 g in 20 ml) and 2,4-O-butylidene D-glucitol (0.1251 g in 10 ml) experiments 8 and 9 were repeated.

4,6-O-Butylidene D-glucitol showed no change in rotation while 2,4-O-butylidene D-glucitol also showed no change and a rotation of - 8.837 instead of the usual small rotation in water at 365 nm.

PROGRAMME 1

```
      PROGRAM ENTROPY (INPUT, OUTPUT, TAPE 5 = INPUT, TAPE 6 = OUTPUT)
      DIMENSION T (3)
      REAL K (3)
      READ (5,100) NOC
100   FORMAT (I 1)
      T (1) =
      T (2) =
      T (3) =
      BOLTZC = 1.3803 E - 16
      H =
      R =
2     READ (5,1-1) K (1)
101   FORMAT (E 9.2)
      A = BOLTZC * T(1)/(K(1)*H)
      DECTAG = R * T(1) * A LOG(A)
      DO 20 I = 2,3
      A = DECTAG/(R*T(I))
      A = H * EXP (A)
20    K(I) = BOLTZC * T (I)/A
      WRITE (6,200) (I, T(I), I, K(I), I = 1,3)
200   FORMAT (1 HO, //, 3(/, 4X, 2HT(, I1, 2H) =, F7.2, 3X, 2HK(,I1,2H)=,
                                                              11.4))
      WRITE (6,201) DELTAG
201   FORMAT (1H , 4X, 10H DELTA   G =  , E 13.6)
      A = K(2) * T (1) / (K(1) * T(2))
```

```
      B = R * T (1) * T (2) / (T(2) - T(1))
      DHT1T2 = B * ALOG(A)
      DST1T2 = (DHT1T2 - DELTAG)/T(1)
      WRITE (6,202) DHT1T2, DST1T2
202   FORMAT (1 H  , 9X, 10H DELTA H =  , E13.6,
     3X, 10H DELTA S =  , E13.6, 10X, 18 H FROM
     T (1)  AND  T(2))
      A = K(3) * T(2) / K(2) * T(3)
      B = R * T (2) * T (3)/(T(3) - T(2))
      DHT2T3 = B * A LOG (A)
      DST2T3 = (DHT2T3 - DELTAG)/T(1)
      WRITE (6,203) DHT2T3, DST2T3
203 FORMAT (1 H  , 4X, 10HDELTA H =  , E13.6,
     3X, 10 DELTA S =  , E13.6, 10X, 18H FROM
     T(2)  AND  T(3))
      A = K(3) * T(1)/(K(1) * T(3))
      B = R * T(1) * T(3) /T(3) - T(1))
      DHT1T3 = B * A LOG (A)
      DST1T3 = (DHT1T3 - DELTA G) /T(1)
      WRITE (6, 204) DHT1T3, DST1T3
204   FORMAT (1 H  , 4X, 10H DELTA  H  =  , E 13,6,
     3X, 10 H DELTA  S  =  , E 13.6, 10X, 18H FROM  T(1)  AND  T(3))
      NOC = NOC -1
      IF (NOC.GTO) GO TO 2
      STOP
      END
      DATA
```

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CHAPTER 2

The reaction between Equi-molar quantities of n-Butyraldehyde and D-Glucitol

DISCUSSION AND RESULTS

The reaction between equi-molar quantities of D-glucitol and n-butyraldehyde exhibits rotational minimum which characterises the kinetic and thermodynamic control of the reaction. This reaction has been studied at various substrate concentrations, 0.05 M; 0.1 M; 0.15 M; 0.2 M and 0.25 M. There is no variation in the overall shape of the rotation versus time plot but there are some specific differences.

When the experimental and theoretical plots of rotation versus time are considered, with the theoretical plot for 0.1 M the position of the minima on the rotation scale is -0.184 while experimentally it is -0.254, there are similar variations for all the other substrate concentrations.

INITIAL D-GLUCITOL CONCENTRATION (M)	MINIMA EXPERIMENT 1	CALCULATED	OBSERVED TIME MIN
0.05	-0.191	-0.092	45
0.1	-0.254	-0.184	38
0.15	-0.69	-0.276	36
0.2	-1.06	-0.368	34
0.25	-1.53	-0.46	25

By reference to the figures above it is easy to see that the theoretical position of the minima on the rotation axis varies significantly from that found experimentally. The decay of the 2,3-acetal must be less rapid than shown by the theoretical approach which has utilised values obtained experimentally. By using other data,

i.e. different values for the rate constants, the curve may be adjusted for one substrate concentration, but these data will still not fit another. No data will work universally. Other factors must be involved. If the rearrangement is completely intramolecular there cannot be a universal fit of theoretical and experimental curves. A factor must be involved that retards the decay of the 2,3-acetal during the overall mechanism. The intramolecular process allows the change from the 2,3-acetal to the 2,4-acetal, while an intermolecular reaction would cause hydrolysis to D-glucitol, with subsequent reformation of the 2,3-acetal, thus decreasing the overall decay of the 2,3-acetal. The importance of hydrolysis might be expected to increase as the concentration of products increases since it is a unimolecular process as compared with formation which is bimolecular. This is infact seen to be the case. If the reaction sequence is considered to be;

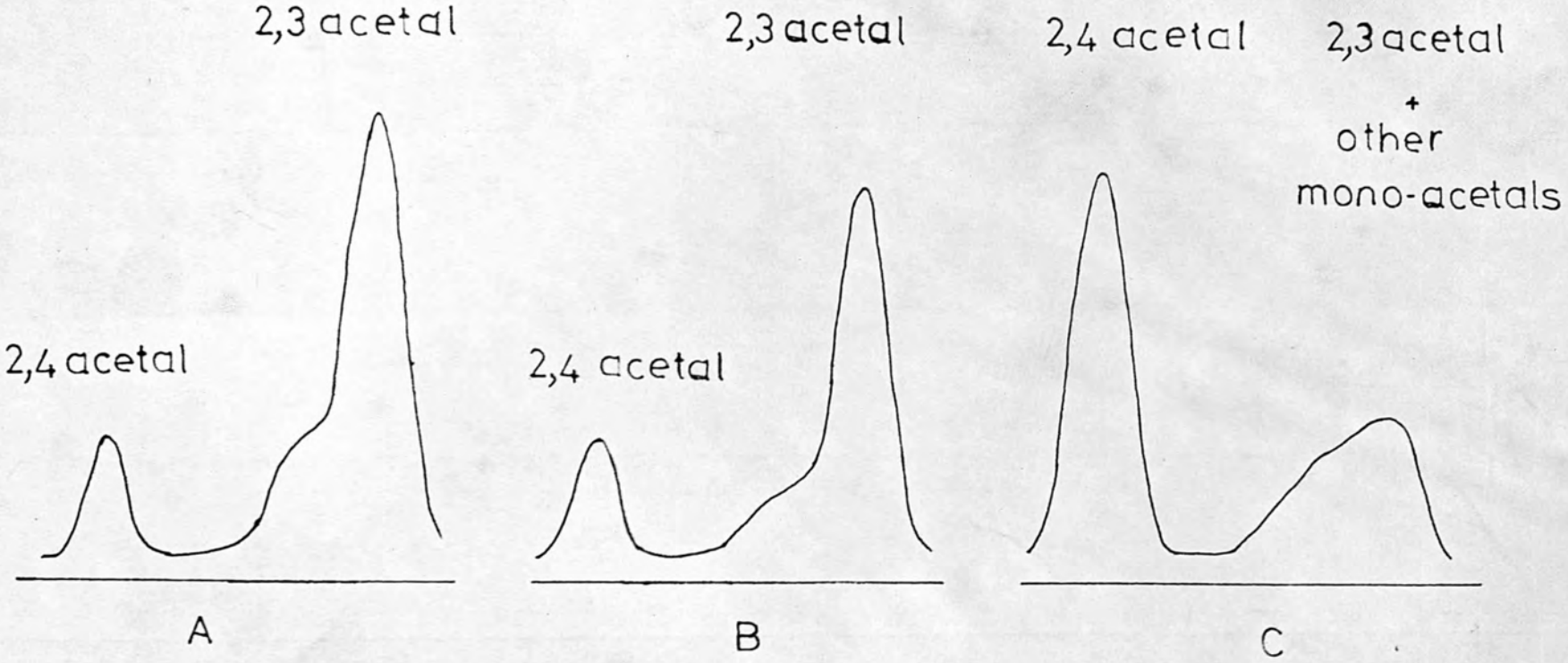
$$\text{2,4 ACETAL} \quad \underset{k_1}{\overset{\beta_1}{\rightleftharpoons}} \quad \text{2,3 ACETAL} \quad \underset{k_2}{\overset{\beta_2}{\rightleftharpoons}} \quad \text{SUBSTRATES}$$

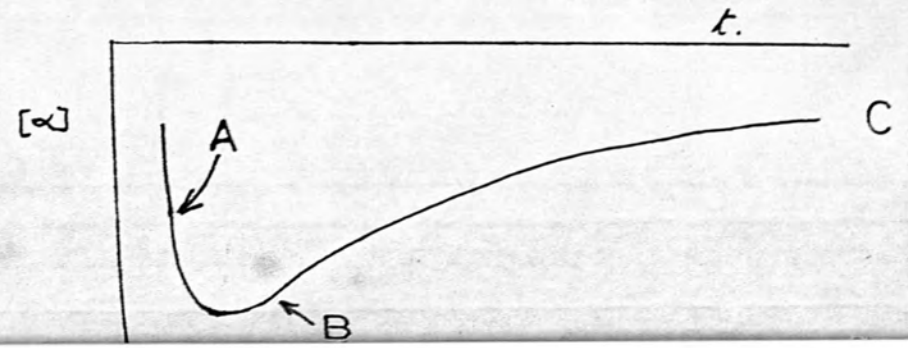
β_2 = rate constant for formation of 2,3-acetal

β_1 = rate constant for rearrangement of 2,3-acetal to 2,4-acetal

The increase in the intermolecular process would affect the balance between β_1 and β_2 and k_1 and k_2. This may shift the position of the rotation minimum along the time axis. The shift may not be explained this simply since a decrease in the rate of decay 2,3-acetal should cause the minimum to shift to longer time. This would give the inverse of experimental results i.e. D-glucitol (0.05 M) gives a minimum at longer time than 0.25 M. Build up of the 2,3-acetal is a bimolecular

process and therefore halving the concentrations should cause a build up at ½ the rate. This would move the minimum to considerably longer time as we move from 0.20 M 0.05 M. The observed shifts must be due to the fact that the overall mechanism is a careful balance between an intramolecular and an intermolecular reaction so that the intermolecular reaction which slows the decay of the 2,3-acetal is more important at the higher concentrations of polyol and aldehyde. Therefore the positions of the minimum is affected to a greater extent, with the result that they are pushed closer together than expected.





V.P.C analysis for the reaction between D-Glucitol (0·2 M) and n-butyraldehyde in Aqueous Hydrochloric Acid

EXPERIMENT 1

The Formation of Mono-Butylidene Acetals of D-Glucitol

The experiment was carried out using substrate concentrations 0.25 M; 0.2 M; 0.15 M; 0.1 M; 0.05 M for D-glucitol and n-butyraldehyde in 1.0 M hydrochloric acid.

The reaction between D-glucitol and n-butyraldehyde may be studied conveniently by two methods; the disappearance of the carbonyl absorption spectrophotometrically at 281 nm or by polarimetry.

(i) Polarimetric Studies

The reactions solutions were prepared at 25° and rapidly mixed and alequots added to the polarimeter tube thermostatted at 25°, and the variation in optical rotation, at -598 nm, with time was studied for each substrate concentration. Each substrate concentration showed the characteristic curve with a minimum.

(ii) Spectrophotometric Studies

The system was set up as for the polarimetric studies and an aliquot was placed in the thermostatted cell and studied by variation in optical density.

RESULTS

The polarimetric studies showed minima for all substrate concentrations.

INITIAL D-GLUCITOL CONC. (M)	MINS TO OBTAIN MINIMA
0.25	25
0.2	34
0.15	35
0.1	38
0.05	44

Spectrophotometric studies enabled an evaluation of the initial rate of uptake of aldehyde together with percentage reaction at significant times.

$$\frac{-d(c=0)}{dt} = \text{RATE OF FORMATION OF PRODUCTS} = k(c=0)(\underline{D}\text{-GLUCITOL})$$

D-glucitol conc. (M)	$\frac{d(c=o)}{dt}$	Pseudo 2nd order rate constant for initial product reaction $lm^{-1}sec^{-1}$
0.25	1.96×10^{-4}	3.14×10^{-3}
0.2	1.25×10^{-4}	3.13×10^{-3}
0.15	7.07×10^{-5}	3.13×10^{-3}
0.1	3.12×10^{-5}	3.12×10^{-3}
0.05	7.6×10^{-6}	3.04×10^{-3}

INITIAL D-GLUCITOL CONC	% REACTION AT POLAROGRAPHIC MINIMA	% REACTION AT EQUILIBRIUM
0.25 M	70%	90%
0.2 M	67%	90%
0.15 M	64%	90%
0.1 M	60%	90%
0.05 M	40%	90%

(iii) Vapour phase chromatographic analysis of the reactions.

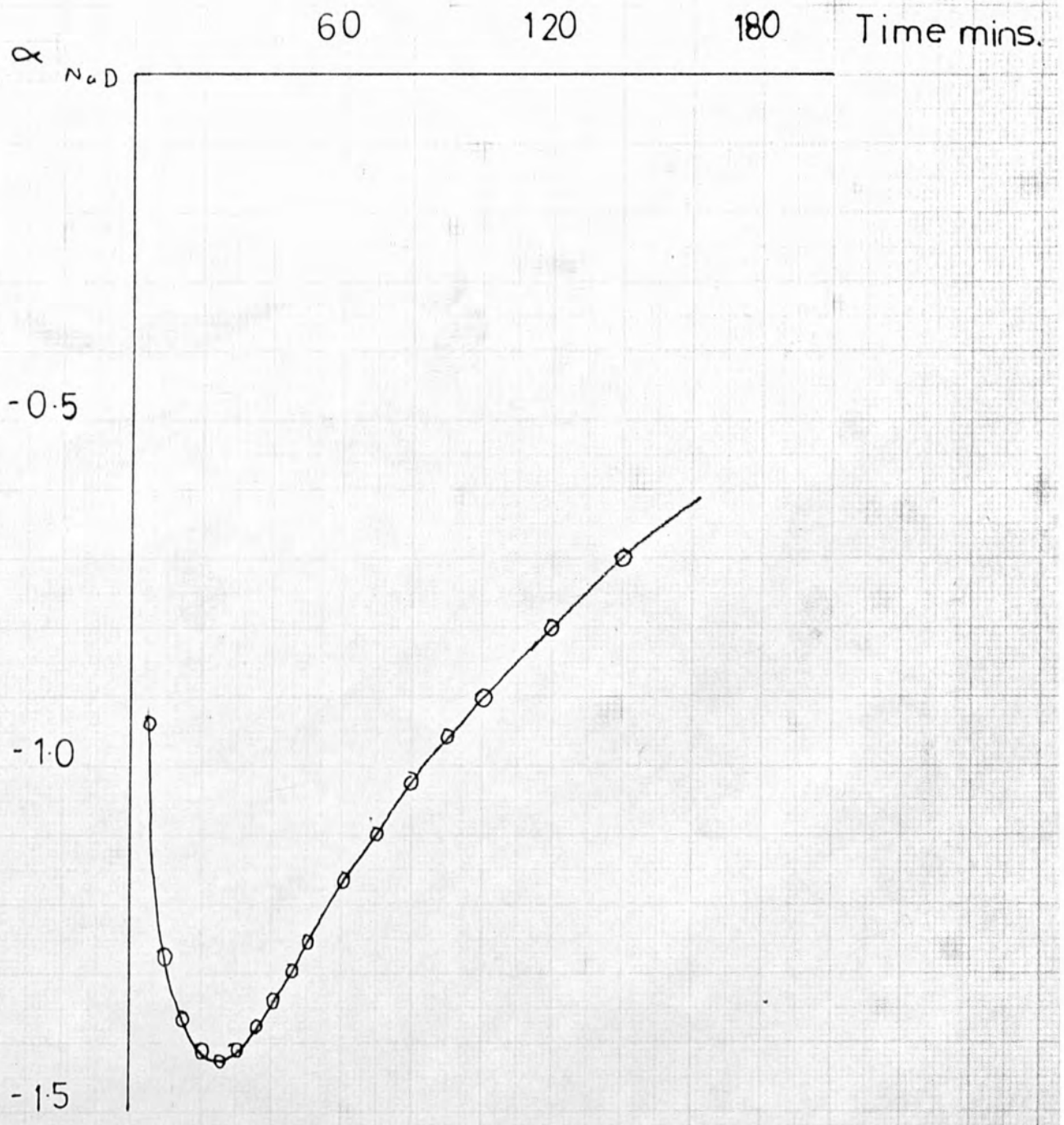
Samples were taken at $\frac{1}{4}$, $\frac{1}{3}$, $\frac{1}{2}$ of the MINIMUM TIME and also the minimum and equilibrium. The qualitative results for all the substrate concentrations were very similar.

This showed (see Pg 135 for an example) that at $\frac{1}{4}$ reaction time → MINIMUM there was a build up of the 2,3-acetal as the product, but the 2,4-acetal was also present. After the minimum the 2,3-acetal disappeared and there was build up of the 2,4-and other acetal products.

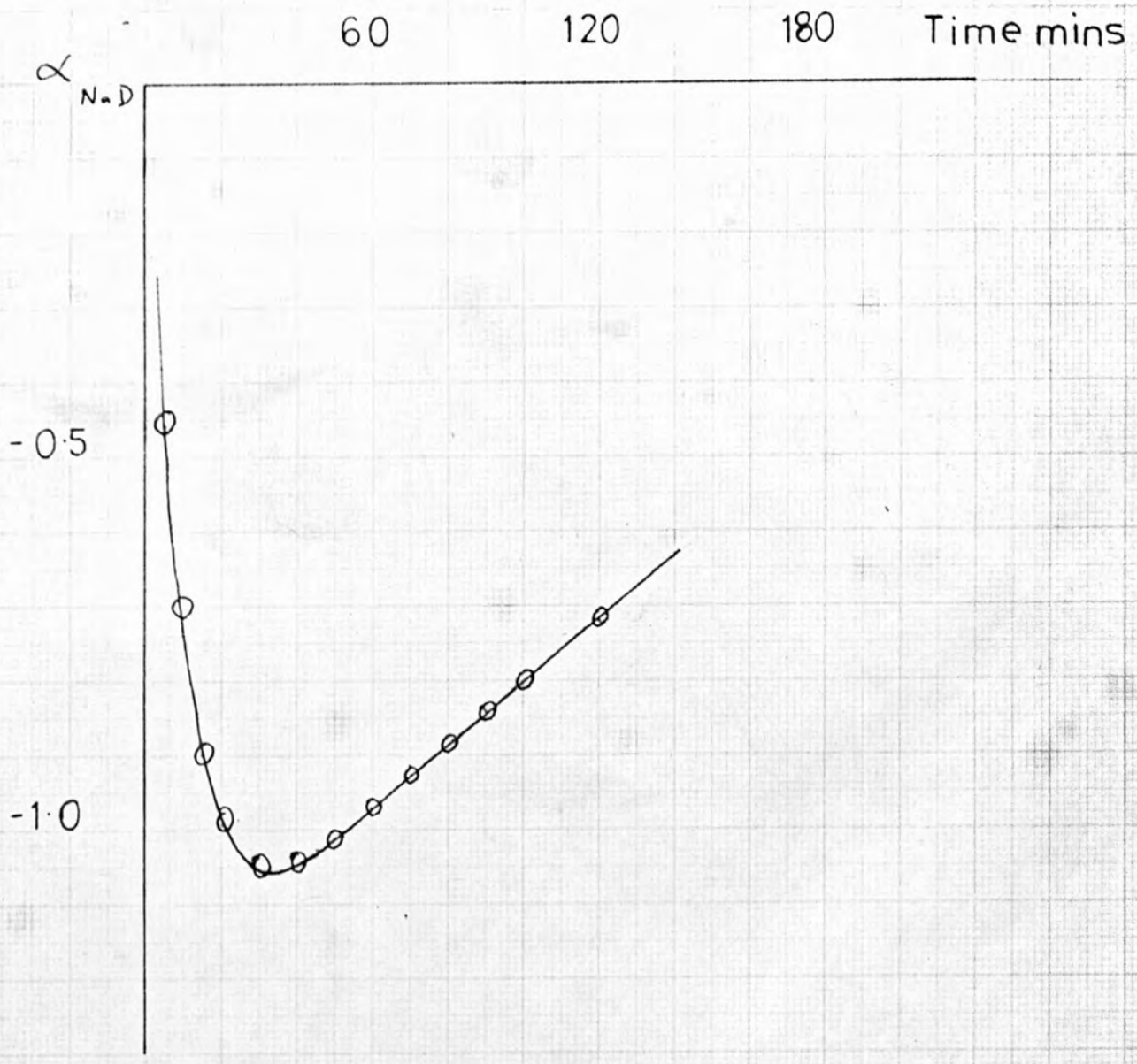
In addition, analysis was carried out at 5, 10, 15, 20 mins of which 5 and 10 mins showed details of significance to add to the other data.

This initial period showed that the 2,3-mono-acetal was the only significant product and therefore a pseudo second order rate constant could be calculated for acetal formation.

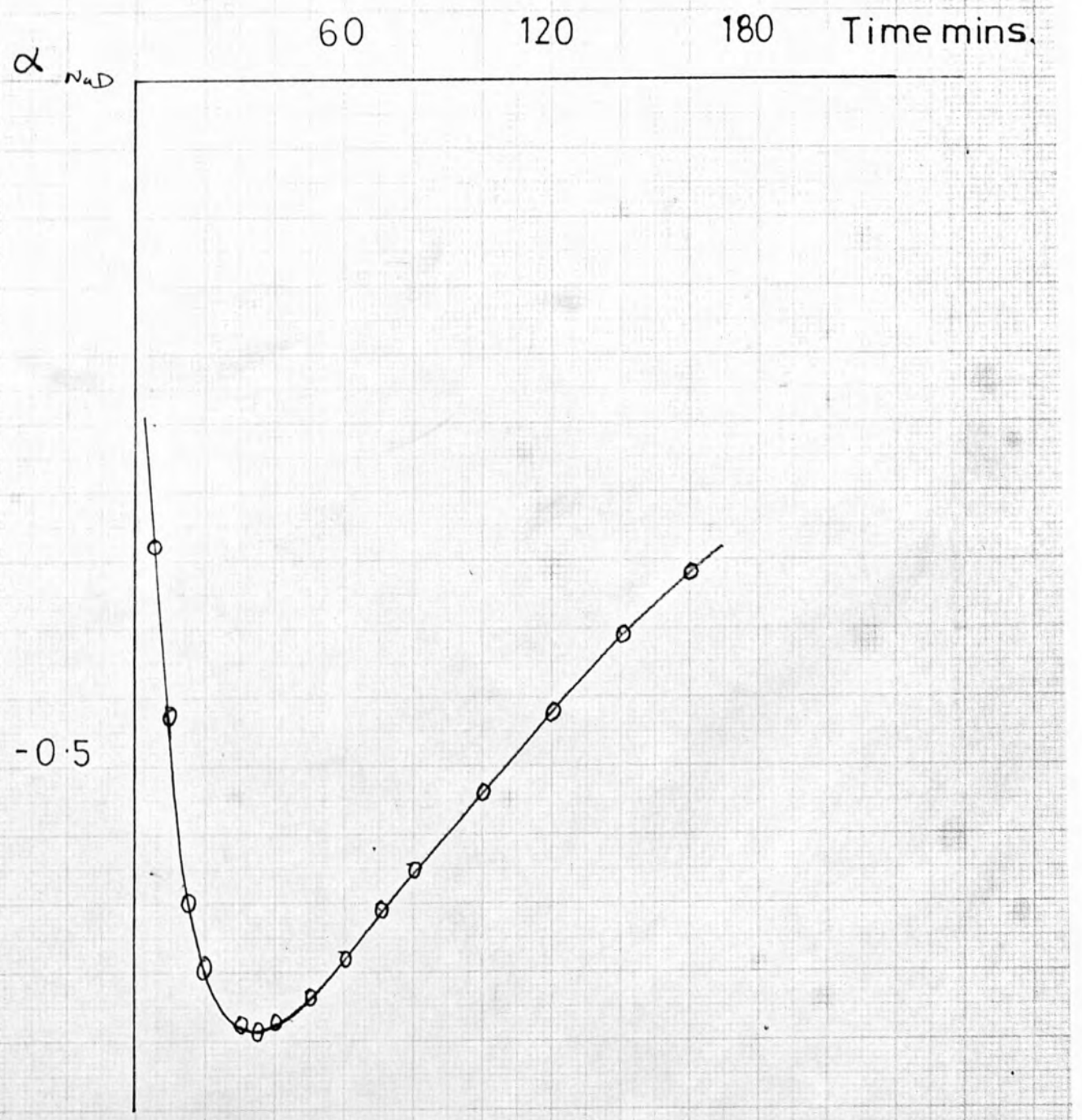
Reaction of n-Butyraldehyde(0·25M) with D-Glucitol(0·25M) in Aqueous Hydrochloric Acid(1·0M) at 25°



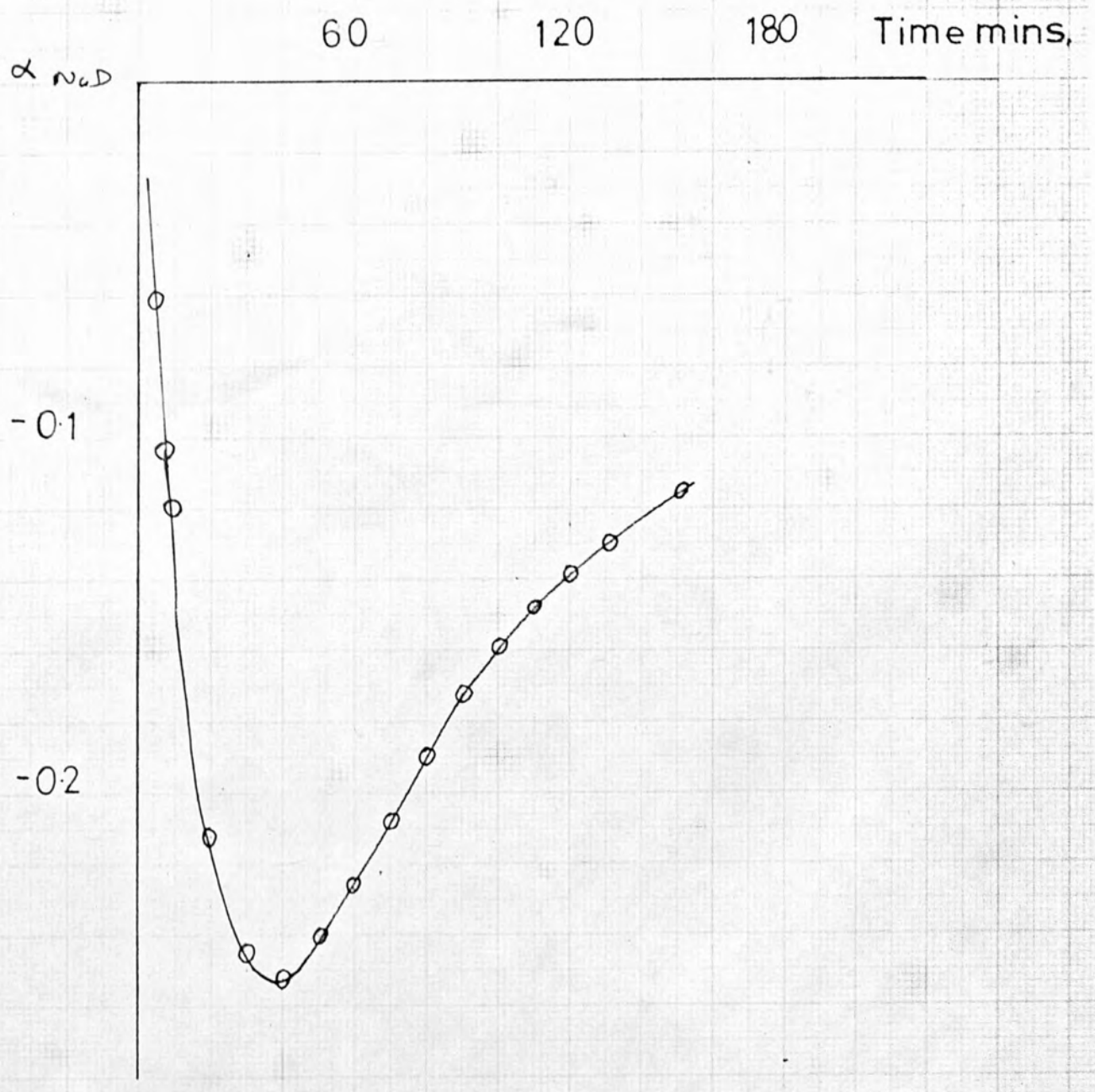
Reaction of n-Butyraldehyde(0·2M) with D- Glucitol (0·2 M) in Aqueous Hydrochloric Acid(1·0 M) at 25°



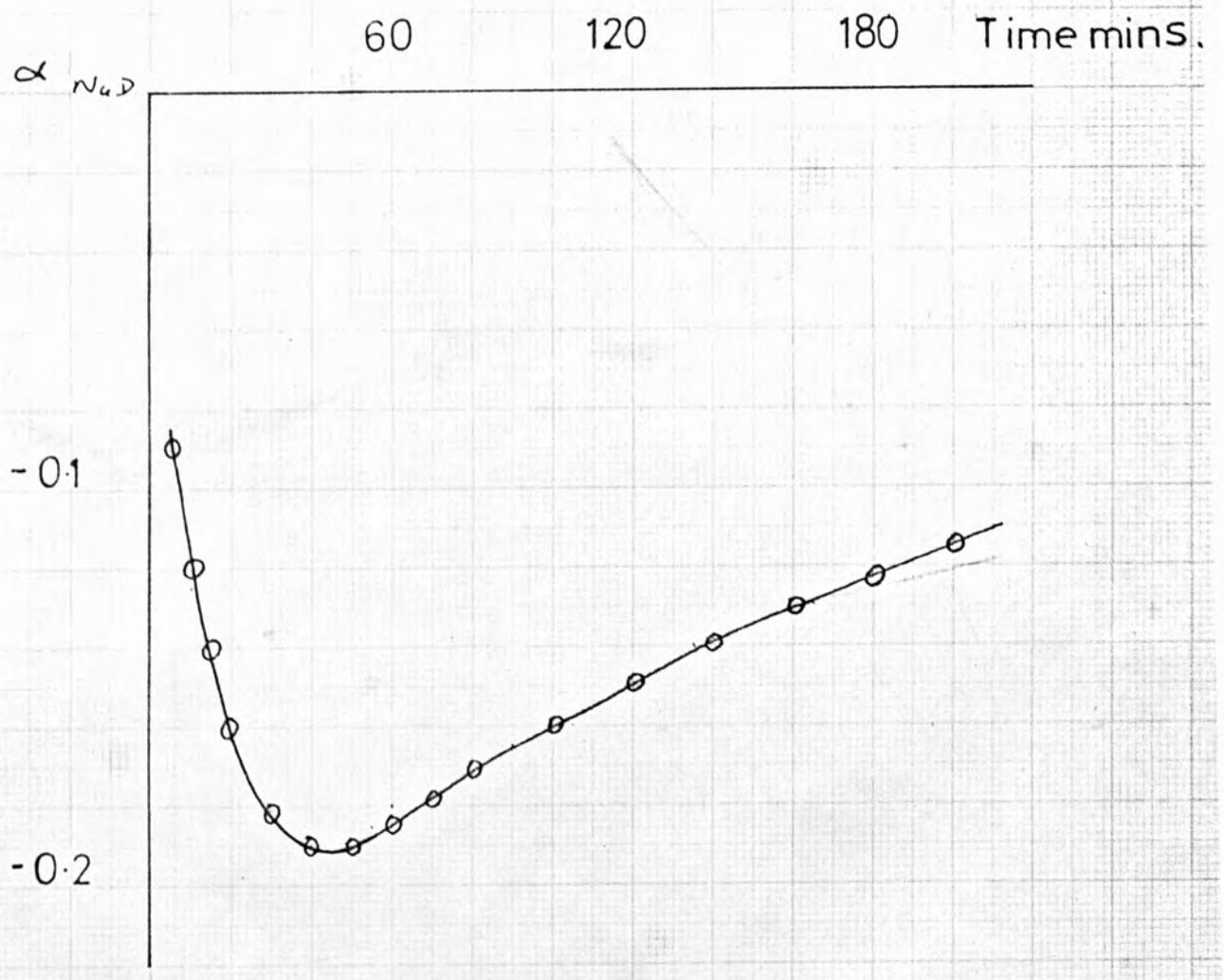
Reaction of n-Butraldehyde(0·15M) with D-Glucitol(0·15M) in Aqueous Hydrochloric Acid(1·0M) at 25°



Reaction of n-Butyraldehyde (0·1M) with D-Glucitol (0·1M) in Aqueous Hydrochloric Acid (1·0M) at 25°



Reaction of n-Butraldehyde(0·05M) with D-Glucitol(0·05 M) in Aqueous Hydrochloric Acid(1·0M) at 25°C



CHAPTER 3

A Mathematical treatment of the Mechanism of Acetal Formation

INTRODUCTION

Reactions involving consecutive - irreversible reactions of any number of steps may be considered mathematically, as can reversible - consecutive, reversible, parallel - consecutive and chain reactions, with the proviso that all steps may be treated kinetically as first order[1]. The above would seem to cover all simple reaction schemes.

DISCUSSION AND RESULTS

The reaction between D-glucitol and n-butyraldehyde in equimolar proportions will not obey first order kinetics under the normal reaction conditions. If a 10:1 molar excess of D-glucitol is used the reaction shows the same rotational minimum and vapour phase chromatography again shows 2,3-acetals followed by the formation of the thermodynamically controlled 2,4-acetal product. The system may now be treated by first order kinetics.

The kinetic and thermodynamic control may be considered as either an intramolecular process or an intermolecular process.

The intermolecular process may be represented by:

$$A_0 \underset{\beta_1}{\overset{k_1}{\rightleftharpoons}} A_1 \underset{\beta_2}{\overset{k_2}{\rightleftharpoons}} A_2 \qquad \text{Scheme 1}$$

C_0 $\quad$ C_1 $\quad$ C_2

C_1^o

k_1 = Rate constant for hydrolysis of A_o

k_2 = Rate constant for formation of A_2

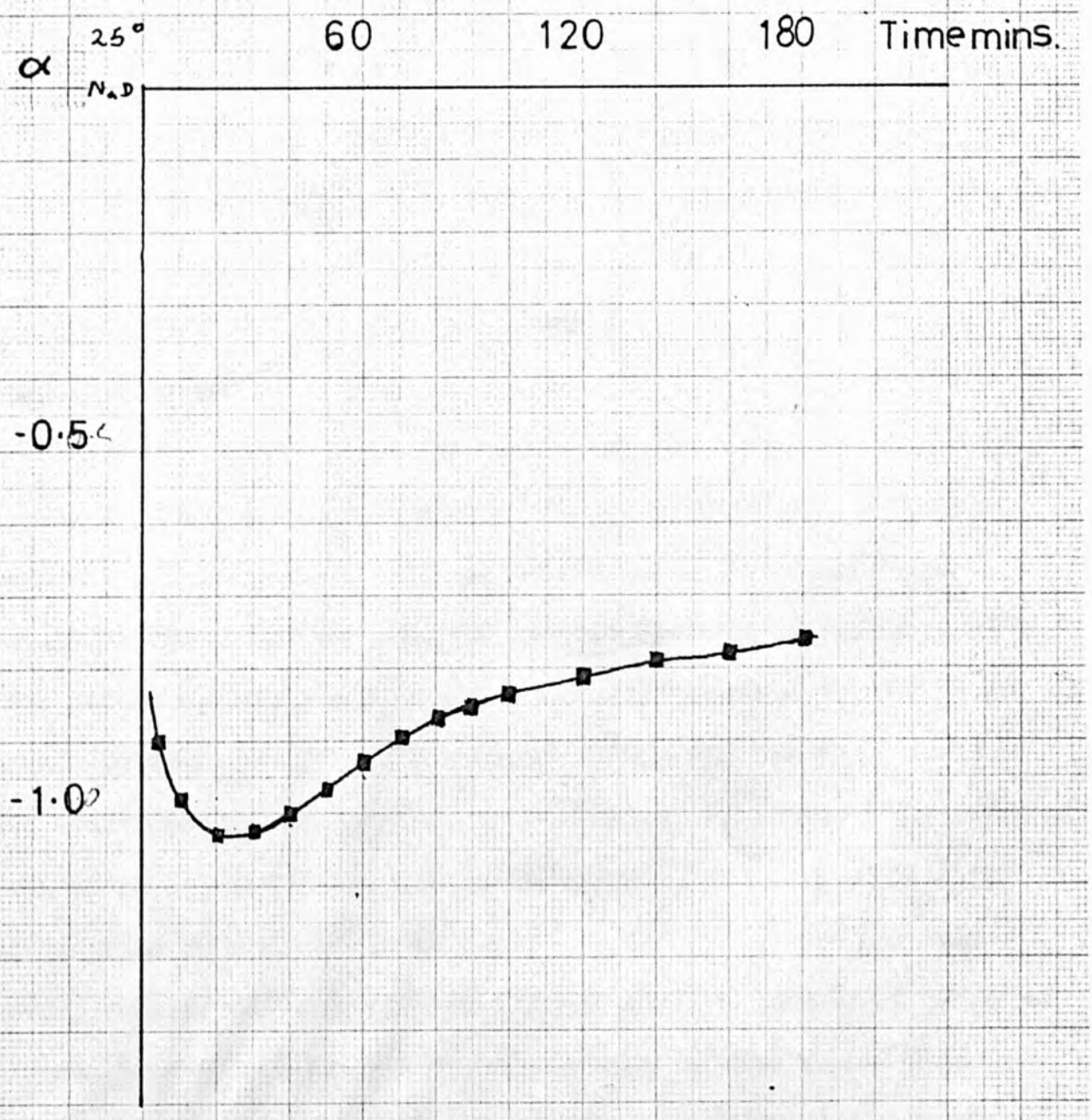
$\beta 1$ = Rate constant for formation of A_o

$\beta 2$ = Rate constant for hydrolysis of A_2

where c_x = concentration of x in moles/l

where C_1, C_2 and C_o are the concentrations of A_1, A_2 and A_o respectively, in moles/litre.

Reaction of n-Butyraldehyde (0·1 M) with D-Glucitol (1·0 M) in Aqueous Hydrochloric Acid (1·0 M) at 25°



Values for k_1; k_2; β_1 and β_2 may be obtained experimentally or estimated from equilibrium concentrations (see chapters 1, and 2). This approach may be represented mathematically (Scheme 1), and the validity may be tested by putting $t = 0$ when the value C_1° for the initial concentration of A_1 is obtained.

If we consider A_1 to be D-glucitol, A_2 to be the 2,3-acetal and A_o to be the 2,4-acetal, the data used provided values for k_1; k_2; β_1 and β_2 in varying ratios to attempt to simulate the rotation versus time curve obtained experimentally. With each set of data a curve characterised by FIG 1 was obtained. By varying the data the magnitude and position of the curve were changed but the shape remained unchanged. The rotation (α) versus t plot showed a very rapid decrease followed by a very slow and slight increase in rotation. This mathematical approach is not adequate to explain the reaction. When the vapour phase chromatograms for the reaction are considered, the build up of the 2,4-acetal becomes rapid as the 2,3-acetal decays . By the intermolecular treatment this does not occur (FIG 2) and therefore an alternative treatment must be sought. If we consider kinetic and thermodynamic control involving steric and electronic effects, we may picture this mathematically as a variation of k_1, k_2, β_1 and β_2 as the reaction proceeds. Therefore using programme C for scheme 1 instead of programme A the data were processed with β_1 and k_2 varying with time. This gave the characteristic curve for acetal formation, (FIG 5), while there was a rapid build up of 2,4-acetal as the 2,3-acetal decayed (FIG 6).

An alternate mechanism would involve an intramolecular reaction

scheme.

$$A_0 \underset{\beta_1}{\overset{k_1}{\rightleftharpoons}} A_1 \underset{\beta_2}{\overset{k_2}{\rightleftharpoons}} A_2 \qquad \text{Scheme 2}$$

$$C_o \qquad C_1 \qquad C_2 \quad C_2^o$$

A_o being the 2,4-acetal, A_1 the 2,3-acetal and A_2 D-glucitol with C_o, C_1 and C_2 their respective concentrations at any time while C_2^o is the original concentration of D-glucitol. Again this scheme may be represented mathematically and written into programme B. With this scheme we see that the rotation versus time plot shows the characteristic minimum that we have come to expect for acetal formation FIG 3. If we use programme D for this scheme with varying k_1, k_2, β_1 and β_2 the curve is "tightened" but the shape unchanged FIG 7, while in both cases, FIG 4 and FIG 8 respectively, there is a rapid decay of the 2,3-acetal while at the same time the 2,4-acetal builds up.

The simple intermolecular mechanism does not explain the reaction sequence for D-glucitol and n-butyraldehyde but the modified sequence will do this to a certain extent. If we are to consider the modified sequence there must be steric and electronic effects which come into importance, in the free D-glucitol, only after some period during the reaction. The intramolecular mechanism on the other hand gives a rotation versus time curve very similar to that found experimentally. The deviation may be explained in that hydrolysis occurs to some extent so that we are dealing with a substantially intramolecular

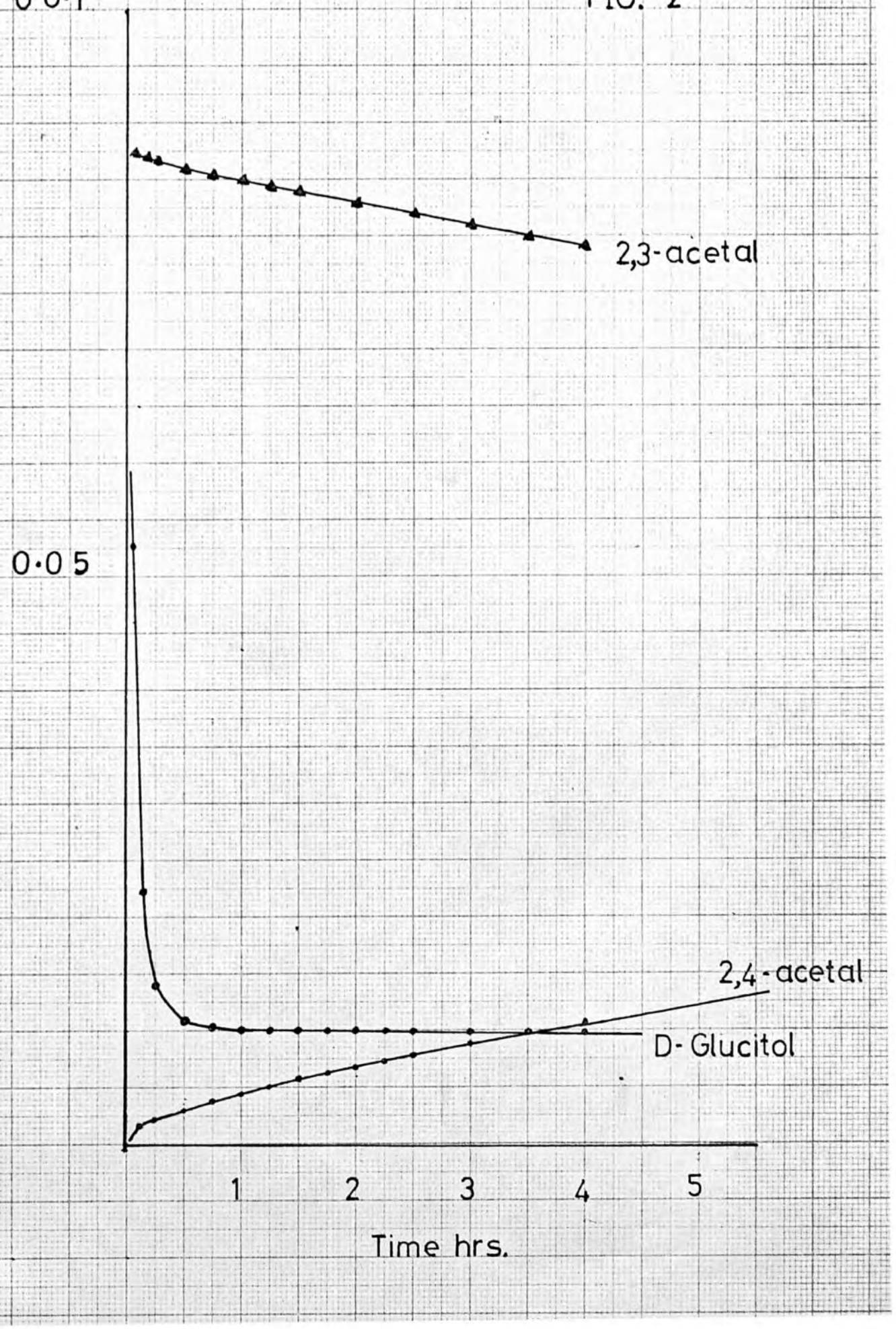
reaction in conjunction with an intermolecular reaction so that the overall mechanism involves both processes. This is to some extent verified by the rearrangement of the 1,2-acetal in non-aqueous media, no aldehyde is liberated, but the five membered ring (as shown by proton magnetic resonance) decays and there is a build up of a six membered ring.

An Intermolecular Mechanism for Acetal Formation

FIG. 1

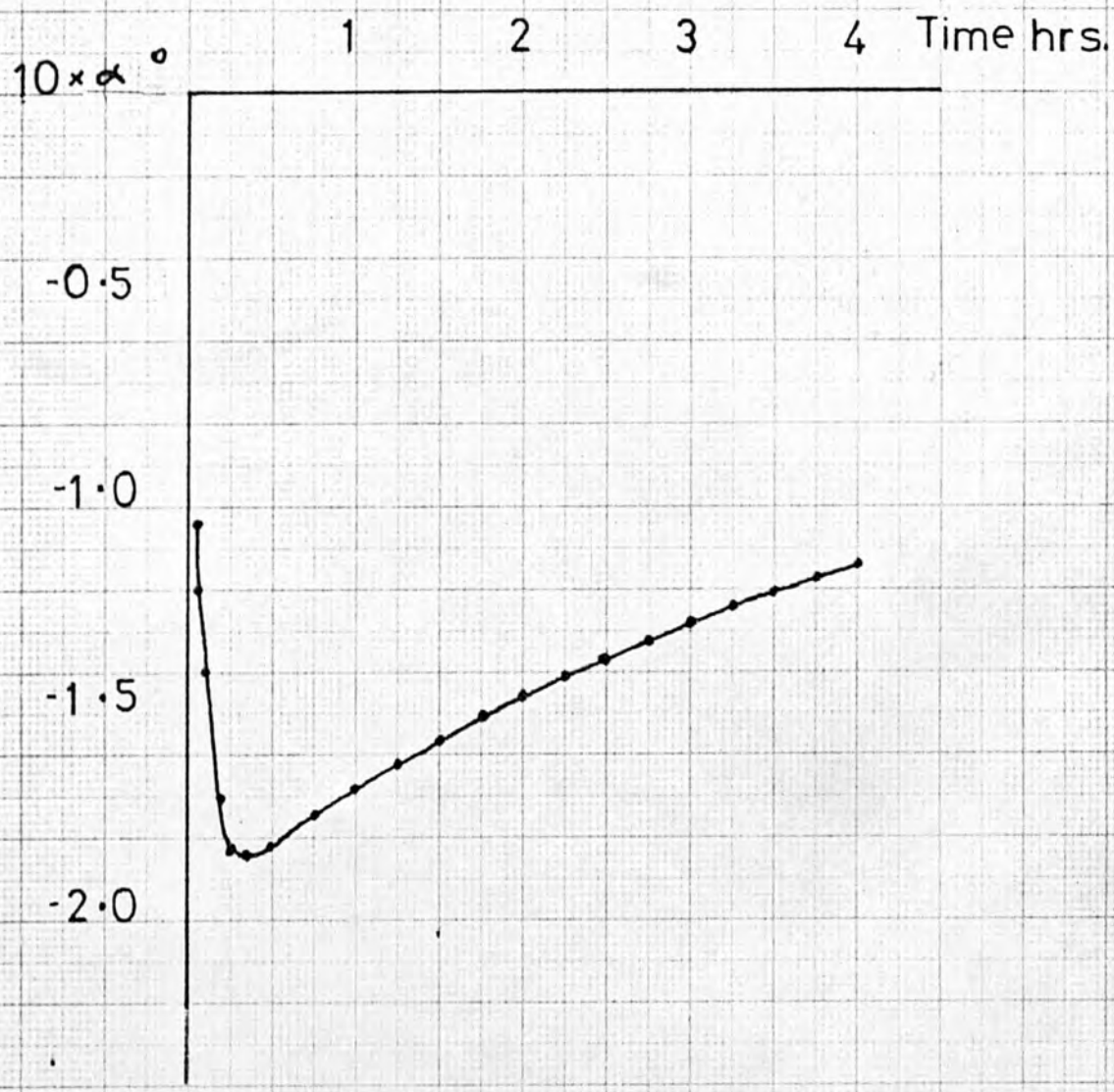
Programme A

FIG. 2



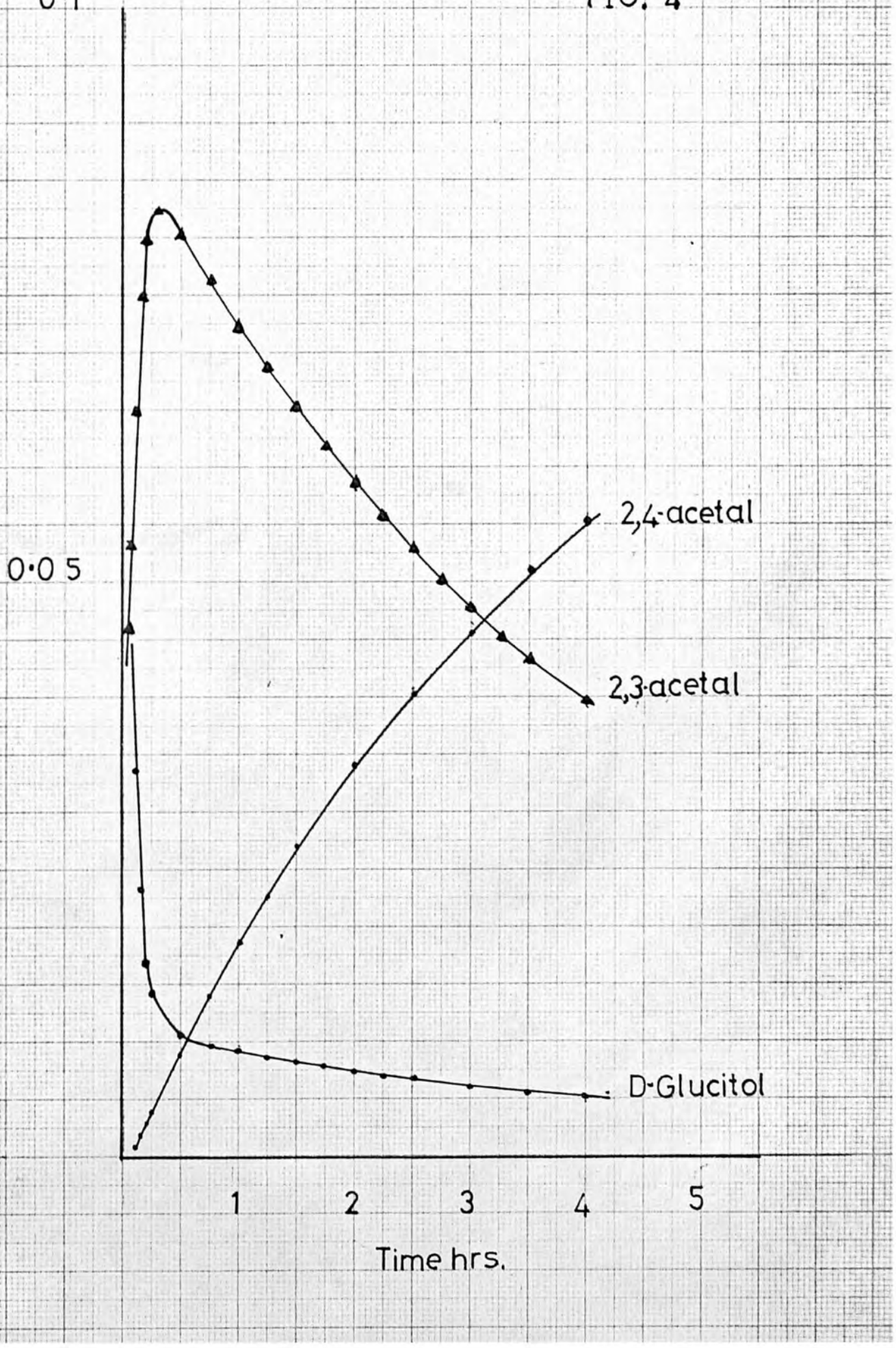
An Intramolecular Mechanism for Acetal Formation

FIG. 3



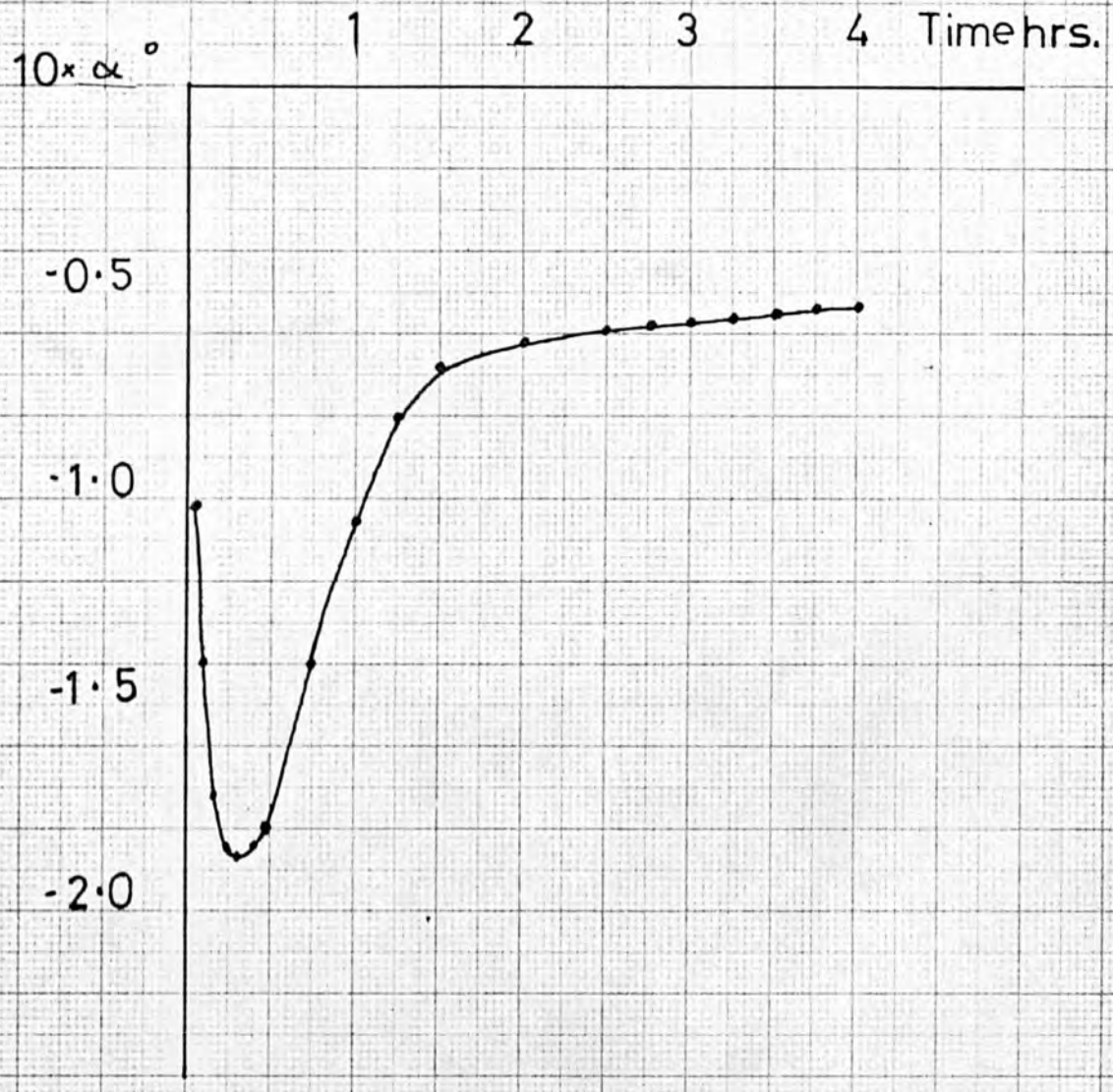
Programme B

FIG. 4

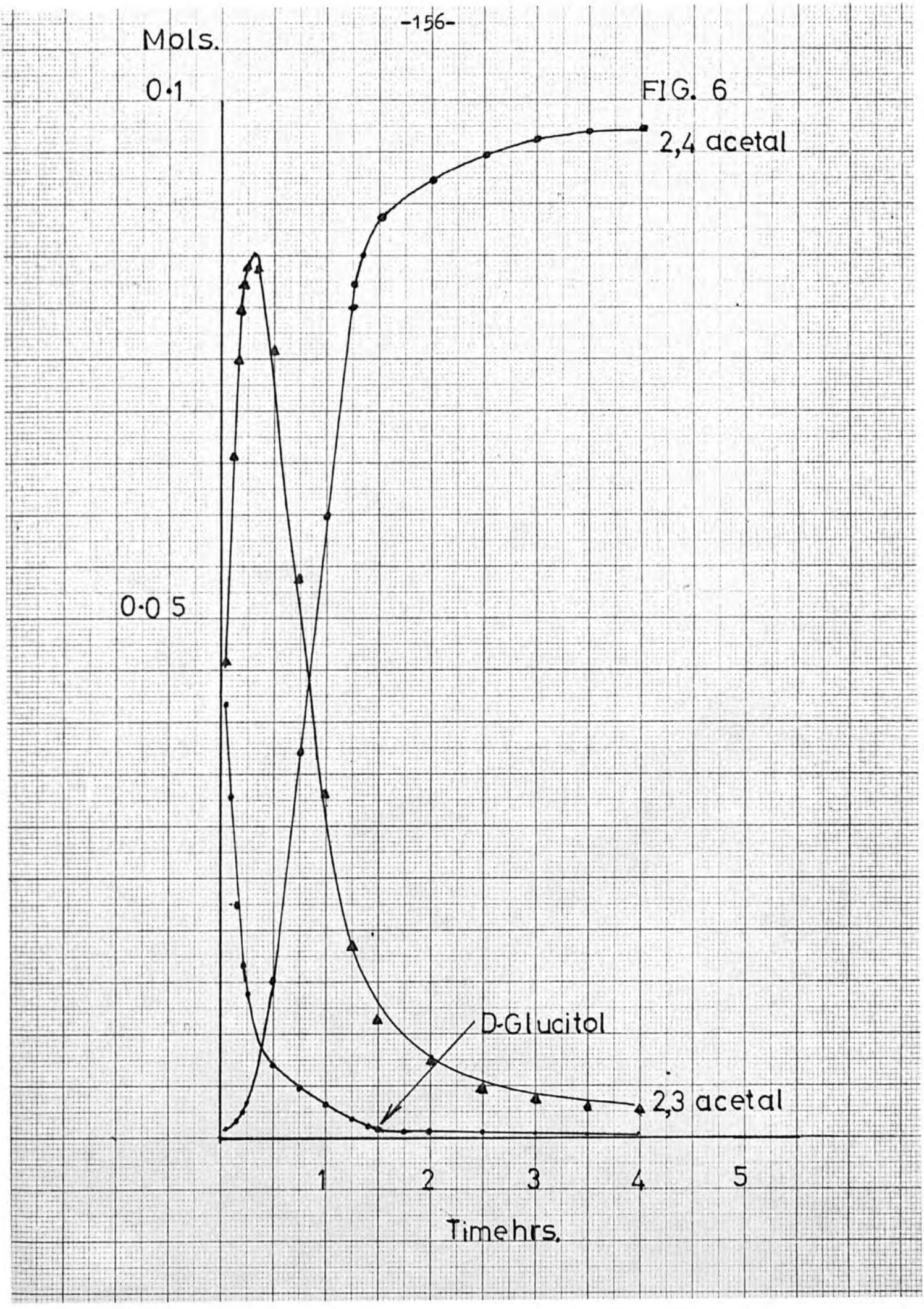


An Intermolecular Mechanism for Acetal Formation using variable Reaction Parameters

FIG. 5

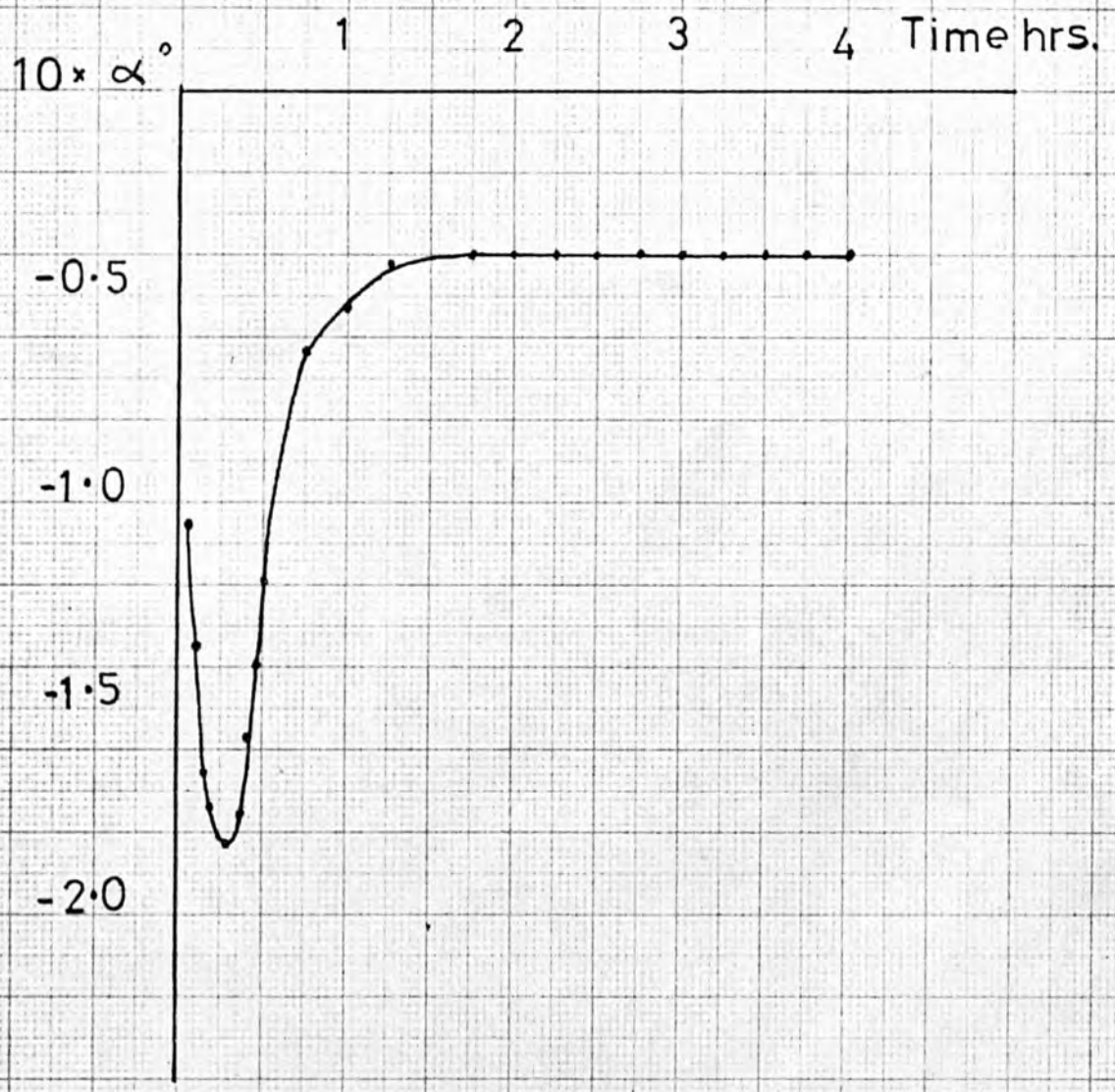


Programme C


Mols.
0·1
0·0 5
FIG. 6
2,4 acetal
D-Glucitol
2,3 acetal
1
2
3
4
5
Timehrs.

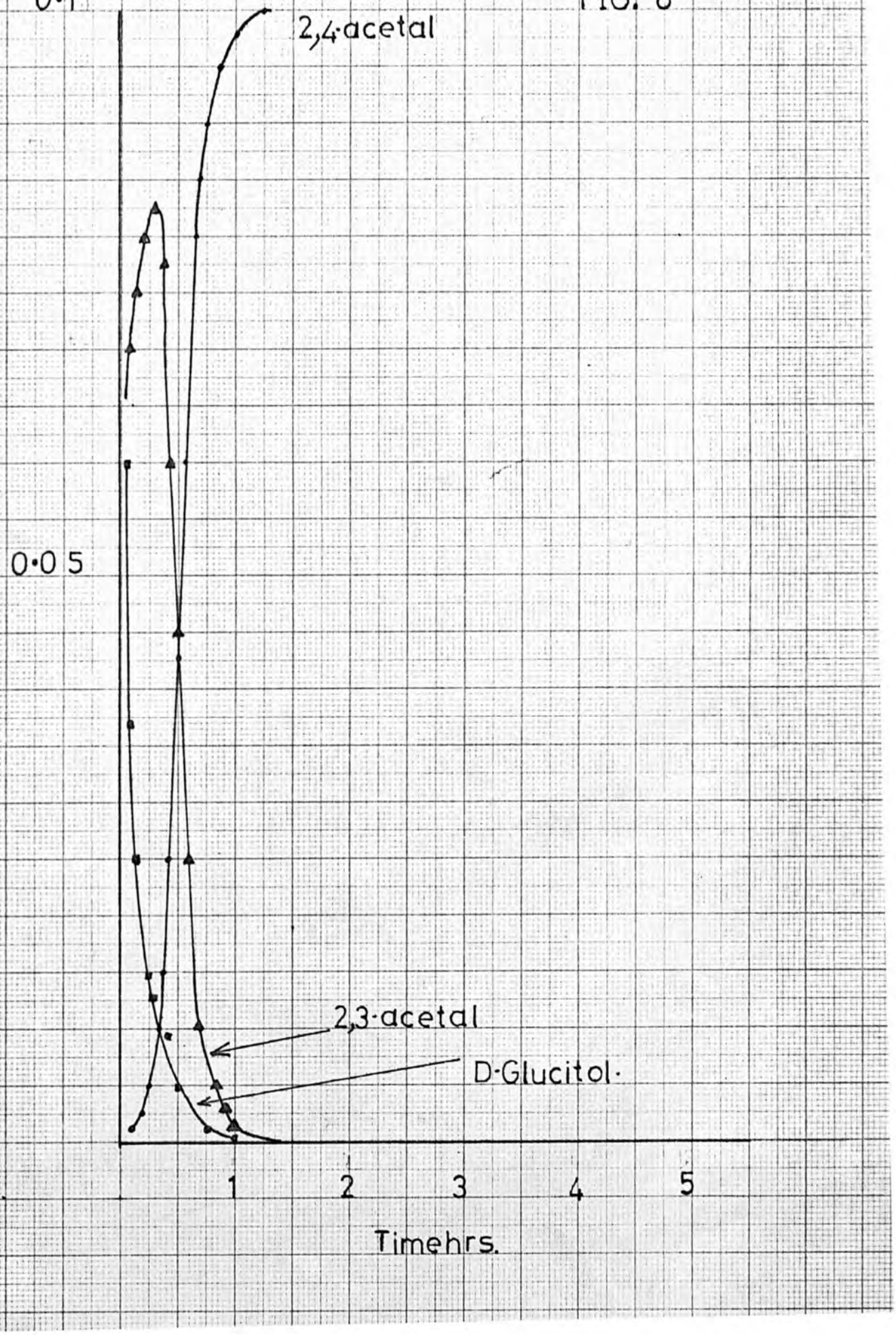
An Intramolecular Mechanism for Acetal Formation using variable Reaction Parameters

FIG. 7



Programme D

FIG. 8

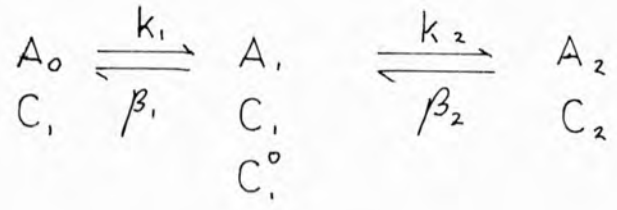


THE PROGRAMMES

Programme A gives the mathematical interpretation of scheme 1, the intermolecular process. Similarly programme C interprets the same scheme taking into account a variation in the value of the rate constants with time.

While programme B gives the mathematical interpretation of scheme 2 the intramolecular process, with programme D the same scheme is interpreted using variable rate constants.

PARALLEL EQUILIBRIA PROGRAMME A



SCHEME 1

```
      PROGRAM ALPHA VT (OUTPUT, TAPE 6 = OUTPUT)
      REAL K1, K2
      BETA 1 =
      BETA 2 =
      K1     =
      K2     =
      A      = 1.0
      B      = K1 + K2 + BETA 1 + BETA 2
      C      = K1 * K2 + K1 * BETA 2 + BETA 1 * BETA 2
      X      = B * B - 4.0 * A * C
      X      = SQRT (X)
      Y      = 2.0 * A
      GAMMA 1= (B-X)/Y
      GAMMA 2= (B+X)/Y
C SIGN OF ROOTS HAVE BEEN REVERSED
      C1 ZERO =                          - use molarity
      C1 ZERO K = C1 ZERO * K2
      C1 ZERO B = C1 ZERO * BETA 1
      A = GAMMA 1 * GAMMA 2
      B = GAMMA 1 * GAMMA 1
```

```
      C    = GAMMA 2 * GAMMA 2
      D    = K1 * BETA 2
      C1X  = D/A
      X    = K1 + BETA 2
      C1Y  = (P-GAMMA 1 * X + D)/(A - B)
      C1Z  = (C-GAMMA 2 * X + D)/(A - C)
      C2X  = K1/A
      C2Y  = (K1 - GAMMA 1)/(A - B)
      C2Z  = (K1 - GAMMA 2)/(A - C)
      COX  = BETA 2/A
      COY  = (BETA 2 - GAMMA 1)/(A - B)
      COZ  = (BETA 2 - GAMMA 2)/(A - C)
      WRITE (6, 201)
201 FORMAT (1H1, 42X, 1HT, 10X, 5H ALPHA)
      A =
      B =                                   MOLAR ROTATIONS
      C =
      T = 0.5
3     X = GAMMA 1 * T
      X = 1.0/EXP(X)
      Y = GAMMA 2 * T
      Y = 1.0/EXP(Y)
      C1 = C1 ZERO * (C1X - C1Y*X - C1Z*Y)
      C2 = C1 ZERO K * (C2X - C2Y*X - C2Z*Y)
      CO = C1 ZERO B * (COX - COY*X - COZ*Y)
```

```
      ALPHA = 0.02 * (A * C 0 + B * C 1 + C * C 2)
      WRITE (6,200) T, ALPHA
200   FORMAT (1 H    , 40X, F5.1, 4X, E 13.6)
      T = T + 1.0
      IF (T .LT. 241.0) GO TO 3
      STOP
      END
```

Considering the initial equation (1) and initial concentration C_1^o we may write;

$$\frac{dC_o}{dt} = \beta_1 C_1 - k_1 C_o$$

$$\frac{dC_1}{dt} = k_1 C_o - \beta_1 C_1 + \beta_2 C_2 - k_2 C_1$$

$$\frac{dC_2}{dt} = k_2 C_2 - \beta_2 C_1$$

For transformed functions;

$$PC_o = \beta_1 C_1 - k_1 C_o$$

$$PC_1 - PC_1^o = k_1 C_o - \beta_1 C_1 + \beta_2 C_2 - k_2 C_1$$

$$PC_2 = k_2 C_2 - \beta_2 C_1$$

Solving these in succession;

$$C_o = \frac{C_1^o \beta_1 (P + \beta_2)}{(P + \gamma_1)(P + \gamma_2)}$$

$$C_1 = \frac{(P + k_1)(P + \beta_2) C_1^o}{(P + \gamma_1)(P + \gamma_2)}$$

$$C_2 = \frac{C_1^o k_2 (P + k_1)}{(P + \gamma_1)(P + \gamma_2)}$$

Where γ_1 & γ_2 are the roots of $\gamma^2 + \gamma(k_1 + k_2 + \beta_1 + \beta_2) + k_1 k_2 + k_1 \beta_2 + \beta_1 \beta_2 = 0$ with signs reversed.

$$C_o = C_1^\circ \beta_1 \left(\frac{\beta_2}{\gamma_1 \gamma_2} - \frac{(\beta_2 - \gamma_1)}{\gamma_1(\gamma_2 - \gamma_1)} e^{-\gamma_1 t} - \frac{(\beta_2 - \gamma_2)}{\gamma_2(\gamma_1 - \gamma_2)} e^{-\gamma_2 t} \right)$$

$$C_1 = C_1^\circ \left(\frac{k_1 \beta_2}{\gamma_1 \gamma_2} - \frac{\gamma_1^2 - \gamma_1(k_1 + \beta_2) + k_1 \beta_2}{\gamma_1(\gamma_2 - \gamma_1)} e^{-\gamma_1 t} - \frac{\gamma_2^2 - \gamma_2(k_1 + \beta_2) + k_1 \beta_2}{\gamma_2(\gamma_1 - \gamma_2)} e^{-\gamma_2 t} \right)$$

$$C_2 = C_1^\circ k_2 \left(\frac{k_1}{\gamma_1 \gamma_2} - \frac{(k_1 - \gamma_1) e^{-\gamma_1 t}}{\gamma_1(\gamma_2 - \gamma_1)} - \frac{(k_1 - \gamma_2) e^{-\gamma_2 t}}{\gamma_2(\gamma_1 - \gamma_2)} \right)$$

The experimental rotation time curve should be reproduced by using C_o, C_1 and C_2 in the equation

$$\alpha = B\ (aC_o + bC_1 + cC_2)$$

where B is a constant for the apparatus used

a, b, c are the specific rotations of the various reactants and products.

This approach using pseudo first order rates is justified since the characteristic curve can be obtained using a 10:1 excess of D-glucitol over n-butyraldehyde thus giving pseudo first order conditions.

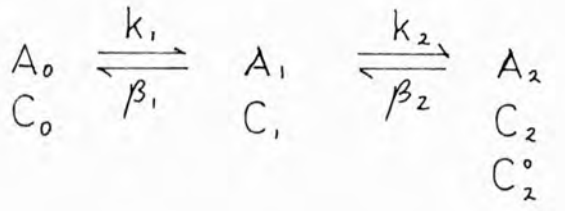
DATA : PROGRAMME A

CONC D-GLUCITOL = 0.1 M

RUN	k_1 min^{-1}	k_2 min^{-1}	β_1 min^{-1}	β_2 min^{-1}
1	2.34×10^{-2}	4.212×10^{-3}	1.87×10^{-1}	4.67×10^{-4}
2	2.34×10^{-2}	1.875×10^{-2}	1.878×10^{-1}	4.67×10^{-4}
3	2.34×10^{-2}	4.212×10^{-3}	4.212×10^{-3}	4.67×10^{-4}
4	9.34×10^{-3}	4.212×10^{-3}	1.878×10^{-1}	4.67×10^{-4}
5	9.34×10^{-3}	1.878×10^{-2}	1.878×10^{-1}	4.67×10^{-4}
6	4.67×10^{-2}	4.212×10^{-3}	1.878×10^{-1}	4.67×10^{-4}

These all gave curves characterised by FIG 1

CONSECUTIVE EQUILIBRIA PROGRAMME B



SCHEME 2

```
      PROGRAM ALPHA VT (OUTPUT, TAPE 6 = OUTPUT)
      REAL K1, K2
      BETA 1 =
      BETA 2 =
      K1 =
      K2 = 1
      A = 1.0
      B = K1 + K2 + BETA 1 + BETA 2
      C = K1 * K2 + K1 * BETA 2 + BETA 1 * BETA 2
      X = B * B - 4.0 * A * C
      X = SQRT (X)
      Y = 2.0 * A
      GAMMA 1 = (B-X)/Y
      GAMMA 2 = (B+X)/Y
C     SIGN OF ROOTS HAVE BEEN CHANGED
      C2 ZERO =
      C2 ZERO B = C2 ZERO * BETA 1 * BETA 2
      C2 ZERO D = C2 ZERO * BETA 2
      A = GAMMA 1 * GAMMA 2
      B = GAMMA 1 * GAMMA 1
```

```
      C = GAMMA 2 * GAMMA 2
      E = K1 * K2
      C1X = K1/A
      C1Y = (K1 - GAMMA 1)/(B - A)
      C1Z = (K1 - GAMMA 2)/(C - A)
      C2A = E/A
      F = K1 + K2 + BETA 1
      C2Y = (B - GAMMA 1 * F + E)/(B - A)
      C2Z = (C - GAMMA 2 * F + E)/(C - A)
      COX = 1.0/A
      COY = 1.0/(B-A)
      COZ = 1.0/(C - A)
      WRITE (6, 201)
201 FORMAT (  H1, 42X, 1HB, 10X, 5H ALPHA)
      A =
      B =
      C =
      T = 0.5
3     X = GAMMA 1 * T
      X = 1.0/EXP(X)
      Y = GAMMA 2 * T
      Y = 1.0/EXP(Y)
      C1 = C2 ZERO D * (C1X + C1Y * X + C1Z * Y)
      C2 = C2 ZERO * (C2X + C2Y * X + C2Z * Y)
      CO = C2 ZERO B * (COX + COY * X + COZ * Y)
```

```
      ALPHA = 0.07 * (A * C1 + B * C2 + C * CO)
200 FORMAT (1H    , 40X, F5.1, 4X, E13.6)
      T = T+1.0
      IF (T .LT. 241.0) GO TO 3
      STOP
      END
```

Considering the initial equation (2) and initial concentration C_2^o we may write;

$$\frac{dC_0}{dt} = \beta_1 C_1 - k_1 C_0$$

$$\frac{dC_1}{dt} = k_1 C_0 - \beta_1 C_1 - k_2 C_1 + \beta_2 C_2$$

$$\frac{dC_2}{dt} = k_2 C_1 - \beta_2 C_2$$

For transformed functions;

$$PC_0 = \beta_1 C_1 - k_1 C_0$$

$$PC_1 = k_1 C_0 - \beta_1 C_1 - k_2 C_1 + \beta_2 C_2$$

$$PC_2 - PC_2^o = k_2 C_1 - \beta_2 C_2$$

Solving these in succession;

$$C_0 = \frac{\beta_1 \beta_2 C_2^o}{(P+\gamma_1)(P+\gamma_2)}$$

$$C_1 = \frac{\beta_2 (P+k_1) C_2^o}{(P+\gamma_1)(P+\gamma_2)}$$

$$C_2 = \frac{(P^2 + P(k_1+k_2+\beta_1) + k_1 k_2) C_2^o}{(P+\gamma_1)(P+\gamma_2)} .$$

Where γ_1 & γ_2 are roots of $\gamma^2 + \gamma(k_1+k_2+\beta_1+\beta_2) + k_1 k_2 + k_1 \beta_2 + \beta_1 \beta_2 = 0$ with signs reversed.

$$C_0 = \beta_1 \beta_2 C_2^0 \left(\frac{1}{\gamma_1 \gamma_2} + \frac{1\ e^{-\gamma_1 t}}{\gamma_1(\gamma_1 - \gamma_2)} + \frac{1\ e^{-\gamma_2 t}}{\gamma_2(\gamma_2 - \gamma_1)} \right)$$

$$C_1 = \beta_2 C_2^0 \left(\frac{k_1}{\gamma_1 \gamma_2} + \frac{(k_1 - \gamma_1) e^{-\gamma_1 t}}{\gamma_1(\gamma_1 - \gamma_2)} + \frac{(k_1 - \gamma_2) e^{-\gamma_2 t}}{\gamma_2(\gamma_2 - \gamma_1)} \right)$$

$$C_2 = C_2^0 \left(\frac{k_1 k_2}{\gamma_1 \gamma_2} + \frac{(\gamma_1^2 - \gamma_1(k_1 + k_2 + \beta_1) + k_1 k_2) e^{-\gamma_2 t}}{\gamma_1(\gamma_1 - \gamma_2)} \right.$$

$$\left. + \frac{(\gamma_2^2 - \gamma_2(k_1 + k_2 + \beta_2) + k_1 k_2) e^{-\gamma_2 t}}{\gamma_2(\gamma_2 - \gamma_1)} \right)$$

DATA : PROGRAMME B

CONC D-GLUCITOL = 0.1 M

RUN	k_1 min^{-1}	k_2 min^{-1}	β_1 min^{-1}	β_2 min^{-1}
1	4.67×10^{-4}	2.34×10^{-2}	4.212×10^{-3}	1.878×10^{-1}
2	4.67×10^{-4}	2.34×10^{-2}	1.875×10^{-2}	1.878×10^{-1}
3	4.67×10^{-4}	2.34×10^{-2}	4.212×10^{-3}	4.212×10^{-3}
4	4.67×10^{-4}	9.34×10^{-3}	4.212×10^{-3}	1.878×10^{-1}
5	4.67×10^{-4}	9.34×10^{-3}	1.875×10^{-2}	1.878×10^{-1}
6	4.67×10^{-4}	4.67×10^{-2}	4.212×10^{-3}	1.878×10^{-1}

These all gave curves characterised by FIG 3

PROGRAMME C

```
      (SCHEME 1, PROGRAMME A WITH VARIABLE K1, K2, BETA 1, BETA 2)
      PROGRAM ALPHA VT (OUTPUT, TAPE 6 = OUTPUT)
      DIMENSION BETA 1(241), BETA 2(241)
      REAL K2(241), K2(241)
      DO 1 I = 1, 25
1     BETA 1(I)
      DO 2 I = 26, 81
      T = I - 0.5
2     BETA 1(I) =
      DO 3 I = 82, 241
3     BETA 1(I) = BETA 1(81)
      DO 4 I = 1,20
4     K2(I) =
      DO 5 I = 21, 91
      T = I - 0.5
5     K2(I)
      DO 6 I = 92, 241
6     K2(I) = K2(91)
      AP =
      BP =
      CP =
      WRITE (6,201)
201   FORMAT (1H1, 42X, 1HT, 10X, 5HALPHA)
      AK = 1.0
```

```
      C1 ZERO =
      DO 7 I = 1, 241
      K1(I) =
      BETA 2(I) =
      D = K1(I) * BETA 2(I)
      B = K1(I) + K2(I) + BETA 1(I) * BETA 2(I)
      C = K(I) * K2(I) + D + BETA 1(I) * BETA 2(I)
      X = B * B - 4.0 * AK * C
      X = SQRT(X)
      Y = 2.0 * AK
      GAMMA 1 = B - X)/Y
      GAMMA 2 = (B + X)/Y
C     SIGN OF ROOT HAVE BEEN CHANGED
      C1 ZERO K = C1 ZERO * K2(I)
      C1 ZERO B = C1 ZERO * BETA 1(I)
      A = GAMMA 1 * GAMMA 2
      B = GAMMA 1 * GAMMA 1
      C = GAMMA 2 * GAMMA 2
      C1X = D/A
      X = K1(I) + BETA 2(I)
      C1Y = (B - GAMMA 1 * X + D)/(A - B)
      C1Z = (C - GAMMA 2 * X + D)/(A - C)
      C2X = K1(I)/A
      C2Y = (K1(I) - GAMMA 1)/(A - B)
      C2Z = (K1(I) - GAMMA 2)/(A - C)
```

```
      COX = BETA 2(I)/A
      COY = (BETA 2(I) - GAMMA 1)/(A - B)
      COZ = (BETA 2(I) - GAMMA 2)/(A - C)
      T   = I - 0.5
      X   = GAMMA 1 * T
      X =   1.0/EXP(X)
      Y =   GAMMA 2*T
      Y =   1.0/EXP(Y)
      C1 = C1 ZERO + (C1X - C1Y*X - C1Z*Y)
      C2 = C1 ZERO K*(C2X - C2Y*X - C2Z*Y)
      C0 = C1 ZERO B*(C0X - C0Y*X - C0Z*Y)
      ALPHA = 0.02*(AP*C0 + BP*C1 + CP*C2)
7     WRITE (6,200) T, ALPHA
200   FORMAT (1H  , 40X, F5.1, 4X, /13.6)
      STOP
      END
```

DATA: PROGRAMME C

This uses variable k_1; k_2; β_1 and β_2

RUN 1 CONC OF D-GLUCITOL = 0.1 M

β_1(T = 1 - 25 MIN = 1.878×10^{-1}

β_1(T = 26 - 81) = -0.00335T + 0.27139

β_1(81 - 241) = $_1$(81)

$\beta_2 = 4.67 \times 10^{-4}$

$k_1 = 2.34 \times 10^{-2}$

k_2 (T = 1 - 20 min) = 4.212×10^{-3}

k_2 (T = 21 - 91) = 0.002623T - 0.048225

k_2 (91 - 241) = k_2 (91)

This gave a curve characteristic of FIG 5 with the characteristic minimum.

PROGRAMME D

```
      (SCHEME 2, PROGRAMME B WITH VARIABLE K1, K2, BETA 1, BETA 2)
      PROGRAM ALPHA VT (OUTPUT, TAPE 6 = OUTPUT)
      DIMENSION BETA 1(241), BETA 2(241)
      REAL K1(241), K2(241)
      DO 1 I=1, 25
1     BETA 2(I) =
      DO 2 I = 26, 81
      T = I - 0.5
2     BETA 2(I) =
      DO 3 I = 82, 241
3     BETA 2(I) = BETA 2(1)
      DO 4 I = 1, 20
4     BETA 1(I) =
      DO 5 I = 21, 91
      T = I - 0.5
5     BETA 1(I) =
      DO 6 I = 92, 241
6     BETA 1(I) = BETA 1(91)
      AP =
      BP =
      CP =
      WRITE (6,201)
201   FORMAT (1H1, 43X, 1HT, 2HC1, 14X, 2HC2, 14X, 2HC0, 10X, 5HALPHA)
      AK =
```

```
      C2 ZERO =
      DO 7 I = 1, 241
      K1(I) =
      K2(I) =
      D = K1(I)*BETA2(I)
      B = K1(I)+K2(I)+BETA1(I)+BETA2(I)
      C = K1(I)*K2(I) + D + BETA1(I)*BETA2(I)
      X = B*B - 4.*C*AK*C
      X = SQRT(X)
      Y = 2.*C*AK
      GAMMA 1 = (B-X)/Y
      GAMMA 2 = (B+X)/Y
C     SIGN OF ROOT HAVE BEEN CHANGED
      C2 ZERO B = C2 ZERO *BETA 1(I) * BETA 2(I)
      C2 ZERO D = C2 ZERO *BETA 2(I)
      A = GAMMA 1 * GAMMA 2
      B = GAMMA 1 * GAMMA 1
      C = GAMMA 2 * GAMMA 2
      E = K1(I) * K2(I)
      C1X = K1(I)/A
      C1Y = (K1(I) - GAMMA 1)/(B - A)
      C1Z = (K1(I) - GAMMA 2)/(C - A)
      C2X = E/A
      F = K1(I) + K2(I) + BETA 1(I)
      C2Y = (B - GAMMA 1 * F + E)/(B - A)
```

```
      C2Z = (C - GAMMA 1 * F + E)/(C - A)
      COX = 1.0/A
      COY = 1.0/(B-A)
      COZ = 1.0/(C-A)
      T   = I-0.5
      X   = GAMMA 1 * T
      X = 1.0/EXP(X)
      Y = GAMMA 2 * T
      Y = 1.0/EXP(Y)
      C1 = C2 ZERO D * (C1X + C1Y* + C1Z*Y)
      C2 = C2 ZERO* (C2X + C2Y*X + C2Z*Y)
      CO = C2 ZERO * (COX + COY*X + COZ*Y)
      ALPHA = 0.02* (AP*C1 + BP*C2 + CP*CO)
7     WRITE (6,200) T, C1, C2, CO, ALPHA
200   FORMAT (1H  ,40X, F5.1, 3(4X,E11.4), 4X, F7.4)
      STOP
      END
```

DATA : PROGRAMME D

RUN 1 CONC OF D-GLUCITOL = 0.1 M

β_1(T = 1-20 MIN) = 4.212×10^{-3} sec^{-1}

β_1(T = 21-19) = 0.002623T - 0.04825

β_1(T = 91-24) = $_1$(91)

β_2(T = 1-25 MIN) = 0.1878

β_2(T = 26-81 MIN) = -0.002529T + 0.308

$_2$(T = 81-241 MIN) = $_2$(81)

$k_1 = 4.67 \times 10^{-4}$ sec^{-1}

$k_2 = 2.34 \times 10^{-2}$ sec^{-1}

This gave a curve characteristic of FIG 7

EXPERIMENT 1

The reaction on n-Butyraldehyde (0.1 M) and D-Glucitol (0.1 M) in aqueous Hydrochloric acid (1.0 M)

The reaction was followed polarimetrically as in all other cases (Experiment 10) giving the same characteristic curve with the rotational minimum. It was however observed that the curve was displaced, to be more negative, while the minimum was not so pronounced. Vapour phase chromatography showed by comparison with standards that we were observing the same mechanism as normal with initial formation of the 2,3-mono-acetal, the kinetically controlled product followed by its decay and build up of the 2,4-mono-acetal, the thermodynamically controlled product.

REFERENCE

1. Rodiguin and Rodiguina

Consecutive Chemical reactions

Published by D. Van Nostrand Co., Inc.

Princeton, New Jersey

CHAPTER 4

The Reaction between Equi-molar Quantities of n-Butyraldehyde and Polyhydroxy Compounds

EXPERIMENT 1

Acid Catalysed Condensation of Xylitol and n-Butyraldehyde

(i) Formation of the di-α-Butylidene-Xylitol

Xylitol (5 g) and n-butyraldehyde (20 ml) were stirred together and concentrated sulphuric acid (0.1 mls) was added. The stirring was continued for 24 hours and the solution was neutralised exactly with saturated sodium hydroxide solution. The mixture was then evaporated to a syrup using water pump pressure and the syrup so formed was distilled. The syrup separated into two fractions; below 120°C which proved to be n-butyraldehyde condensation products and 134-136° 0.2 mm Hg which on hydrolysis (0.5 ml 1R 120H$^+$ resin) gave xylitol.

Analysis	calc	$C_{13}H_{24}O_5$	C 60.0 %	H 9.29 %	O 30.71 %
	found		C 59.8 %	H 9.32 %	O 30.88 %

(ii) Periodate oxidation of the compound from (i)

This was carried out in the normal way.

There was no periodate uptake or formaldehyde liberated.

(iii) Condensation between equi-molar proportions of n-Butyraldehyde and Xylitol

Xylitol (2.1 g) was dissolved in 1 N hydrochloric acid (200 ml) and n-butyraldehyde (1 g) was added. The mixture was shaken vigorously for 5 minutes and then left for 24 hours at room temperature. The solution was then neutralised with saturated sodium hydroxide solution, the solution was then evaporated to a syrup which was extracted with

ethanol.

t.lc (methyl ethyl ketone saturated with water) gave two spots Rf = 0.43, Rf = 0.69. The latter corresponded to the di-acetal.

The syrup obtained from the ethanol extract was separated on a silica gel column eluting with methyl ethyl ketone saturated with water. Compound Rf 0.69 was a syrup identical to the di-acetal prepared previously. The compound Rf 0.43 was a syrup which slowly crystallised and was recrystallised from ethanol.

Analysis calc for $C_9H_{18}O_5$ C 52.41% H 8.80% O 38.79%

C 52.4% H 8.78% O 38.82%

MP 108-109°

(iv) Periodate oxidation of the mono-acetal from (iii)

This was carried out in the normal way, without periodate uptake or liberation of formaldehyde.

EXPERIMENT 2

Condensation of n-Butyraldehyde and L-Rhamnitol (6 Deoxy L-Mannitol)

A solution of 0.1 M n-butyraldehyde and 0.1 M Rhamnitol were prepared in 0.1 M hydrochloric acid and the reaction followed polarimetrically at 365 nm. The polarimetric curve was smooth showing no intermediate while the vapour phase chromatograms of the reaction by sampling at 10 mins, 30 mins and 60 mins showed only the build up of a single compound.

EXPERIMENT 3

The Condensation of n-Butyraldehyde and Various Hexitols and Substituted Hexitols

(i) Condensation between n-Butyraldehyde and D-Glucitol

D-Glucitol (1.82 g) and n-butyraldehyde (0.7211 g) were added to water (50 ml) and complete solution obtained, the solution was then made up to 100 mls with 2 M hydrochloric acid (50 ml) giving 0.1 M solution of substrate in 1 M hydrochloric acid. The reaction was followed polarimetrically at 365 nm and spectrophotometrically at 281 nm. Spectrophotometrically we can see that the reaction is complete after approximately 90 mins while the polarimetric curve shows the formation of an intermediate at 30 mins which previous work has shown to be the 2,3 acetal which further rearranges to a 2,4 acetal. Vapour Phase Chromatography showed the same in this case.

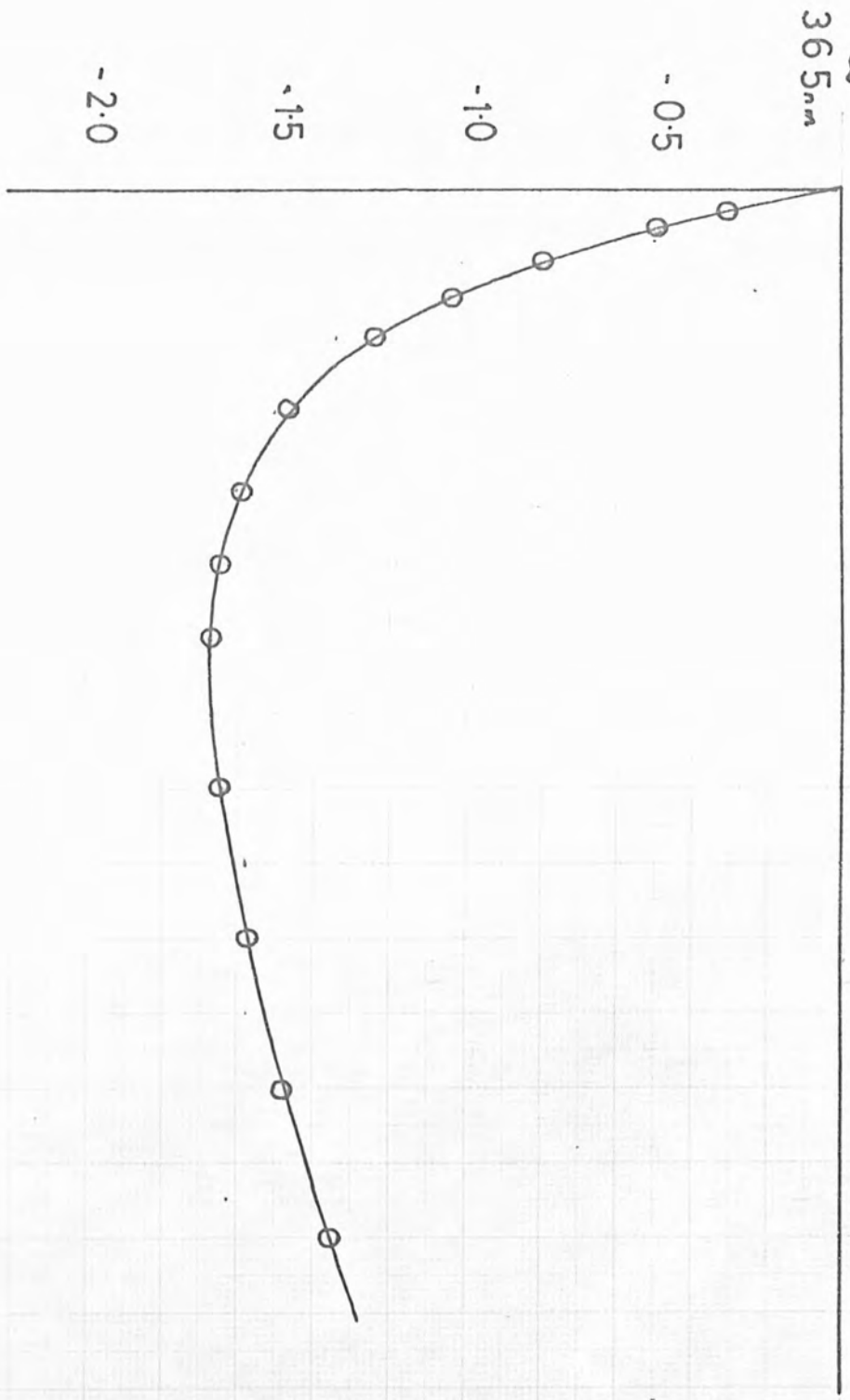
(ii) Condensation of n-Butyraldehyde and D-Mannitol

A solution of 0.1 M D-Mannitol and 0.1 M n-butyraldehyde in 1 M hydrochloric acid were prepared as for D-glucitol and the reaction followed polarimetrically. This showed a smooth curve up to 30 mins when emulsion occurred, this emulsion deposited crystals after 24 hours. These were filtered off and isolated, and shown to be identical to tri butylidene Mannitol by melting point and mixed melting point.

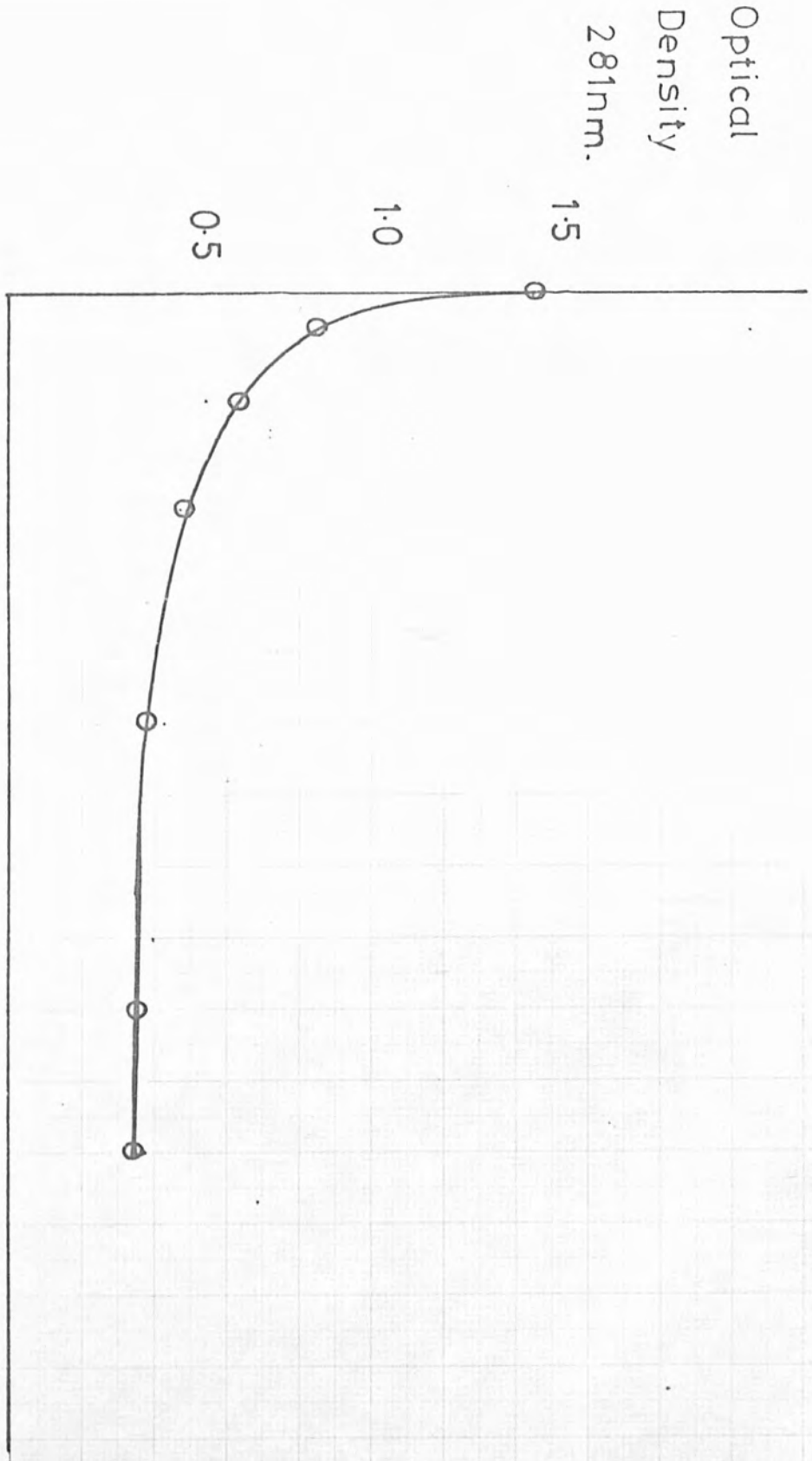
MP = 82-83°

MIXED MP = 82-83°

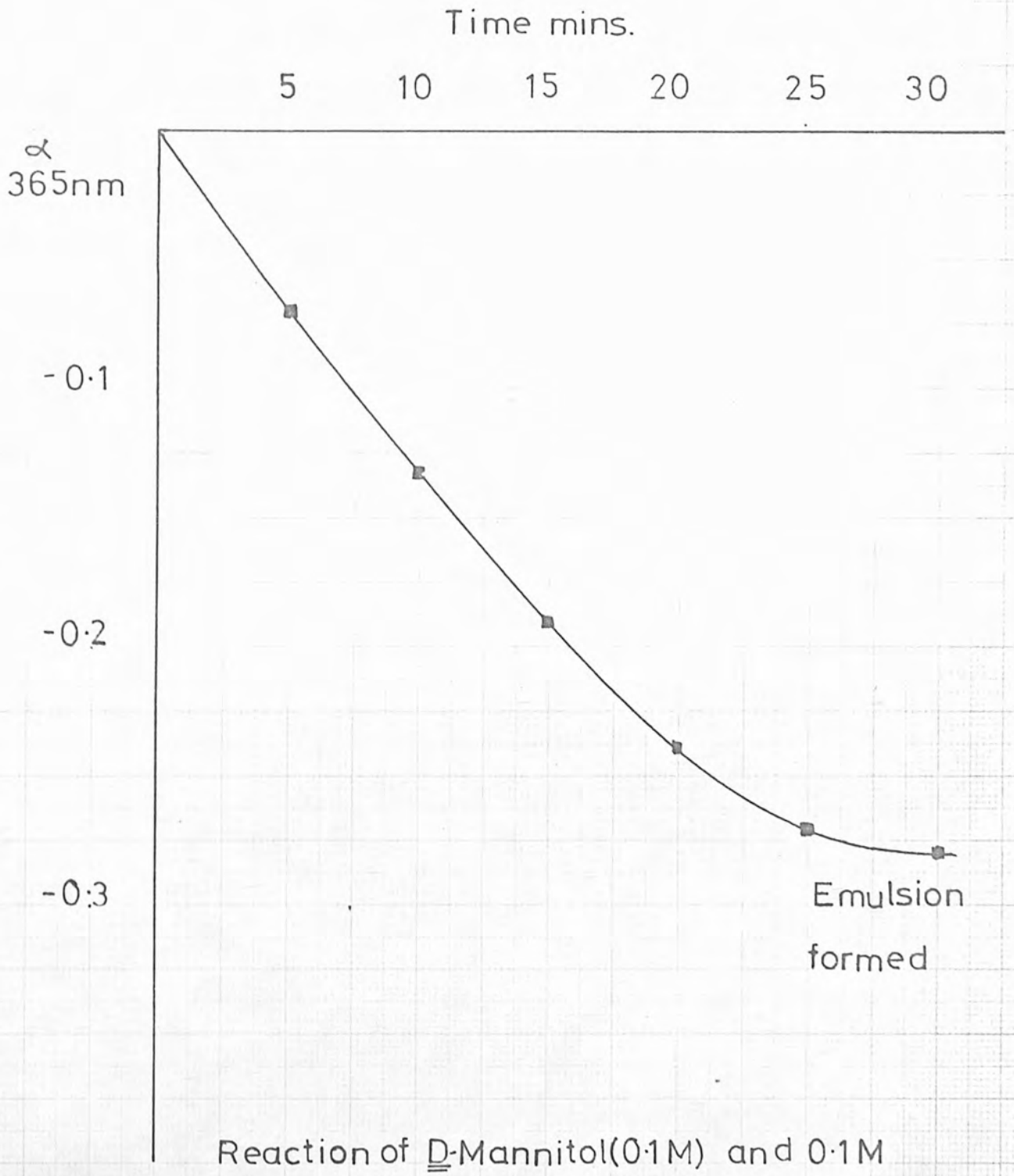
Reaction of L-Rhamnitol and n-Butyraldehyde (1:1 molar) Aqueous HCl (0·1M) at 25°C



Reaction of D-Glucitol (0·1 M) and 0·1 M n-Butyraldehyde in Aqueous HCl (1·0M) at 25°C



Reaction of D- Glucitol (0·1 M) and 0·1 M
n-Butyraldehyde in Aqueous HCl (1·0 M) at 25°C



Reaction of D-Mannitol(0·1M) and 0·1M n-Butyraldehyde in HCl(1·0M) at 25°

SECTION 4

An Investigation of the Ketals of D-Glucitol

CHAPTER 1

The Acid Catalysed formation of Ketals from Acetone and D-Glucitol

INTRODUCTION

The first product obtained from the acetonation of D-glucitol was the triketal isolated by Speier[13] in 1895 by a direct condensation of acetone and D-glucitol in the presence of 1% hydrogen chloride. Later workers studying this condensation have been able to isolate mono- and di-ketals. Pressmann, Anderson and Lardy[1] again obtained the triketal by sulphuric acid catalysis. Using zinc chloride as catalyst they isolated 1,2-O-isopropylidene D-glucitol and 1,2;5,6-di-O-isopropylidene D-glucitol and by further acetonation of the diketal were able to obtain the triketal identical to that first obtained by Speier[13] and so concluded that the triketal must have the 1,2;3,4-5,6 ketal structure. This result was verified by Bourne, Mc Sweeney, Stacey and Wiggins[9] who subjected the triketal to partial acid hydrolysis and isolated the 3,4-O-isopropylidene-D-glucitol and the 3,4;5,6-di-O-isopropylidene D-glucitol as crystalline products and infer the presence of 1,2;3,4-di-O-isopropylidene D-glucitol in a syrupy mixture by degradative and chromatographic methods, while an indirect synthesis has given 1,2;5,6-di-O-isopropylidene L-glucitol.[18]

DISCUSSION AND RESULTS

1. ZINC CHLORIDE CATALYSIS

Zinc chloride under anhydrous conditions acts as a Lewis acid and is therefore a fairly mild catalyst compared with the catalytic action of concentrated sulphuric acid or the other mineral acids. Previous work has suggested that the first step in the action of zinc chloride as a catalyst is the formation of a zinc chloride carbonyl complex[14].

$$ZnCl_2 + 2R_2C=O \longrightarrow ZnCl_2(R_2C=O)_2$$

In the case of benzaldehyde the complex[14] has been isolated and it shows the absence of carbonyl frequencies in the infra-red suggesting participation of the carbonyl group in the formation of the complex, making the carbonyl carbon more susceptible to nucleophilic attack.

The reaction between D-glucitol and acetone in the presence of zinc chloride could be considered to be as follows[14].

$$ZnCl_2((CH_3)_2C=O)_2 + \text{D-GLUCITOL} \longrightarrow \text{PRODUCT} + ZnCl_2(H_2O)_2$$

No assumption can be made about the primary mode of attack although formation of a hemi-ketal can be postulated from other work with trichloroacetaldehyde[15]. There is no direct evidence in the case of acetone because the reaction is so rapid that even at depressed temperatures the only products that are seen are the cyclic ketals.

As has been stated previously the only products from direct condensation of acetone and D-glucitol which have been isolated are the 1,2-O-isopropylidene D-glucitol, 1,2;5,6 di-O-isopropylidene D-glucitol and tri-O-isopropylidene D-glucitol, and a syrup which settled out before the di-ketal crystallised. Pressmann, Anderson and Lardy[1] concluded from the low periodate consumption that this di-ketal could not contain free vicinal hydroxyl groups. However the syrup obtained at the same point in the same reaction was shown to be mainly uncrystallised 1,2;5,6-di-O-isopropylidene D-glucitol (Experiment 17). Analysis of the zinc chloride catalysed reaction by paper chromatography did not yield any further information while thin layer chromatography using ethyl methyl ketone saturated with water as the developing agent with silica gel plates was only able to separate three portions which proved to be the mono-, di and tri-ketals.

Vapour phase chromatography however showed up the true complexity of this reaction. By this technique it was possible to show that there were in fact six reaction products so that the chromatograms showed six well defined peaks (FIG 1) after a period of 3 hours when the reaction was at equilibrium. The reaction was studied by quenching the reaction at intervals and analysing it by vapour phase chromatography. Initial quenching of the reaction after five minutes showed the presence of two products which by comparison with standards were evidently 1,2-O-isopropylidene D-glucitol and 1,2;5,6 di-O-isopropylidene D-glucitol. Further analysis of the reaction at fifteen minutes, thirty minutes and

three hours showed that the reaction became more complex with time until finally at three hours there were six products. As can be seen (FIG 1) the products change as equilibrium is approached. By consideration of the analysis at the initial time (i.e. 5 mins) it can be seen that the 1,2-mono-ketal and the 1,2;5,6-di-ketal are in approximately equal amounts suggesting that there is extremely rapid initial attack at the primary hydroxyls followed by cyclisation. The 1,2 mono-ketal is present during direct synthesis but indirect synthesis of the 5,6-mono-ketal (Experiment 23) has shown that this is completely absent in the initial stages of the direct synthesis.

From this we may conclude that the initial ring formation must be at C_1 and C_2 followed by a rapid secondary formation of the ring at C_5 and C_6. As the reaction proceeds analysis by vapour phase chromatography shows that the 3,4-mono-ketal is formed together with the 1,2;3,4-di-ketal, and the 3,4;5,6-di-ketal and the tri-ketal. By consideration of the relative amounts, the 1,2;5,6-di-ketal is the second most abundant ketal and from this it might well be concluded that initial substitution enhances the reactivity of the C_6 or C_5 hydroxyl and enhances the formation of this ring. This may either be a direct solvent effect or a combination of solvent effect and conformational effects after the initial ketal formation.

2. MINERAL ACID CATALYSIS

(a) Anhydrous dimethyl formamide and hydrogen chloride gas. Under anhydrous conditions with equi-molar quantities of acetone and L-glucitol the major product is the 1,2-L-isopropylidene L-glucitol with only minor amounts of other acetals. This suggests the hypothesis that there is initial cyclisation at C_1 and C_2.

By comparison of the above reaction with that of zinc chloride catalysis it is evident that there is a difference between the homogeneous and inhomogeneous reaction since in the inhomogeneous reaction we have rapid formation of the tri-ketal and the diketals. This must be due to the fact that L-glucitol is only slightly soluble and it is the soluble portion that reacts with the excess acetone. This still leaves the C_1, C_2 hydroxyls more reactive but enhances the reactivity of the other hydroxyls of the small amount of D-glucitol in solution while in the completely homogeneous reaction this constraint does not apply.

(b) Sulphuric acid. The initial absence of the 1,2-mono-ketal further suggests that once this is formed there is a very rapid reaction at other positions giving di-ketals and the tri-ketal, since after a period of time the 1,2-mono ketal is seen together with all the other ketals (FIG 3).

3. PARTIAL ACID HYDROLYSIS OF THE TRIKETAL

This work has only verified previous work[9] as it has shown that compounds III, IV are 3,4-O-isopropylidene D-glucitol and 3,4;5,6 di-O-isopropylidene D-glucitol respectively and that the triketal is the 1,2;3,4-5,6 tri-O-isopropylidene D-glucitol and that the initial ring which is hydrolysed is the 5,6-ketal ring.

From the synthetic studies it has been shown that the 1,2-mono-ketal is probably the first ring system formed and that the 5,6-mono-ketal is extremely unstable and not found in the direct synthetic process. Moreover, hydrolysis studies have again shown the 5,6-ketal ring to be more susceptible to hydrolysis than the other ketal ring involving the primary hydroxyl (i.e. the 1,2-ketal). We might conclude from this that it is a steric effect or that electronic factors are involved. There would seem to be very little or no difference in the electronic environments of the rings, suggesting that it is the difference in the steric environments of the two rings which is decisive.

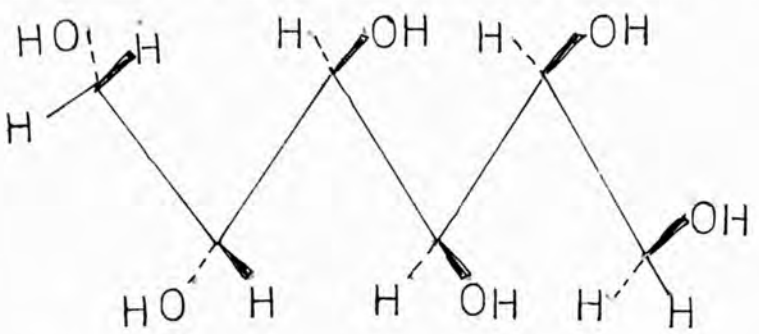
Proton magnetic resonance studies on the ketals have shown that the 3,4-ketal ring is in a different environment to the 1,2-and 5,6-ketal rings but it has shown no difference in the environments of these two rings.

From the above results we can only conclude that the D-glucitol molecule is not symmetrical in reaction, [illegible] (the crystal

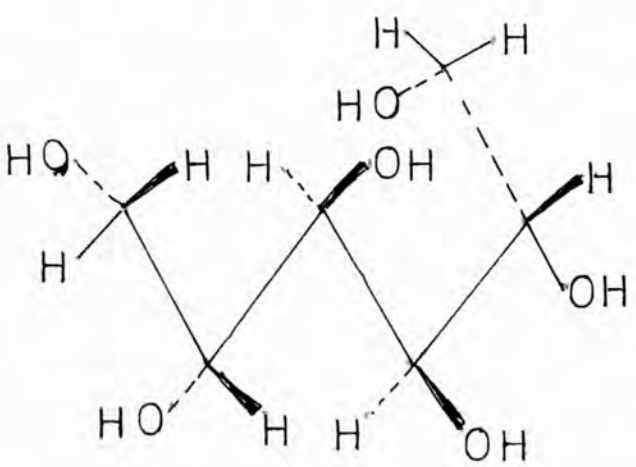
structure of L-glucitol[15] shows it to be a bent molecule with the C_2-C_3 bond rotated out of the planar zig-zag conformation so as to avoid the eclipsed interaction between the hydroxyls at C_2 and C_4.)

CONFORMATION OF D-GLUCITOL

(i) CARBON CHAIN IN PLANAR ZIG-ZAG CONFORMATION



(ii) FOUND



It is very difficult to find a satisfactory explanation of this variation in reactivity which seems to be characteristic of D-glucitol not only in this case but in other similar cases.

ACID CATALYSED CONDENSATION OF ACETONE WITH D-GLUCITOL

MATERIALS

The acetone was AnalaR grade dried over anhydrous magnesium sulphate. Commercial grade D-glucitol was analysed by electrophoresis (vanadate) to check for mannitol[2,3].

EXPERIMENT 1

Preparation of 1,2-O-Isopropylidene-D-Glucitol[1] (COMPOUND 1)

D-Glucitol (100 g) was added to a solution of zinc chloride in acetone (180 g of a 25% solution) and the suspension was shaken for approximately two and a half hours. Potassium carbonate solution (180 g of a 50% solution) was then added and the mixture further shaken for fifteen minutes. The resulting slurry was then filtered, and the residue was washed with acetone (150 ml) and the combined filtrates were concentrated to a syrup under reduced pressure. This syrup was extracted with hot acetone (400 ml) until only a small opaque mass remained. The acetone solution was decanted and cooled at -5° for two days when a white solid was deposited. This was recrystallised from ethanol giving white needles.

MP 167.5 - 168° Yield 4.8 g = 4.8% wrt starting material

LIT MP 167 - 167.5°C

$[\alpha]_D^{17.5} = -10.63$ [c 2.46 g in ethanol]

EXPERIMENT 2

Preparation of the acetate of 1,2-O-Isopropylidene D-Glucitol[1]

1,2-O-Isopropylidene-D-Glucitol (0.25 g) was added to acetic anhydride (1 ml) and pyridene (7.5 g) and the mixture left at room temperature for one day. The mixture was then evaporated to a syrup, which was taken up in ethanol. The ethanolic solution deposited white crystals on cooling. The crystals were recrystallised twice from ethanol.

MP 92.5 - 93.5°

LIT MP 93.0 - 93.5°

YIELD 0.39 g 88.7%

EXPERIMENT 3

Preparation of the benzoate of 1,2-O-Isopropylidene D-Glucitol[1]

1,2-O-isopropylidene D-Glucitol (0.25 g) was added to a cooled solution of benzoyl chloride (1 ml) and pyridine (7.5 ml). The mixture was left in the dark for five days at room temperature. The mixture was then poured into a large volume of ice water when a syrup was deposited. The syrup was extracted with ether, the ether extract was washed with water four times, dried over anhydrous magnesium sulphate and concentrated to a syrup. The syrup was taken up in ethanol and the solution stored at -15° for three days when white crystals were deposited. These were recrystallised twice from ethanol.

MP 97.5 - 98°

LIT MP 97.5 - 98°

YIELD 0.49 g = 69%

EXPERIMENT 4

Preparation of the bis phenyl boronate of 1,2-O-Isopropylidene D-Glucitol

1,2-O-Isopropylidene D-Glucitol (0.05 g) was dissolved in dry methanol (2 ml) and phenyl boronic anhydride (0.047 g)(1 mol ketal : 2 mol Phenyl boronic acid). The methanol was evaporated off. The only solid so obtained was taken up in petroleum ether (BP 60-80°C) and filtered. The filtrate was evaporated to a white solid which was recrystallised from petroleum ether (BP 60 - 80°C).

Repeated recrystallisation gave fine feathery needles.

MP 103-104°C

YIELD 0.051 g = 60%

$(\alpha)_D^{26}$ = 7.728° (c 2.404 in pyridine)

Infrared spectrum (KBr DISC)

No peak at 3500 cm^{-1} absence of hydroxyl

Peaks at 1600 cm^{-1}, 1500cm^{-1}, 1300cm^{-1} characteristic of phenyl boronate

EXPERIMENT 5

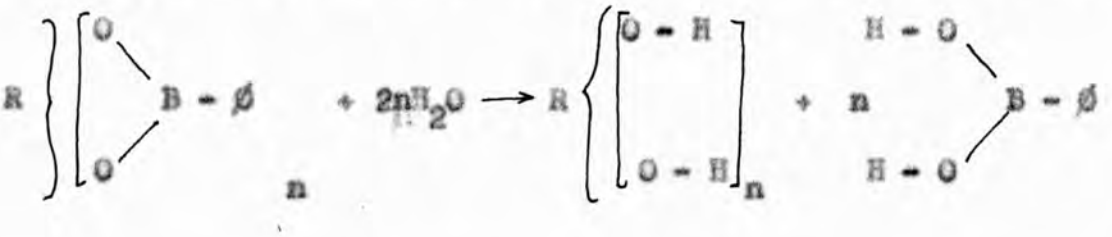
Boron analysis of the phenyl boronate of 1,2-O-Isopropylidene D-Glucitol[4,17]

The boron content was determined spectrophotometrically due to the liberation of phenyl boronic acid which absorbs at 219 nm.

A calibration curve relating optical density to amount of boron present was obtained by dissolving phenyl boronic anhydride (0.6710 g) in 50% aqueous methanol (2 l).

Aliquots of this solution (0.5 ml, 1 ml, 3 ml, 4 ml and 5 ml) were withdrawn and made up to 100 ml and their optical densities measured at 219 nm. These results were used to draw the calibration graph (FIG 1).

The estimation of boron in organo-boron compounds, when boron is attached to a carbon atom requires drastic treatment and therefore it is more convenient to use the optical density of the $\phi - B\diagup\diagdown$. This is possible for phenyl boronates of polyhydroxy compounds because under the conditions of the reaction there is rapid and complete hydrolysis.



The phenyl boronate (0.0088 g) was dissolved in 50% aqueous methanol (10 ml), an aliquot (2 ml) was removed and diluted to 10 ml and the optical density measured at 219 nm.

STANDARD BORON SOLUTION	OPTICAL DENSITY	g BORON/100 ML
0.5 ml in 100 ML	0.145	1.745×10^{-5} g
1.0 ml in 100 ML	0.295	3.49×10^{-5} g
3.0 ml in 100 ML	0.868	10.47×10^{-5} g
4.0 ml in 100 ML	1.15	13.96×10^{-5} g
5.0 ml in 100 ML	1.42	17.45×10^{-5} g

Optical Density of Compound = 0.792 = 9.7×10^{-5} g boron/100 ml

0.0088 g compound should contain 9.662×10^{-5} g boron/100 ml

Calculated % boron for a bis phenyl boronate = 5.49%

Observed% boron for a bis phenyl boronate = 5.51%

Analysis Calculated C 64.008% H 6.13% B 5.49%

Observed C 64.09% H 6.06% B 5.51%

EXPERIMENT 6

Determination of the number of vicinal hydroxyl groups in Compound 1 by periodate oxidation[5]

Solutions (0.015 M) of sodium metaperiodate and potassium iodate (Analar Grade), were made up by dissolving in both cases (0.8349 g) in 250 mls). Aliquots (1 ml) of the solutions were diluted two hundred and fifty times and the optical density, of the resulting solutions, were measured at 223 nm with water as the reference.

Considering the sodium metaperiodate solution to contain 0%IO_3^- and 100%IO_4^- and the potassium iodate solution to contain 100%IO_3^- and 0%IO_4^- a linear calibration graph relating optical density to percentage composition of any solution containing a mixture of the two ions at this dilution was drawn.

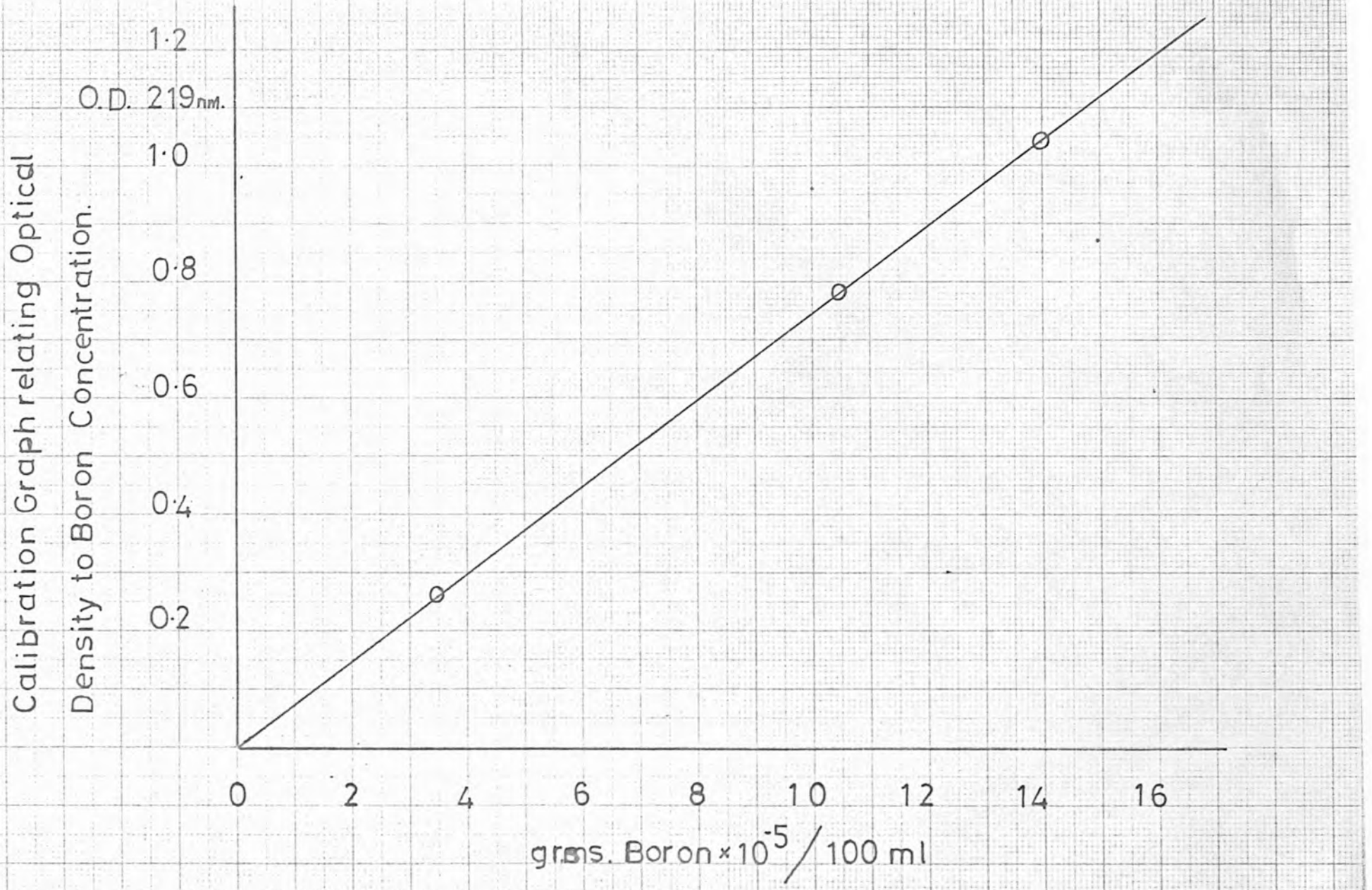
%IO_3^-	%IO_4^-	OPTICAL DENSITY 223 nm
0	100	0.579
100	0	0.100

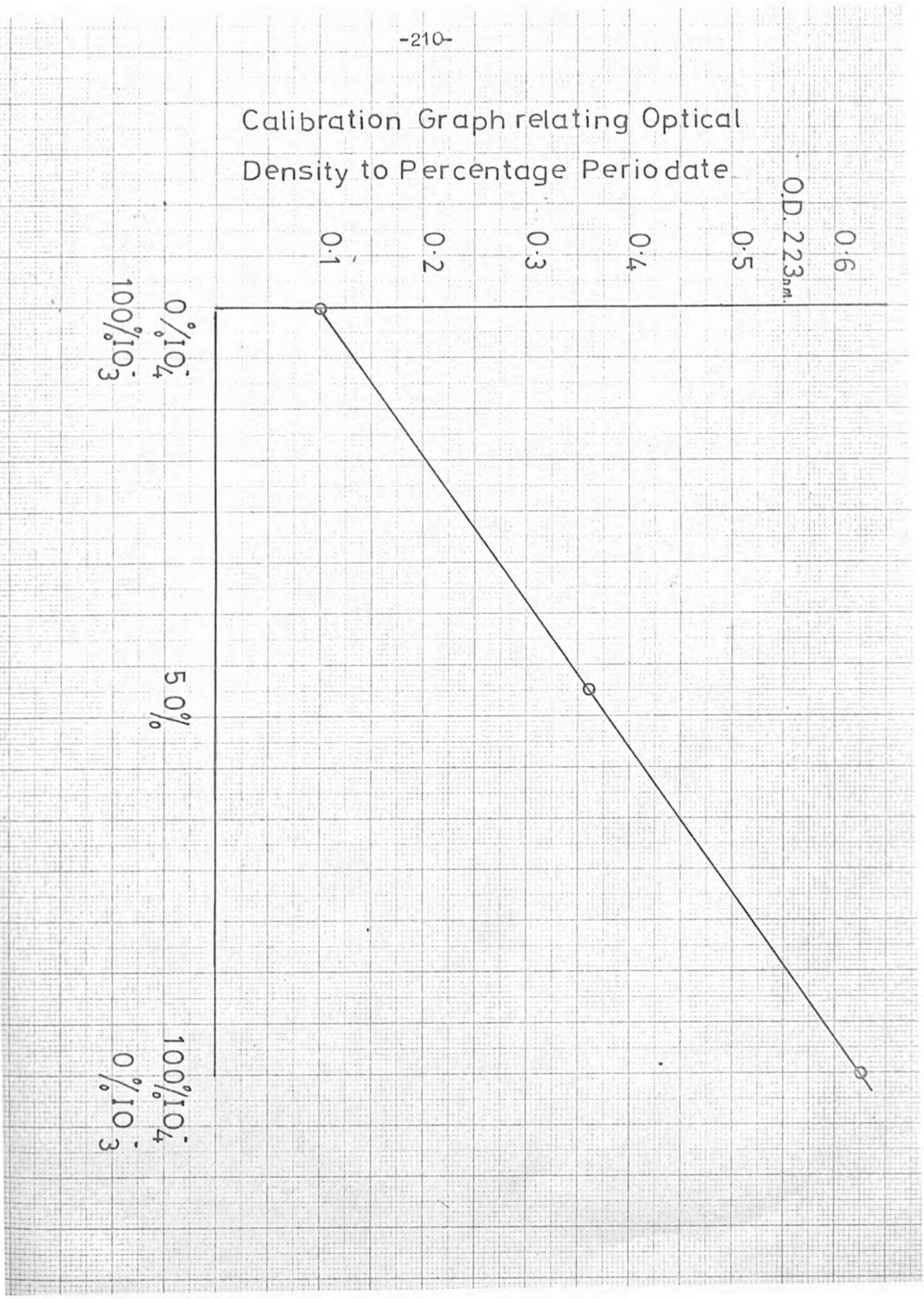
Compound 1 (c 0.01 g) was weighed out accurately and dissolved in the 0.015 M sodium metaperiodate solution (10 ml). At convenient intervals, aliquots (1 ml) were removed, diluted two hundred and fifty times and their optical density measured. From the calibration graph the %IO_3^- in the solution could be deduced and this represents the %IO_4^- reduced by the compound. Hence the number of mols of periodate reduced by one mol of compound 1 can be calculated. The method was checked using 2,5-O-Methylene Mannitol as a standard compound.

COMPOUND	WEIGHT TAKEN	OPTICAL DENSITY AT 4 HRS	$\%IO_4^-$ CONSUMED	MOLAR UPTAKE
Compound 1	0.0095 g	0.187	82.7	3.0
Compound 1	0.0104 g	0.147	90.6	3.0
Compound 1	0.0083 g	0.237	72.3	3.0
2,5-O-Methylene Mannitol	0.0101 g	0.435	34.0	1.01

Since one mol of Compound 1 requires 3.0 mol of periodate for oxidation it must contain 3 pairs of vicinal hydroxyl. groups per molecule.

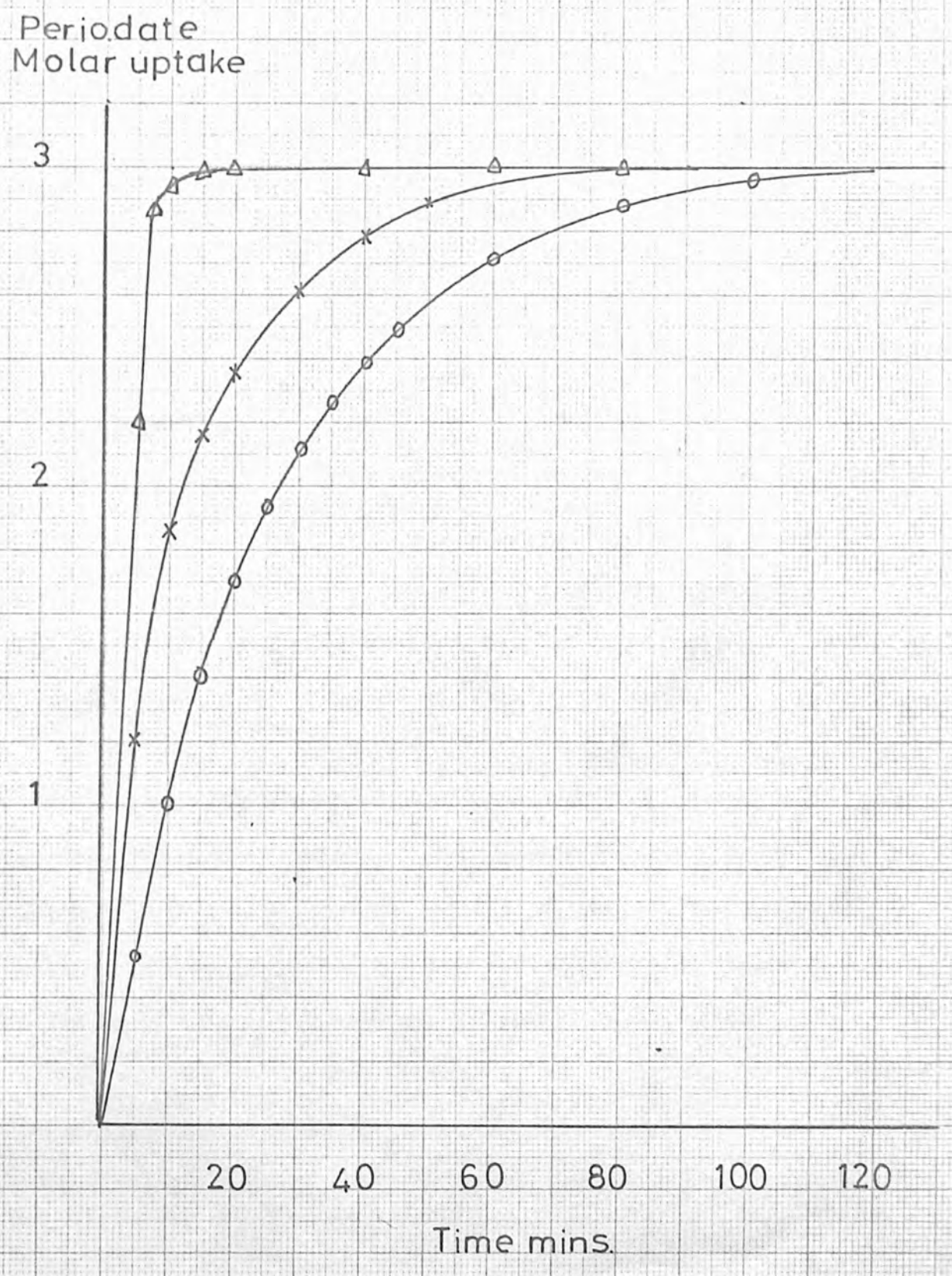
Calibration Graph relating Optical Density to Boron Concentration.




Calibration Graph relating Optical
Density to Percentage Periodate
O.D. 223nm.
0·1
0·2
0·3
0·4
0·5
0·6
0%IO4-
100%IO3-
50%
100%IO4-
0%IO3-

Periodate uptake with time for

1,2 O-Isopropylidene D-Glucitol



EXPERIMENT 7

Estimation of the Formaldehyde liberated by periodate oxidation of Compound 1[6,7,8]

The formaldehyde was estimated spectrophotometrically, by its colour reaction in the presence of chromotopic acid. The reagent was prepared by dissolving chromotropic acid sodium salt (0.2 g) in water (20 ml) and adding 12.5 M sulphuric acid (80 ml) (i.e. H_2O : Conc. H_2SO_4 1 : 2 v/v).

The same solution of 2,5-O-Methylene Mannitol and compound 1 in sodium metaperiodate solution were used as for the preceeding experiment. After 20 hrs, aliquots (1 ml) from the 2,5-O-Methylene Mannitol solution were diluted accurately with water to 10 ml, 20 ml and 50 ml. The solution of compound 1 (1 ml) was diluted to 10 ml with water. From the diluted solutions, 1 ml was transferred to a 20 ml stoppered test tube and a fifth tube containing water (1 ml) as a blank. Into each tube was delivered 20% aqueous sodium sulphite solution (0.1 ml) from a micro burette, and chromotropic acid reagent (8.4 ml) from a burette.

The five tubes were heated for one hour in a boiling water bath during which time violet colouration of varying intensities developed. After cooling, 0.4% aqueous thiourea solution (0.5 ml) was added to the solution from a pipette; thus bringing the total volume in each tube to 10 ml.

The optical densities at 570 nm of the four sample solutions were measured, with the blank solution in the reference cell. Under

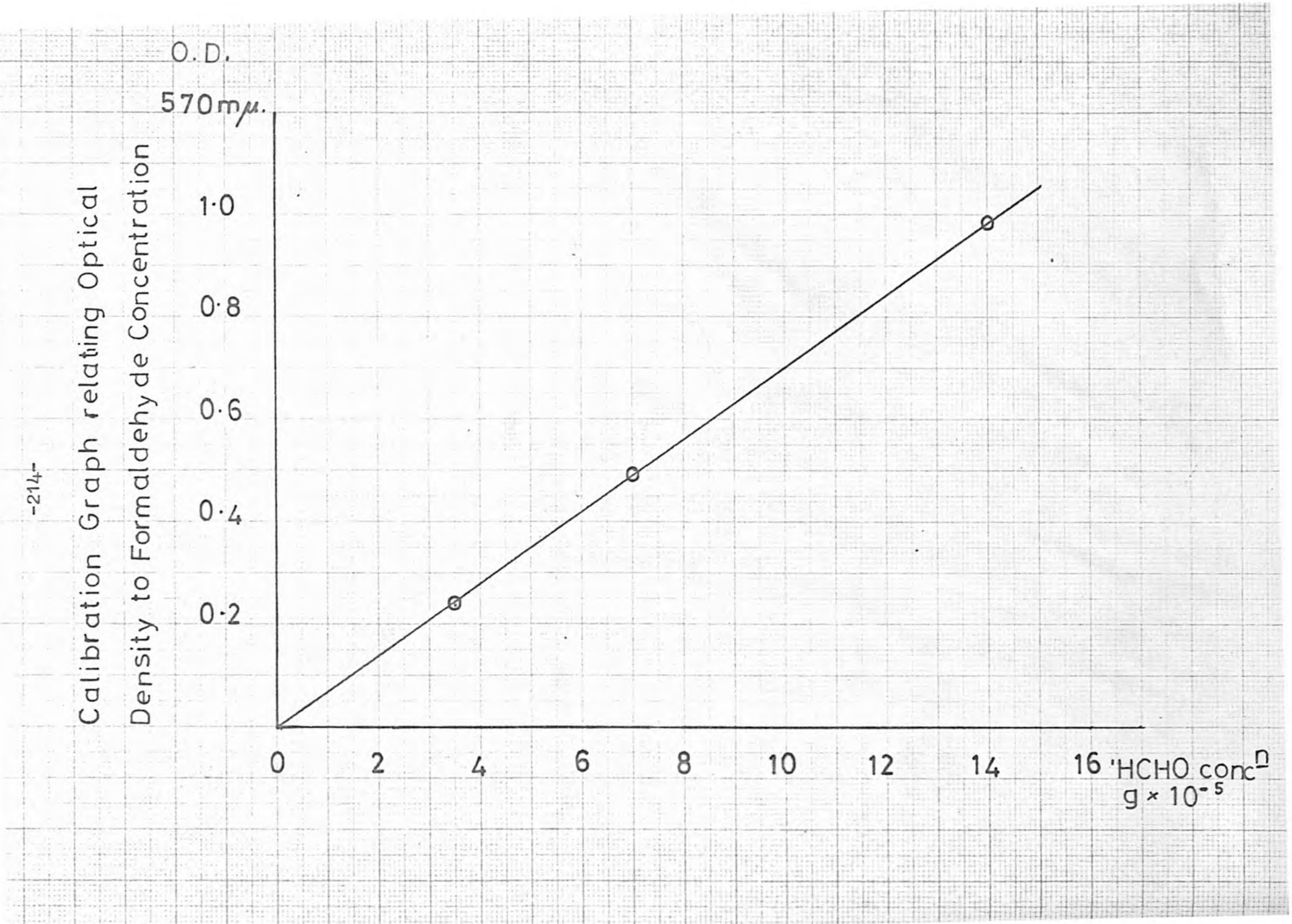
these conditions the 2,5-O-Methylene-Mannitol gave rise to an equimolar quantity of formaldehyde and by plotting optical density against this calculated formaldehyde concentration, a linear calibration graph was obtained.

FORMALDEHYDE CONCENTRATION g/10 ml	OPTICAL DENSITY AT 570 nm
17.47×10^{-5} g	1.24
6.98×10^{-5} g	0.5
3.49×10^{-5} g	0.267

The sample solution prepared from compound 1 had an optical density of 0.955 and from the calibration graph this corresponded to a formaldehyde concentration of 13.5×10^{-5} g/10 ml formaldehyde.

1 mol of compound 1 gave 1.02 mol of formaldehyde on periodate oxidation.

Calibration Graph relating Optical Density to Formaldehyde Concentration



EXPERIMENT 8

Preparation of 1,2:5,6-Di-O-Isopropylidene-D-glucitol (Compound 2)[1]

D-Glucitol (100 g) was shaken with zinc chloride and acetone as in experiment 1 for four hours and the reaction mixture worked up in the same way. The syrup so obtained was then extracted with petroleum ether (BP 80-100°C)(500 ml). The liquid was decanted and cooled to room temperature, a syrup settled out and the solvent again decanted. The solvent was stirred at -12°C and after 12 hours crystals were deposited. These were filtered and recrystallised successively from di-butyl ether and again petroleum ether (BP 80-100°C) to give crystals.

MP 94.5 - 95.5°C

LIT MP 95.0 - 95.5°C

EXPERIMENT 9

Investigation of the syrup first deposited from the petroleum ether in Experiment 8

The syrup (1 g) was freeze dried leaving a syrup which was dissolved in pyridine (20 ml) and this solution was cooled in ice and benzoyl chloride (1.5 ml) was slowly added over 15 minutes. The mixture was left at room temperature for 24 hours and then poured into ice water. A syrup was formed which crystallised on scratching. This was crystallised and recrystallised from ethanol.

MP 134 - 134.5°

YIELD 10.1 g

By comparison with an authentic sample[1] this proved to be the dibenzoate of 1,2:5,6-di-O-Isopropylidene D-Glucitol.

LIT MP 134 - 135°

EXPERIMENT 10

Preparation of the dibenzoate of 1,2-5,6-Di-O-Isopropylidene-D-Glucitol[1]

1,2-5,6-Di-O-Isopropylidene-D-Glucitol (1 g) was dissolved in pyridine (20 ml) and the solution cooled in ice water. Benzoyl chloride (1.5 ml) was slowly added over 15 minutes and the solution left at room temperature for 24 hours. The solution was then poured into ice water giving a syrup which crystallised on scratching and which after successive recrystallisations from ethanol gave white crystals.

MP 134 - 135°

LIT MP 134 - 135°

YIELD 1.6 g

EXPERIMENT 11

Determination of the number of vicinal hydroxyl groups in Compound II by periodate oxidation

The method identical to that used for experiment 6 for compound 1 was used with the following results.

Weight of sodium metaperiodate in 100 ml	= 0.3326 g
Weight of potassium iodate in 100 ml	= 0.3326 g
Weight of compound II taken	= 0.0110 g
Optical Density	= 0.510
% Uptake	= 26.5 %
Molar Uptake	= 1.06 mols
2,5-O-methylene mannitol weight taken	= 0.1011 g
Optical Density	= 0.493
% Uptake	= 36.4 %
Molar Uptake	= 1.01 mols

EXPERIMENT 12

Estimation of formaldehyde liberated by periodate oxidation of compound II

The method used was described in experiment 7.

Result:- Mols of formaldehyde/mol of compound II = 0.0 mols.

EXPERIMENT 13

Preparation of Tri-O-Isopropylidene-D-Glucitol[1,9]

D-Glucitol (20 g) was added to a solution of acetone (250 ml) and concentrated sulphuric acid (2 ml). The D-Glucitol rapidly went into solution and the solution was left at room temperature for 24 hours. The solution was then neutralised with 0.88 ammonia (7 mls) and potassium carbonate (50 g) and the mixture was shaken for 30 mins. The mixture was then filtered and the residue washed with acetone (50 ml). The combined filtrates were concentrated (50 mls) and this was added to ice water (1 l) with vigorous stirring. A syrup was deposited which solidified on scratching. This solid was filtered and recrystallised from aqueous acetone (1:2 made slightly ammoniacal to retard hydrolysis). Fine needles were slowly deposited.

MP 46 - 47°

LIT MP 46°

YIELD 10.7 g

EXPERIMENT 14

Partial acid hydrolysis of Tri-O-Isopropylidene-D-Glucitol[9]

Tri-acetone D-Glucitol (32.3 g) was dissolved in absolute alcohol (792 ml) containing 5 N hydrochloric acid (16.2 ml) and the mixture was left at room temperature for 95 minutes. The mixture was then cooled to 0° and neutralised exactly with barium carbonate. The mixture was filtered and the solid residue washed with ethanol. The combined filtrates were evaporated to a syrup under reduced pressure. The syrup so obtained was extracted with dry acetone cooled in an ice bath. The acetone solution was evaporated to a syrup which was dissolved in ethanol (30 ml) and this ethanolic solution was poured into ammoniacal iced water, the oil which was precipitated soon solidified and was recrystallised from aqueous acetone (2:1) giving fine needles.

MP 46 - 47°

YIELD 1.1 g

By melting point and mixture melting point this was shown to be identical with the starting material.

The aqueous solution from above was evaporated to a syrup which was extracted with cold benzene leaving a solid which was recrystallised from acetone giving a solid.

MP 89 - 90°

LIT MP 89 - 90°

YIELD 0.75 g

This is compound III.

The benzene solution was evaporated to a syrup which was distilled at 0.1 mm and 110-112°C giving a colourless syrup as distillate. This was crystallised from petroleum ether (BP 40 - 60°C) giving white crystals.

MP 56 - 57°

LIT MP 56 - 56.5°

YIELD 0.8 g

This is compound IV.

After distillation a colourless residue remained this is compound V.

EXPERIMENT 15

Determination of the number of vicinal hydroxyl groups in Compounds III and IV by periodate oxidation

A method identical to that used in experiment 6 for compound I was used with the following results.

Weight of sodium metaperiodate in 100 mls water = 0.3326 g

Weight of potassium iodate in 100 mls water = 0.3326 g

Weight of compound III taken = 0.0097 g

Weight of compound IV taken = 0.0067 g

COMPOUND	OPTICAL DENSITY	% UPTAKE	MOLAR UPTAKE
III	0.352	53.5 %	1.90
IV	0.566	16.5 %	1.08

Uptake of 2,5-O-Methylene-Mannitol

Weight taken = 0.01011 g

Optical Density = 0.453

% Uptake = 36.4 %

Molar Uptake = 1.01 mols

EXPERIMENT 16

Estimation of formaldehyde liberated by the periodate oxidation of compounds III and IV

The method was repeated as for experiment 7.

Mols of formaldehyde liberated per mol of compound III = 1.99 mols

Mols of formaldehyde liberated per mol of compound IV = 1.1 mols

EXPERIMENT 17

Investigation of the syrup left after the distillation

COMPOUND V

The syrup left after the vacuum distillation did not crystallise and was shown to be a mixture of two compounds by vapour phase chromatography (in poly phenoxy-phenoxy benzene on silicone treated celite (p.p.e.) at 175°).

The syrup was subjected to periodate oxidation in the usual way. The mixture (0.5 g) was dissolved in sodium metaperiodate (0.5 M 50 mls) and left in the dark for 24 hours at room temperature, the solution was then neutralised, saturated with sodium chloride and extracted with chloroform. The chloroform solution was dried and evaporated to a syrup which was dissolved in 50% aqueous ethanol (50 mls) and warmed on a water bath with 1R 120H$^+$ resin (0.5 g) for 1 hour. The resin was filtered off and the ethanolic solution evaporated to a syrup. The syrup so obtained was spotted on paper and subjected to descending liquid chromatography using butanol/pyridene/water (6/4/3).

Using standards the syrup was shown to contain xylose and arabinose. (No Rf values can be quoted in this case as it is necessary to allow the solvent front to run off the paper to obtain separation).

EXPERIMENT 18

Analysis of the Zinc Chloride catalysed reaction between D-Glucitol and Acetone using Vapour Phase Chromatography

Experiment 1 was repeated on 0.005 of the original scale and the reaction was stopped by the addition of sodium hydroxide (2 ml of 5 NORMAL) after 5 minutes, 15 minutes, 30 minutes and 3 hours. The samples were evaporated to dryness and extracted with pyridine. The pyridine extracts were dried and aliquots were converted into their trimethyl silyl ethers in the usual way[10]. These were analysed by vapour phase chromatography using a 10% ppe column at 173°

SAMPLE TIME	R.V of peaks relative to D-GLUCITOL
5 mins	1; 1.24; 1.56
15 mins	1; 1.24; 1.38; 1.53; 1.80
30 mins	1; 1.24; 1.38; 1.53; 1.80
3 hrs	1; 1.23; 1.38; 1.48; 1.77; 2.23 and a shoulder at 1.92

Standard Isopropylidene D-Glucitols gave the following results.

R.V 1 = D-GLUCITOL

R.V 1.24 = 1,2-O-Isopropylidene-D-Glucitol

R.V 1.38 = 3,4-O-Isopropylidene-D-Glucitol

R.V 1.48 = 1,2;5,6-Di-O-Isopropylidene-D-Glucitol

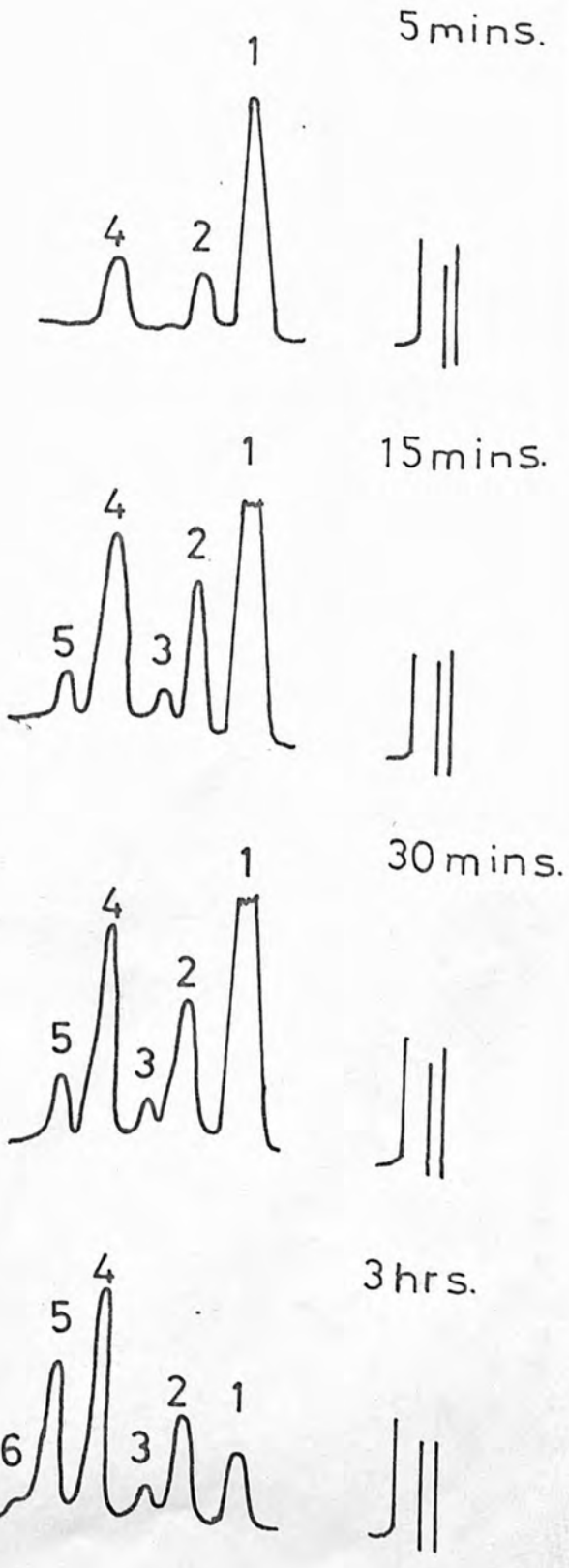
R.V 1.77 = 1,2;3,4-Di-O-Isopropylidene-D-Glucitol

R.V 1.92 = 3,4;5,6-Di-O-Isopropylidene-D-Glucitol

R.V 2.23 = Tri-O-Isopropylidene-D-Glucitol

Fig.1

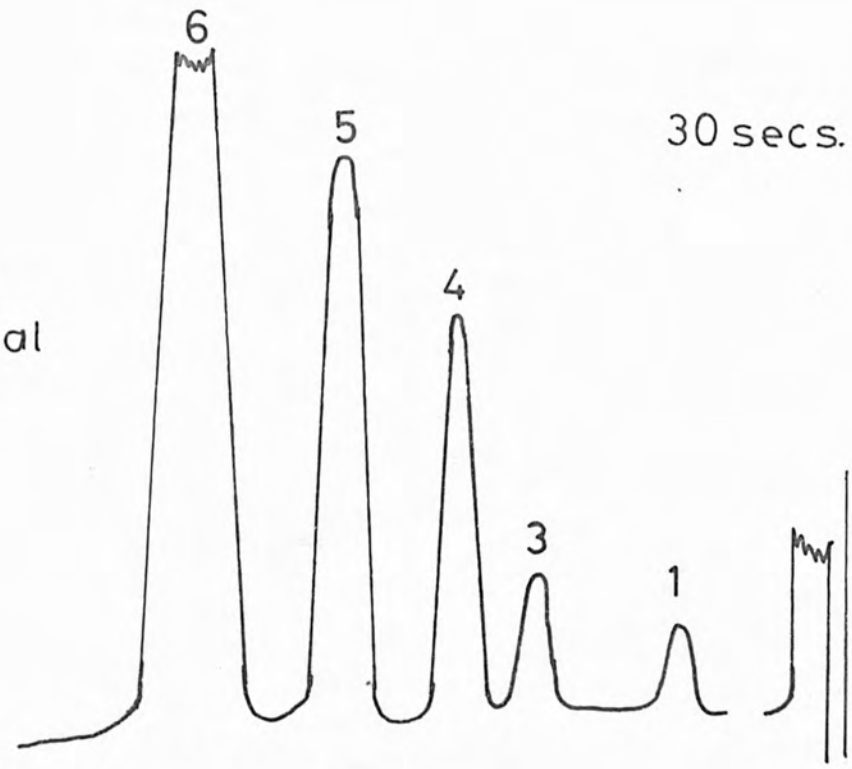
Anhydrous Zinc Chloride Catalysed Reaction of D-Glucitol and Acetone



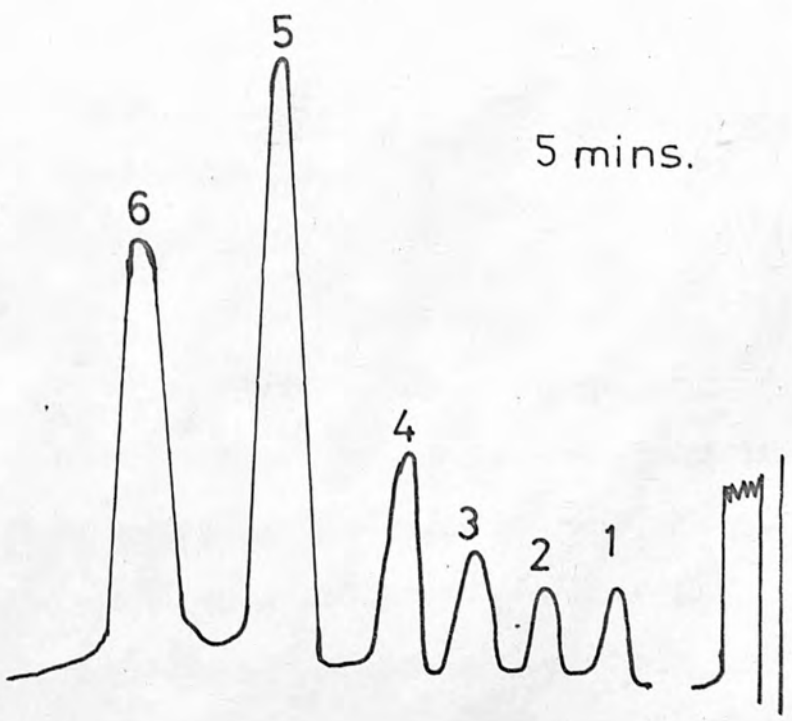
1. D-Glucitol
2. 1,2-mono-ketal
3. 3,4 " "
4. 1,2;5,6 di-ketal
5. 1,2;3,4 " "
6. 3,4;5,6 " "
7. 1,2;3,4-5,6 tri-ketal

Sulphuric Acid Catalysed Reaction of D-Glucitol and Acetone

1. D-Glucitol
2. 1,2 mono-ketal
3. 3,4 " "



4. 1,2;5,6 di-ketal
5. 1,2;3,4 " "
6. 1,2;3,4;5,6 tri--ketal



EXPERIMENT 19

Analysis of the sulphuric acid catalysed reaction between D-Glucitol and Acetone by Vapour Phase Chromatography

D-Glucitol (1 g) and acetone (10 ml) were mixed and concentrated 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 yielding a syrupy solid which was extracted with pyridine (1 ml). The pyridine solution (0.2 ml) was used to prepare the trimethyl silyl derivatives[10] which were analysed by vapour phase chromatography.

TIME	R.V relative to D-Glucitol
30 sec.	1; 1.32; 1.84; 2.29; 2.79
PEAK RATIOS	1: 1.6 : 6.5 : 8.5 : 34
5 mins	1; 1.1; 1.32; 1.84; 2.29; 2.79
PEAK RATIOS	1: 1 : 1.23: 2.76:10.95: 6.517

Standards show R.V 1 = D-Glucitol

1.1 = 1,2-O-Isopropylidene-D-Glucitol

1.32 = 3,4-O-Isopropylidene-D-Glucitol

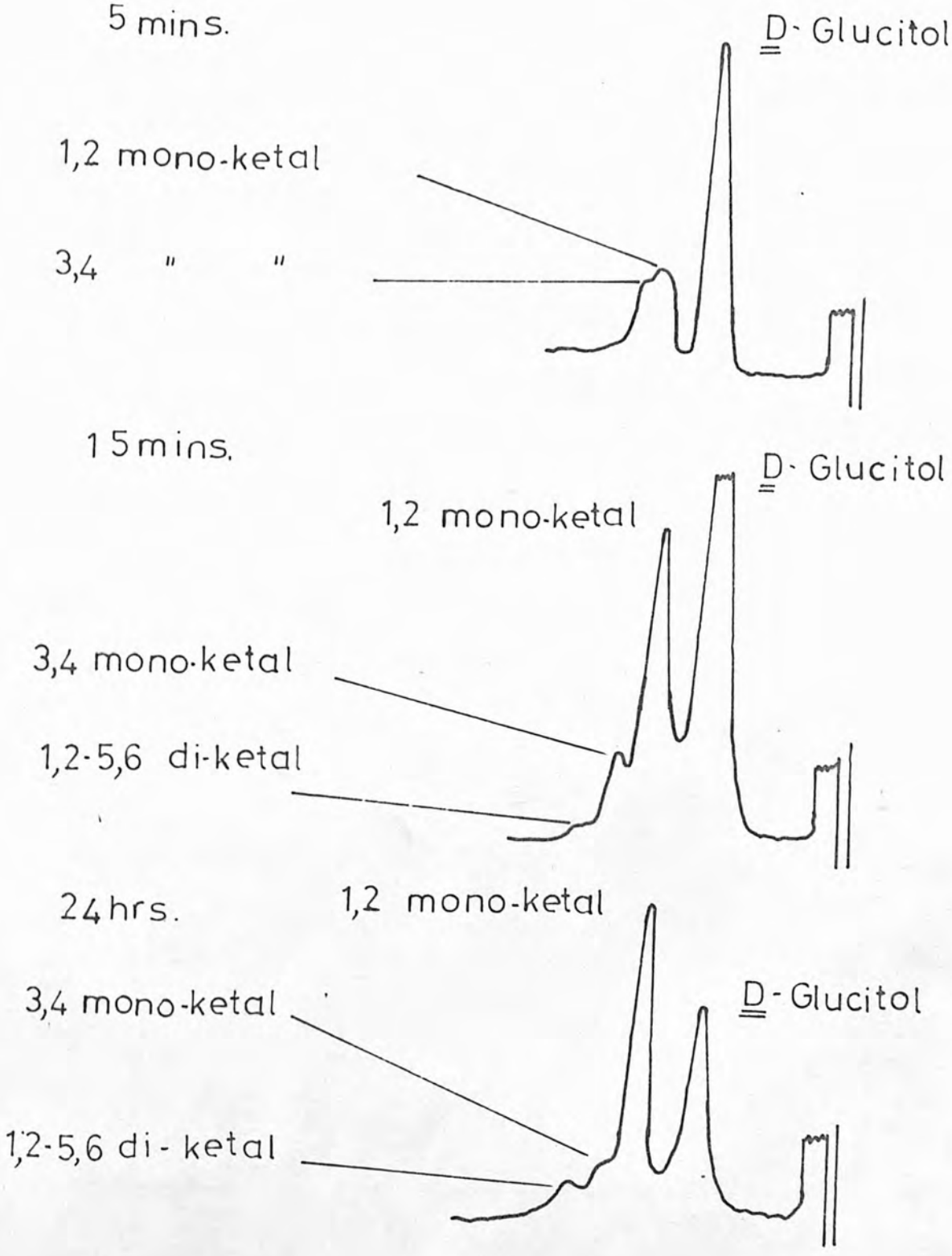
1.84 = 1,2;5,6-Di-O-Isopropylidene-D-Glucitol

2.29 = 1,2;3,4-Di-O-Isopropylidene-D-Glucitol

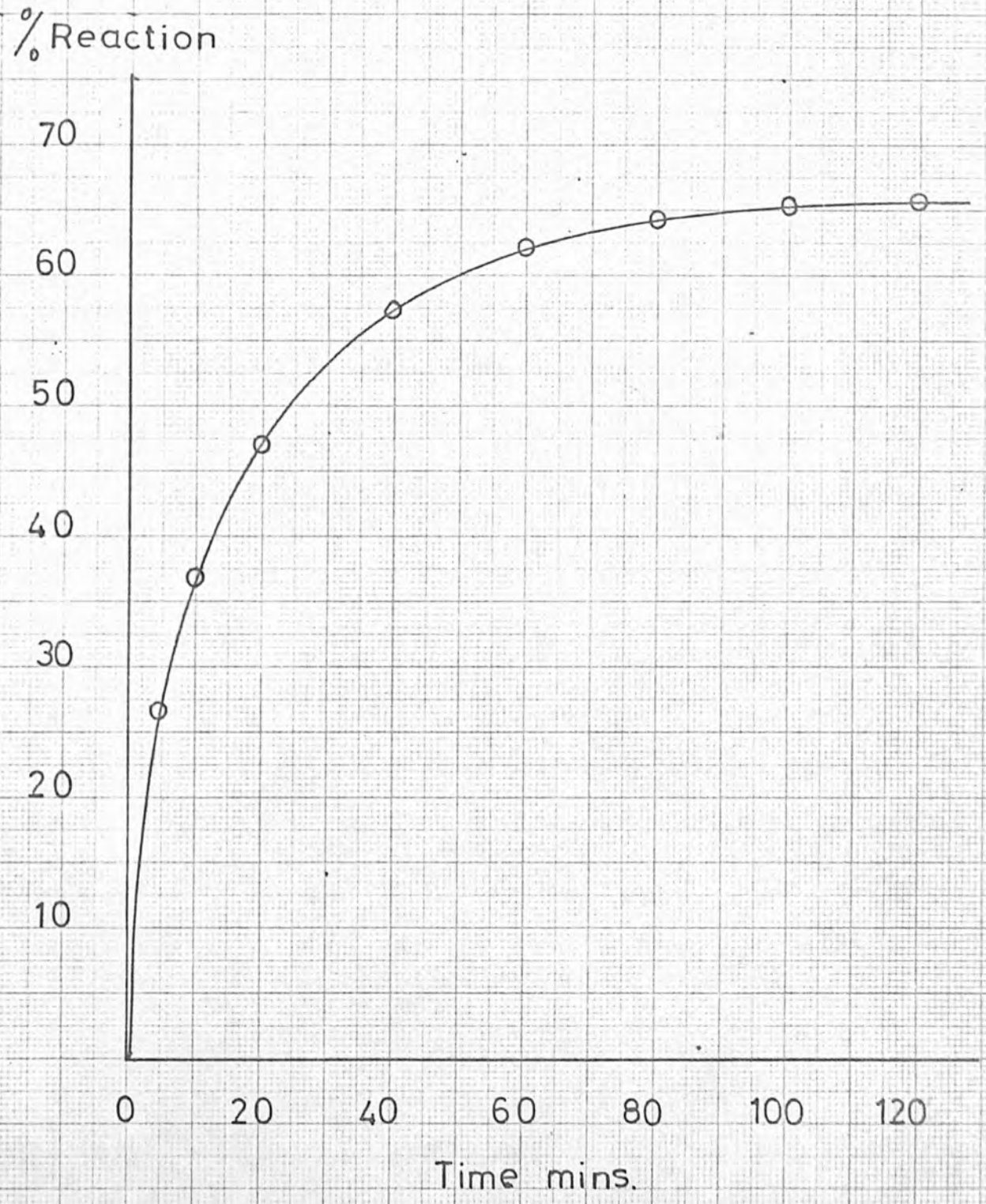
2.79 = Tri-O-Isopropylidene-D-Glucitol

Samples taken at 15 minutes, 20 minutes, 30 minutes, 60 minutes and 3 hours showed no change in the number of constituents but a higher proportion of tri-O-isopropylidene-D-Glucitol while the others decreased.

Reaction of D-Glucitol and Acetone (1:1 molar) in Anhydrous D.M.F/HCl (1·1 M) at 25°



Reaction of D-Glucitol and Acetone (1:1 molar) in Anhydrous D.M.F. / HCl (1·1 M) at 25°.



EXPERIMENT 20

Reaction between D-Glucitol and Acetone in D.M.F./HCl

D-Glucitol (10 g) was dissolved in 1.11 N HCl/DMF and acetone (4.035 ml) was added and the mixture made up to 100 mls. Thus giving a 1:1 solution of acetone and D-Glucitol.

Samples were removed at intervals and analysed by vapour phase chromatography in the normal way.

Peaks at RV = 1 = D-Glucitol

RV = 1.1 = 1,2-O-Isopropylidene-D-Glucitol

RV = 1.32 = 3,4-O-Isopropylidene-D-Glucitol

RV = 1.84 = 1,2:5,6-Di-O-Isopropylidene-D-Glucitol

The 3,4-mono-and 1,2:5,6-Di-O-Isopropylidene ketals were only in trace amounts.

EXPERIMENT 21

Preparation of 5,6-O-Isopropylidene L-Glucitol (COMPOUND VI)

A direct reaction between D-Glucitol and acetone had failed to give the above compound.

(a) Preparation of 2,4-Benzylidene D-Glucitol[11,12]

D-Glucitol (25 g) was dissolved in water (25 ml) and concentrated hydrochloric acid (25 ml) was added followed by benzaldehyde (13.5 g). This mixture was shaken for seven hours and then cooled in ice water and filtered. The residue was washed with ice water and recrystallised from ethanol. Fine needles were precipitated and filtered before the gelatinous dibenzylidene D-glucitol formed.

MP 172 - 173.5°C

LIT MP 176 - 177°C

On recrystallisation from aqueous ethanol (1:6) the MP rose to 176-177°C. This is because the initial material must be contaminated with the diacetal.

$(\alpha)_D^{21^\circ C}$ = -1.1 (c 1.5 in H_2O)

(b) Preparation of 2,4-O-Benzylidene-5,6-O-Isopropylidene-D-Glucitol[11]

2,4-O-Benzylidene-D-Glucitol (10 g) was dissolved in acetone (200 ml) and anhydrous copper sulphate (20 g) was added. This mixture was shaken for 24 hours. The mixture was then filtered and the filtrate concentrated to give a white solid which was recrystallised from benzene giving a white crystalline compound. This was recrystallised four times from benzene which raised the melting point 4°C.

MP 183-183.5°

LIT MP 179-179.5°

YIELD 10.3 g

ANALYSIS	CALCULATED	%C	61.92	%H	7.145	%O 30.933
	ACTUAL	%C	61.89	%H	7.15	%O 30.96

(c) Hydrogenation of 2,4-O-Benzylidene 5,6-O-Isopropylidene D-Glucitol

2,4-O-Benzylidene 5,6-O-Isopropylidene-D-Glucitol (5 g) was dissolved in dry methanol and palladium black (5 g) was added as catalyst for hydrogenation. Hydrogenation was carried out at low pressure (4-6 atmospheres) until no further hydrogen was taken up. The palladium black was filtered off under nitrogen and the filtrate evaporated under reduced pressure giving a colourless syrup which crystallised to a white crystalline solid, which could not be readily recrystallised. Vapour phase chromatography showed it to be pure RV 1.58 (5% apeigon K 195°) and different from any other mono Isopropylidene-D-Glucitol. The compound decomposed rapidly with the liberation of acetone and the formation of D-Glucitol so that no satisfactory C/H analysis was obtained.

MP 46-48°

$(\alpha)_D^{25}$ + 10.8 (c 1.05 in pyridine)

EXPERIMENT 22

Analysis of Compound VI

(a) Determination of vicinal hydroxyls by periodate oxidation

The method identical to that used in experiment 6 for compound 1 was used with the following results.

Molar uptake = 2.98 mols

(b) Determination of liberated formaldehyde from periodate oxidation

The method was repeated as for experiment 7.

Mols of formaldehyde liberated/mol of compound = 0.99 mols.

EXPERIMENT 23

The acid hydrolysis of Tri-Isopropylidene-D-Glucitol[9]

(Experiment 14) was repeated and analysed by quenching at intervals and analysing the samples so produced by vapour phase chromatography as their trimethyl silyl ethers (5% Apeigon K 195°C). The initial stages were those of the most interest and showed that the initial product of hydrolysis was a compound of RV 1.77, which was shown by comparison with a standard to be the 1,2:3,4 di-O-isopropylidene D-Glucitol.

CHAPTER 2

Physical investigations into the structures of Acetone ketals of D-glucitol

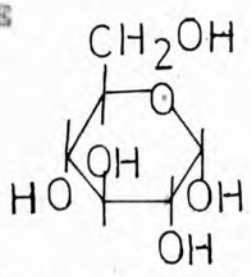
MASS SPECTROMETRY OF ACETALS AND KETALS

INTRODUCTION

The structure of the acetals and ketals of monosaccharides depends on the stereochemistry of the parent monosaccharides. Therefore the acetals and ketals of various stereoisomeric monosaccharides i.e. D-glucose; D-mannose and D-galactose, will be structural isomers. For the preferential formation of the acetals and ketals a cis 1,2-or cis 1,3-diol system is required. Thus epimers will give derivatives which differ in actual bonding and are no longer merely stereoisomers but structural isomers and therefore mass spectrometry can be a very useful method for the determination of structure.

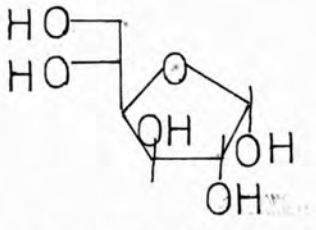
Empirically it is seen that ketals preferentially contain 1,3-dioxolane ring systems and acetals the 1,3-dioxane ring system. Therefore we might predict the stereochemistry of the ketals and acetals of monosaccharides.

GLUCOSE



ONE cis-1,2-diol

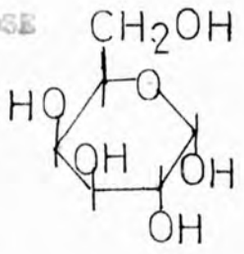
TWO cis-1,3-diol



ONE cis 1,2 diol

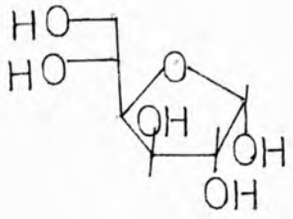
Thus for α -D-glucose to form ketals the furanose form should be favoured while the formation of the acetal should favour the pyranose

with the formation of a 4,6-acetal.

GALACTOSE 

TWO cis 1,2-diols

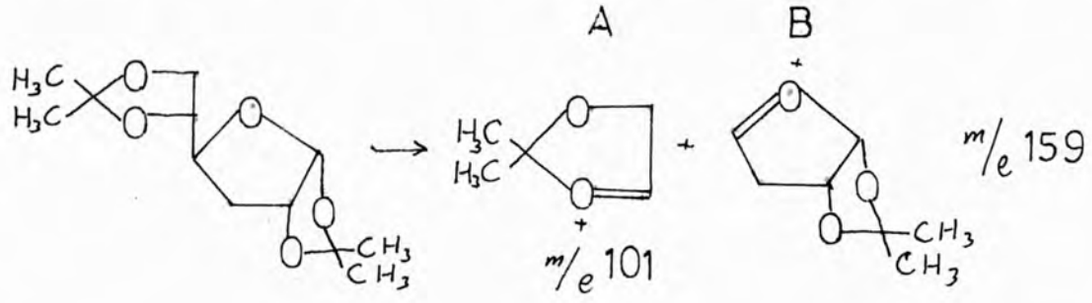
ONE cis 1,3-diols



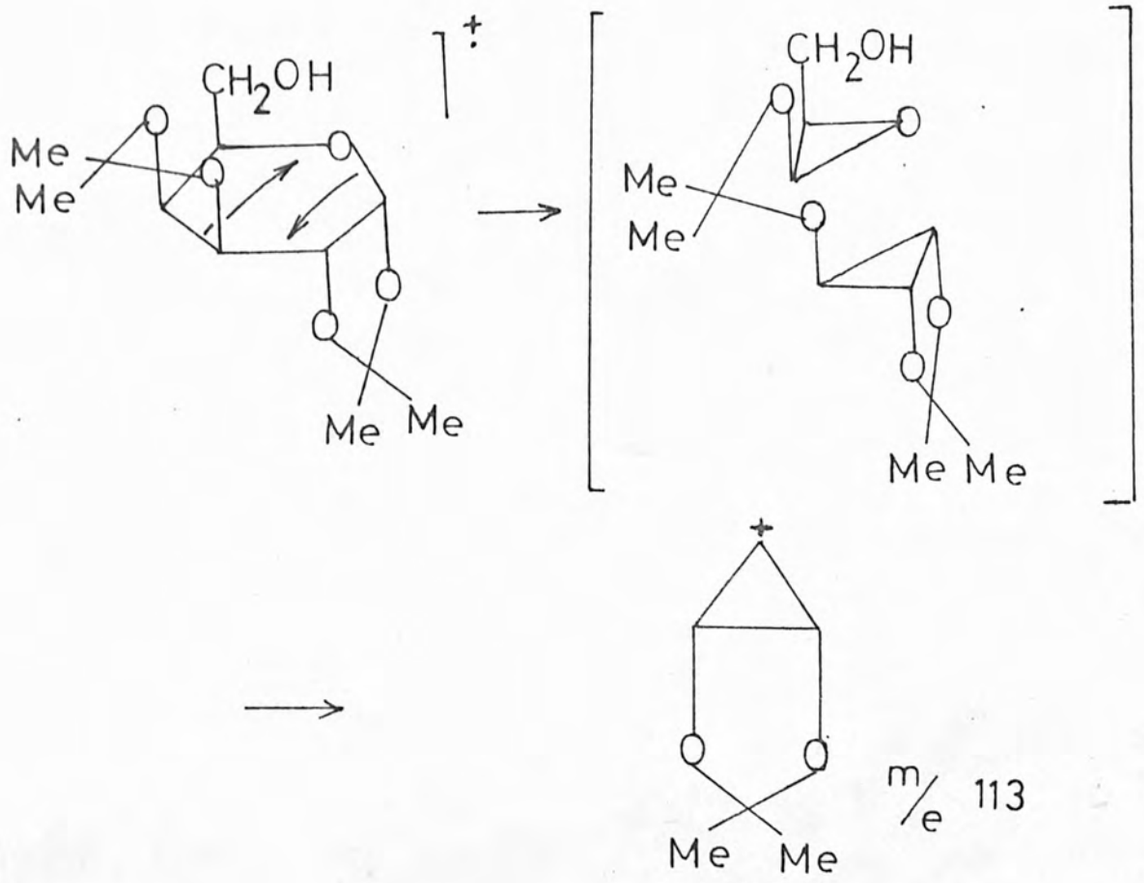
ONE cis 1,2-diol

Galactose should form both ketals and acetals in the pyranose form rather than the furanose form. These facts which have been shown to be correct by routine chemical techniques can be further substantiated by mass spectrometry.

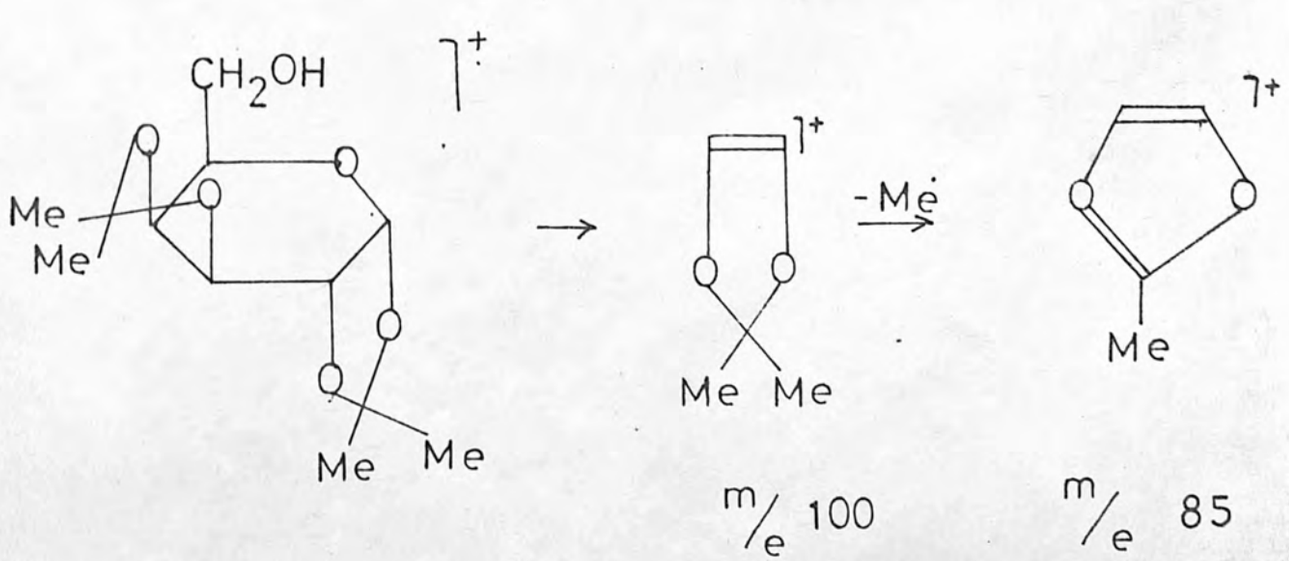
Thus the reaction between the above monosaccharides and acetone under mineral acid catalysis yields crystalline di-ketals, which have been classified as 1,2;5,6-di-O-isopropylidene α-D-glucofuranose and 1,2;5,6-di-O-isopropylidene α-D-galactopyranose. By considering the mass spectra the chemical evidence is substantiated[19].

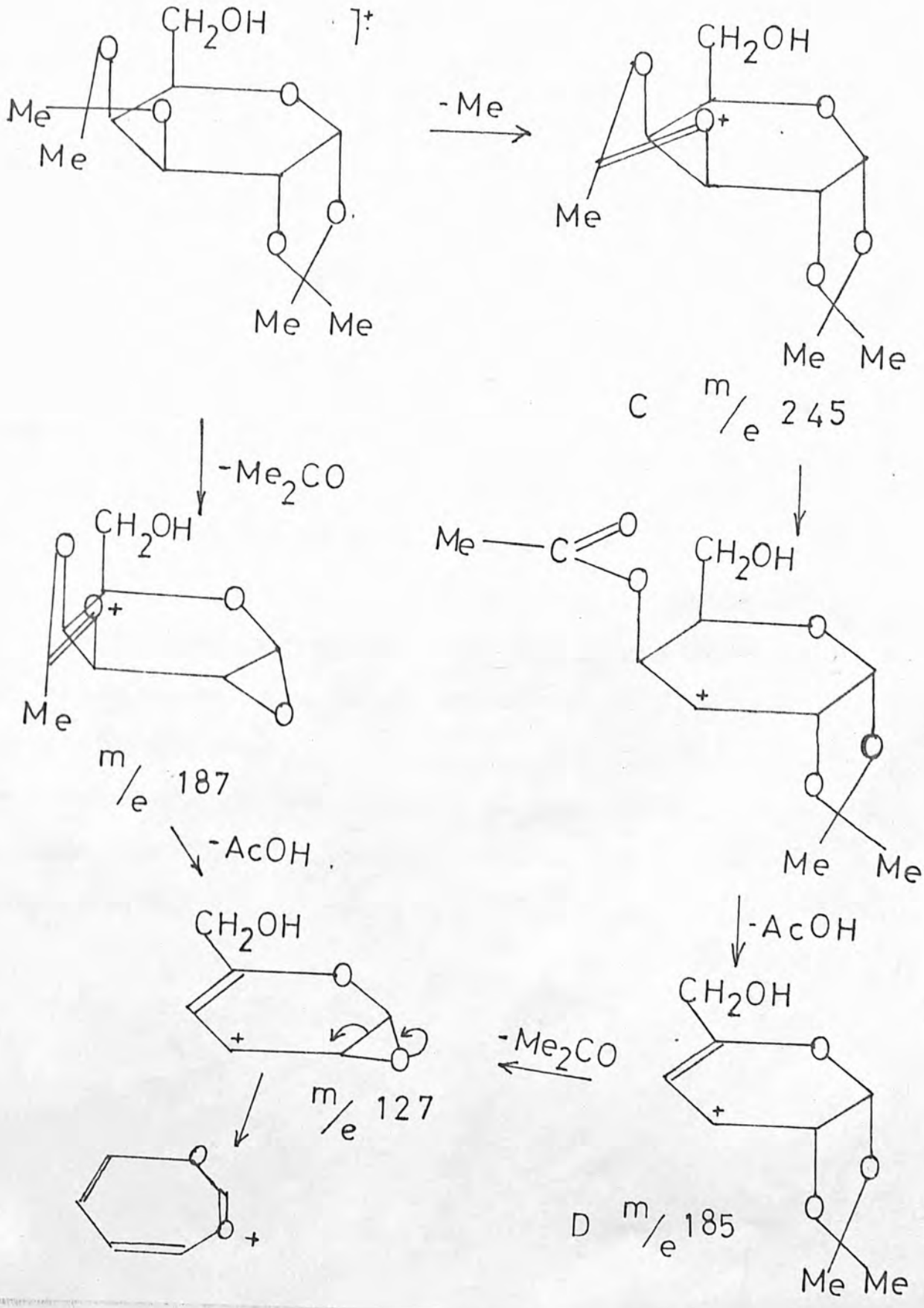


Both these fragments (A and B) further fragment forming fragments characteristic of all monosaccharide isopropylidene ketals.


CH2OH
Me
Me
Me Me
CH2OH
Me
Me
Me Me

Me Me
m/e 113


CH2OH
Me
Me
Me Me
-Me
Me
Me Me
m/e 100
m/e 85


CH2OH
Me
Me
Me Me
-Me
Me
Me Me
C m/e 245
-Me2CO
Me — C
CH2OH
Me
m/e 187
-AcOH
CH2OH
m/e 127
-AcOH
CH2OH
-Me2CO
D m/e 185
Me Me

This shows the greater complexity of fragmentation of the pyranose form although fragments C and D are common to both but much less intense as the fragmentation giving A and B predominates.

This example shows how mass spectra can be used to distinguish and also show the stereochemistry of structural isomers.

With acetals a similar process can be seen so that the stereo-isomerism can be elucidated.

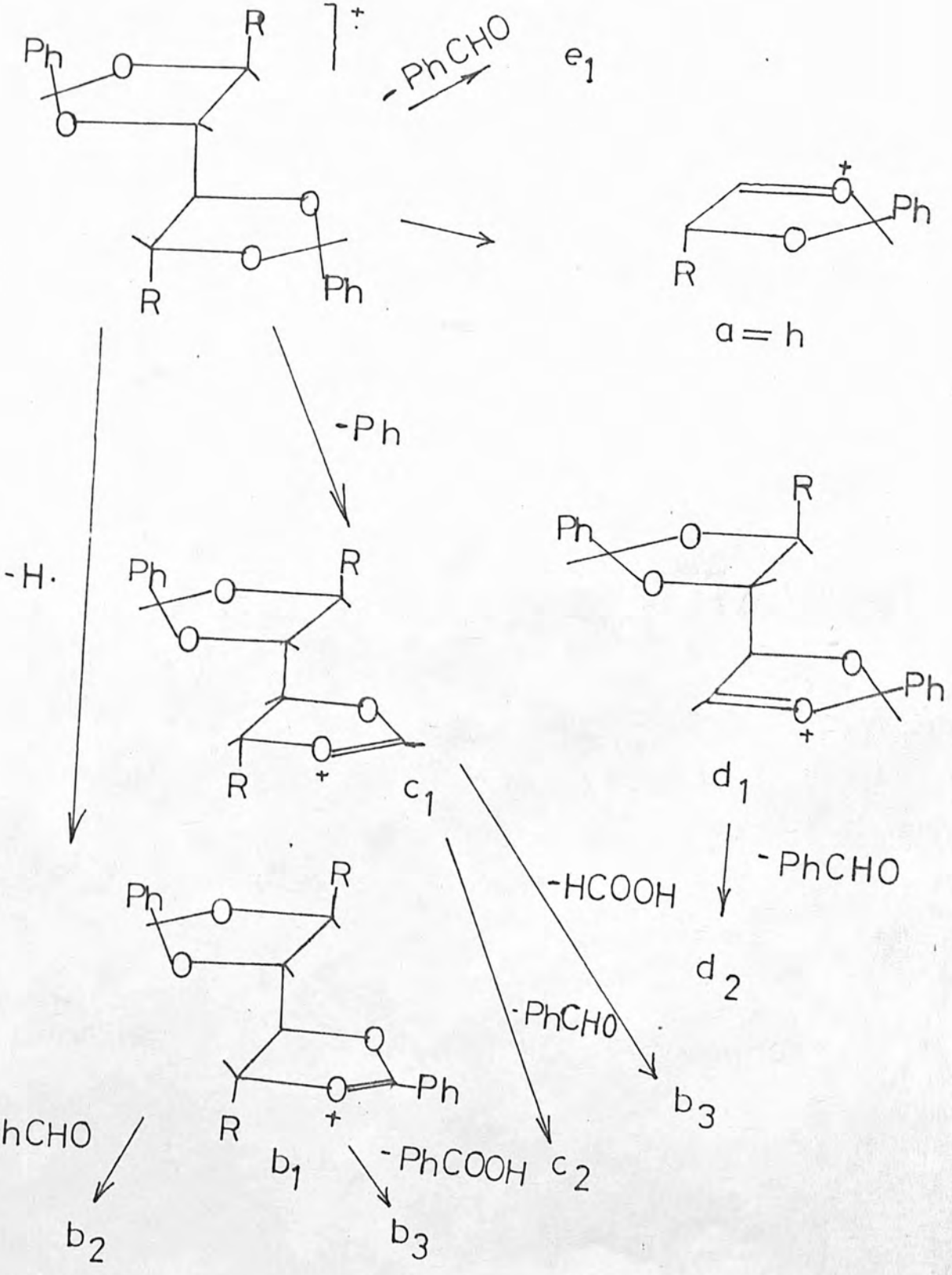
When however we consider not the aldoses bu the alditols[20] the nature of the problem changes.

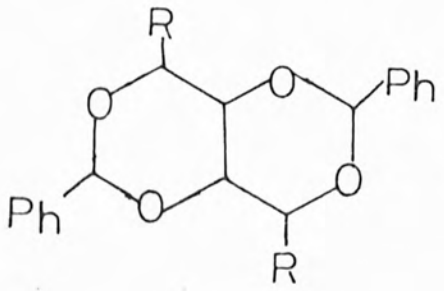
The ion 'a' in the case of a symetrical molecule has $\frac{m}{e} = \frac{M}{2}$ and would be expected for the system containing two non-fused 1,3 dioxolane rings.

If we consider the analagous system containing the fused 1,3 dioxane rings the absence of 'h' would show the difference directly.

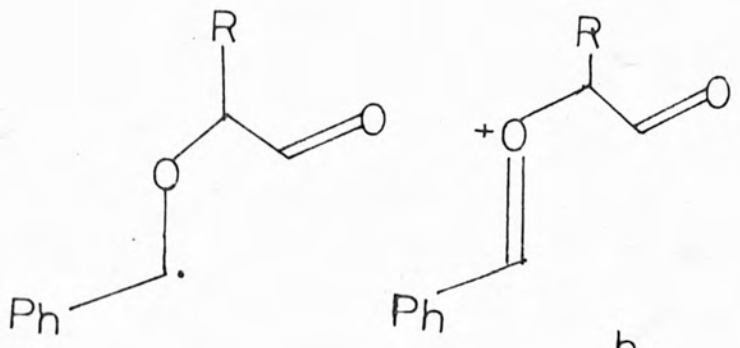
Thus it is not the formation of $h = \frac{M}{2}$ which will characterise the compound but its ability to form f_1 and subsequently f_2 and f_3 which will show the difference.

Consequently the determination of the stereochemistry of acetals and ketals of alditols requires a more detailed study of the mass spectrum than does a similar study of a similar aldose series.


-PhCHO
e1
a = h
-Ph
-H·
c1
d1
-PhCHO
d2
-HCOOH
-PhCHO
b3
-PhCHO
b1
-PhCOOH
c2
b2
b3

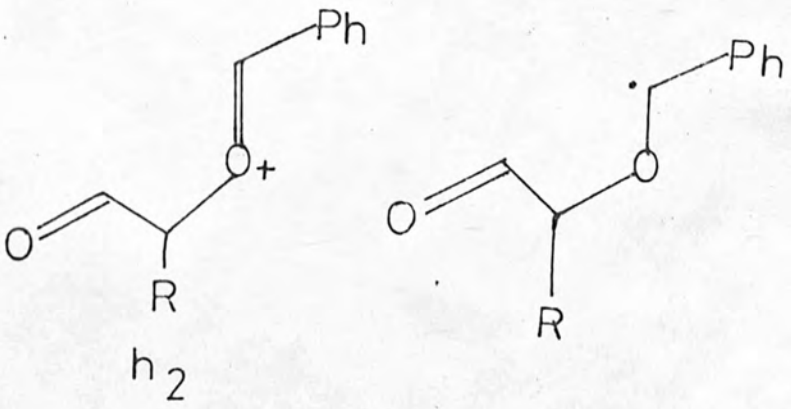


ions corresponding to 'a', 'b', 'c', 'd'.



h_1

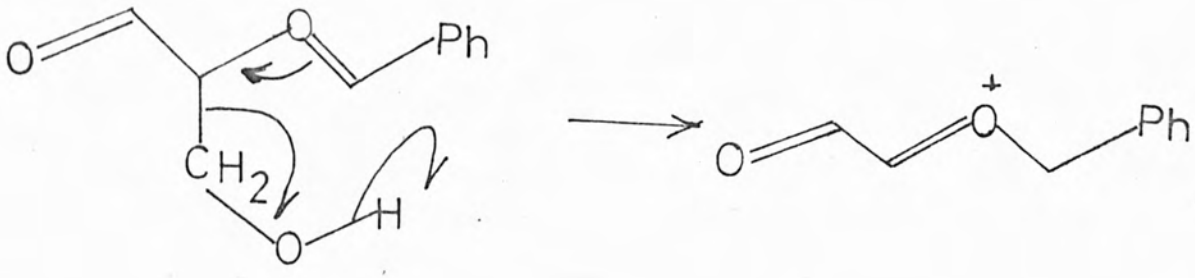
+ +



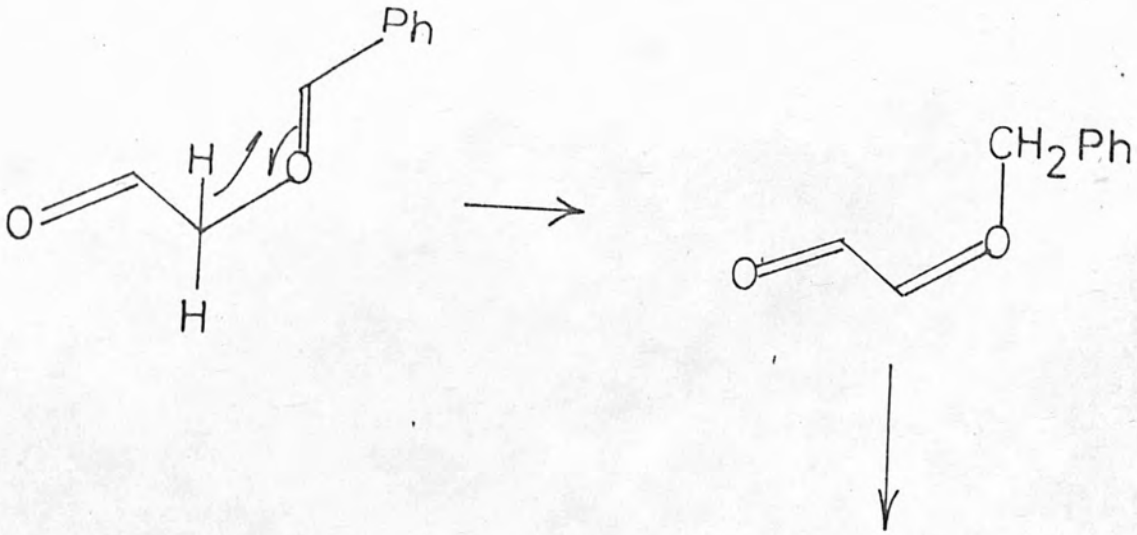
h_2

Depending on R, h_1 & h_2, the ion rearranges.

R = CH_2OH

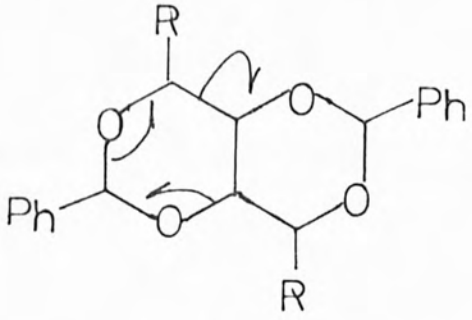


R = H

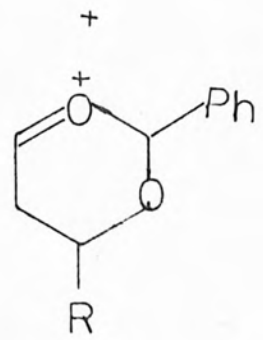


OCH—CHO + CH_2Ph

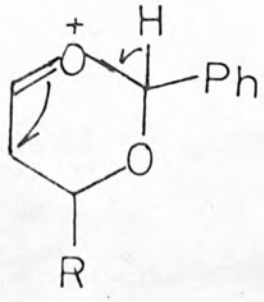
Fragmentation also occurs as follows:



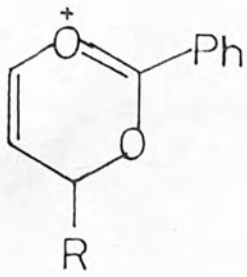
$\longrightarrow$ PhCHO + RCHO



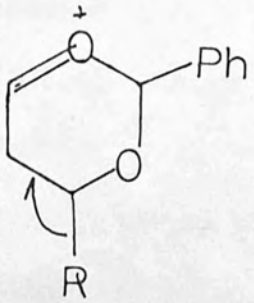
f_1



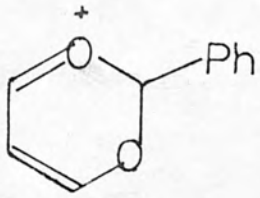
$\longrightarrow$



f_2



$\longrightarrow$



f_3

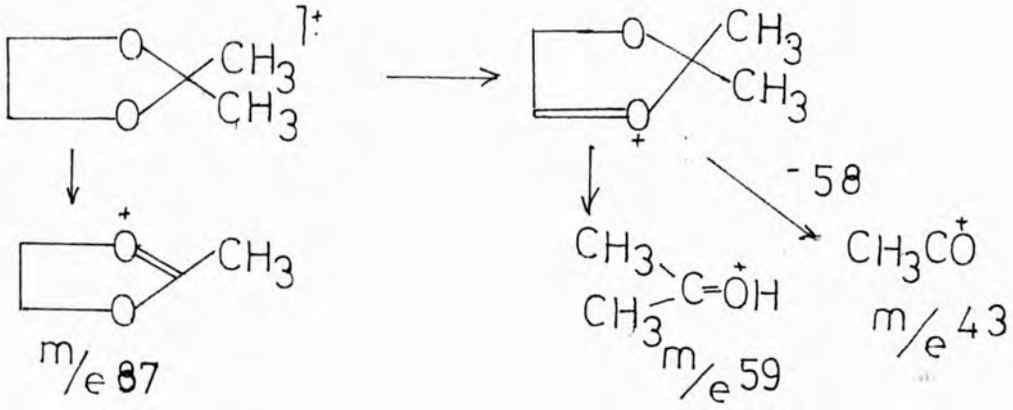
RESULTS

(i) 2,2 DIMETHYL DIOXOLAN

The mass spectrum of 2,2 dimethyl dioxolan (FIG 1) exhibits a small mass peak M^+ at $\frac{m}{e}$ 102 together with the intense peak at $\frac{m}{e}$ 101 which corresponds to the loss of a proton.

The most significant peaks however occur at $\frac{m}{e}$ 43, 59 and 87.

Thus we could conclude that the fragmentation pattern was follows.



This fragmentation should appear as part of the significant fragmentation pattern of all isopropylidene ketals if the so far assumed structures are correct.

(ii) MONO-KETALS

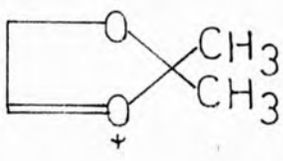
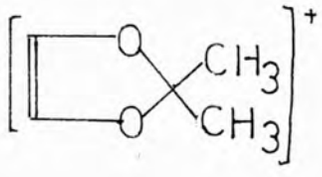
The fragmentation patterns of 1,2-O-isopropylidene and 3,4-O-isopropylidene-D-Glucitol will be considered together with mention of the differences.

In many respects their spectra are similar; there are however enough differences to be able to differentiate the two compounds.

The M^+ peak is small and common to both at $\frac{m}{e}$ 222 likewise M-15 at $\frac{m}{e}$ 207.

Losses in the form of fragments of the free carbohydrate chain i.e. $\frac{m}{e}$ 31, $\dot{C}H_2$-OH are again common to both as are the fragmentations of the single ketal ring as described previously giving the peaks $\frac{m}{e}$ 43, 59 and 73. The differences however can be seen in the replacement of the $\frac{m}{e}$ 101 peak of the 1,2-O-isopropylidene-D-glucitol by $\frac{m}{e}$ 100 peak of the 3,4-O-isopropylidene-D-glucitol.

Thus

$\frac{m}{e}$ 101  is replaced by $\frac{m}{e}$ 100 

Thus indicating its position at the middle of the carbohydrate chain rather than at the extremity.

Further 3,4-O-isopropylidene-D-glucitol has a large peak at $\frac{m}{e}$ 103 which may be the loss of acetone and $\dot{C}H_2$-OH

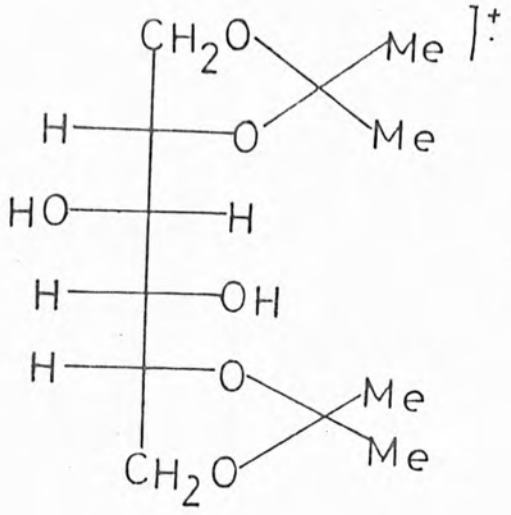
CH -OH

i.e. M - (58 + 61) from the mass ion.

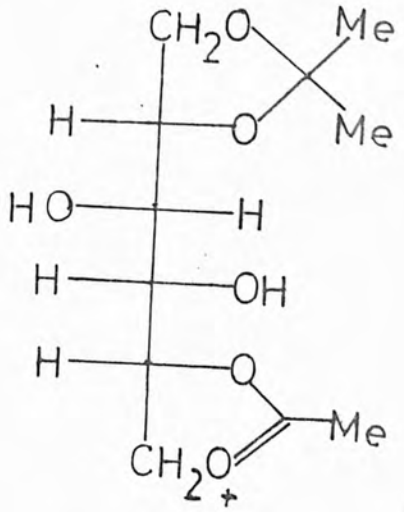
(iii) 1,2:5,6 DI-O-ISOPROPYLIDENE-D-GLUCITOL

This compound exhibits a fragmentation pattern which is quite different and characteristic of this compound, thus showing that the rings are separated by more than a single C-C bond.

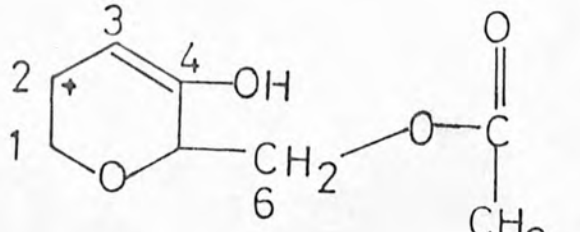
This compound has a notable peak at $\frac{m}{e}$ 229 which is not present in the other ketals and also $\frac{m}{e}$ 171.

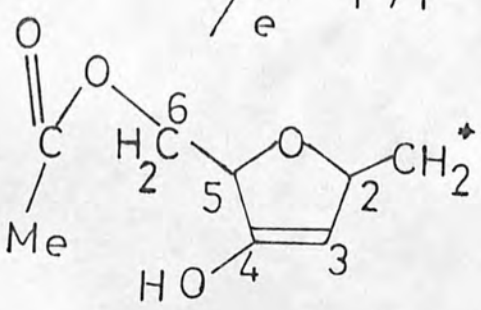


- Me
- 15

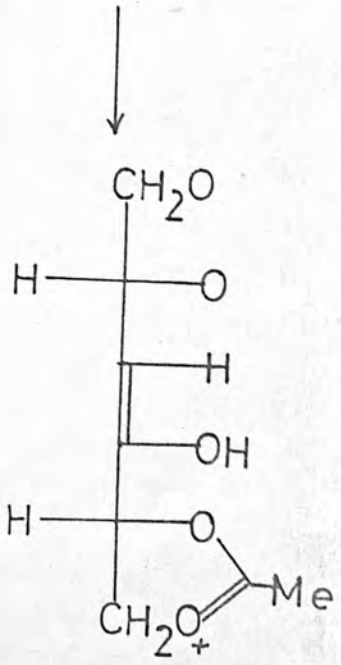


m/e 247



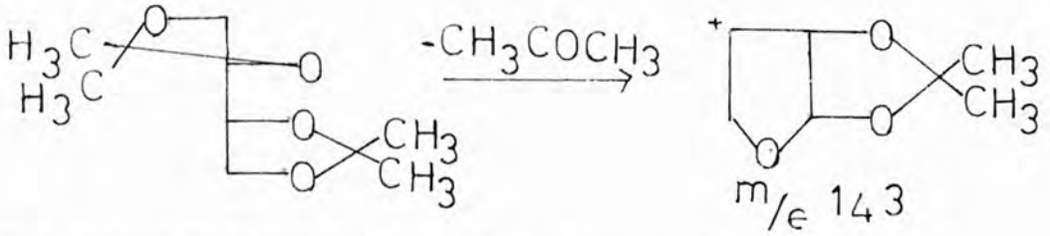


m/e 171



m/e 229

The other fragments are identical to those of all other ketals. Further fragmentations which are not characteristic of the other molecules are then the fragmentations of the ion $\overset{m}{e}$ 201 and in particular $\overset{m}{e}$ 143.



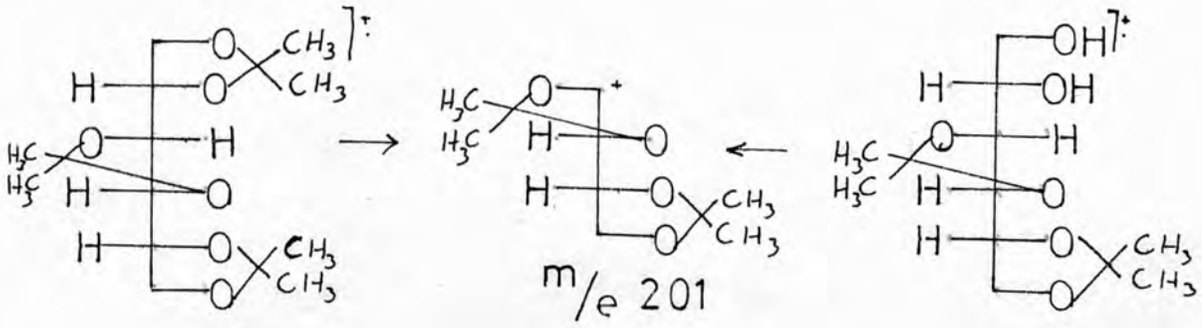
(iv) TRI-ISOPROPYLIDENE-3,4;5,6 DI-O-ISOPROPYLIDENE-D-GLUCITOL

In these two compounds we have adjacent rings and we can see this fact in the fragmentation pattern so that further structural evidence can be elucidated.

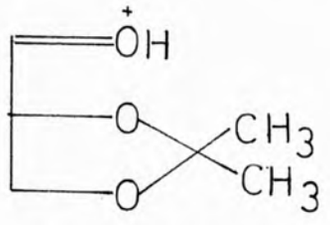
For 3,4;5,6 di-O-isopropylidene-D-glucitol we can see the fragmentation patterns which characterise the fragmentation of the single ring together with losses from the free chain. While the presence of the peak at $\overset{m}{e}$ 247 shows that the compound is a di-ketal.

The triketal shows a peak at $\overset{m}{e}$ 287 showing it to contain 3 ketal rings and the absence of peaks at 30 or 31 showing the absence of free carbohydrate chain.

Thus although both molecules contain adjacent ketal rings they can be identified. Apart from this the main patterns would appear to be the same.



One further peak is characteristic of the above diketal and also 1,2-O-isopropylidene-D-glucitol which is not common to the others, this is m/e 131. For this we would require clearage of the C_3 - C_4 bond.



This could also be present for a molecule where the ketal spans C_2 - C_3 thus leaving primary hydroxyl on C_1 free. This however can be discounted in these cases from the other evidence.

DISCUSSION

The classical techniques of partial acid hydrolysis and qualitative and quantitative periodate oxidation had determined the structure of the isopropylidene ketals of L-Glucitol the assumption being made that during the chemical processes there had been no rearrangement. The mass spectral studies on the ketals has further clarified the picture so that we can see that the complete series of ketals contain non-fused 1,3-dioxolan ring systems as had been previously postulated. The mass spectra show further that the position of the rings in the incompletely substituted ketals is also the same as determined by chemical techniques. Thus, the mass spectral studies have been complimentary to the chemical analyses as long as there has been no rearrangement under the instrumental conditions.

Instrumental conditions:- Mass spectra were all run by the University of London Intercollegiate Research Service at The School of Pharmacy.

Temperature 250°, Electron volts 70, Insertion mode - Direct

EXPERIMENTAL

(a) To simplify the analysis the mass spectrum of 22 dimethyl dioxolan was first considered.

Preparation of 22-Dimethyl Dioxolan (isopropylidene ethane diol[21])

Ethane diol (100 ml) was dissolved in acetone (400 ml) and concentrated sulphuric acid (20 ml) was added very slowly with shaking. The two phase mixture that was produced was heated on a water bath with stirring until the mixture was homogeneous (24 hours). The solution was then neutralised with barium carbonate and filtered. The filtrate was distilled and the fraction between 92-93°C was collected. This was redistilled twice collecting a colourless liquid.

FOUND BP 92.5 - 93°C $n_D^{20} = 1.3955$

LITERATURE BP 92 - 93°C $n_D^{20} = 1.3954$

(b) The ketals of D-Glucitol

1,2-O-isopropylidene-D-Glucitol

3,4;O-isopropylidene-D-Glucitol

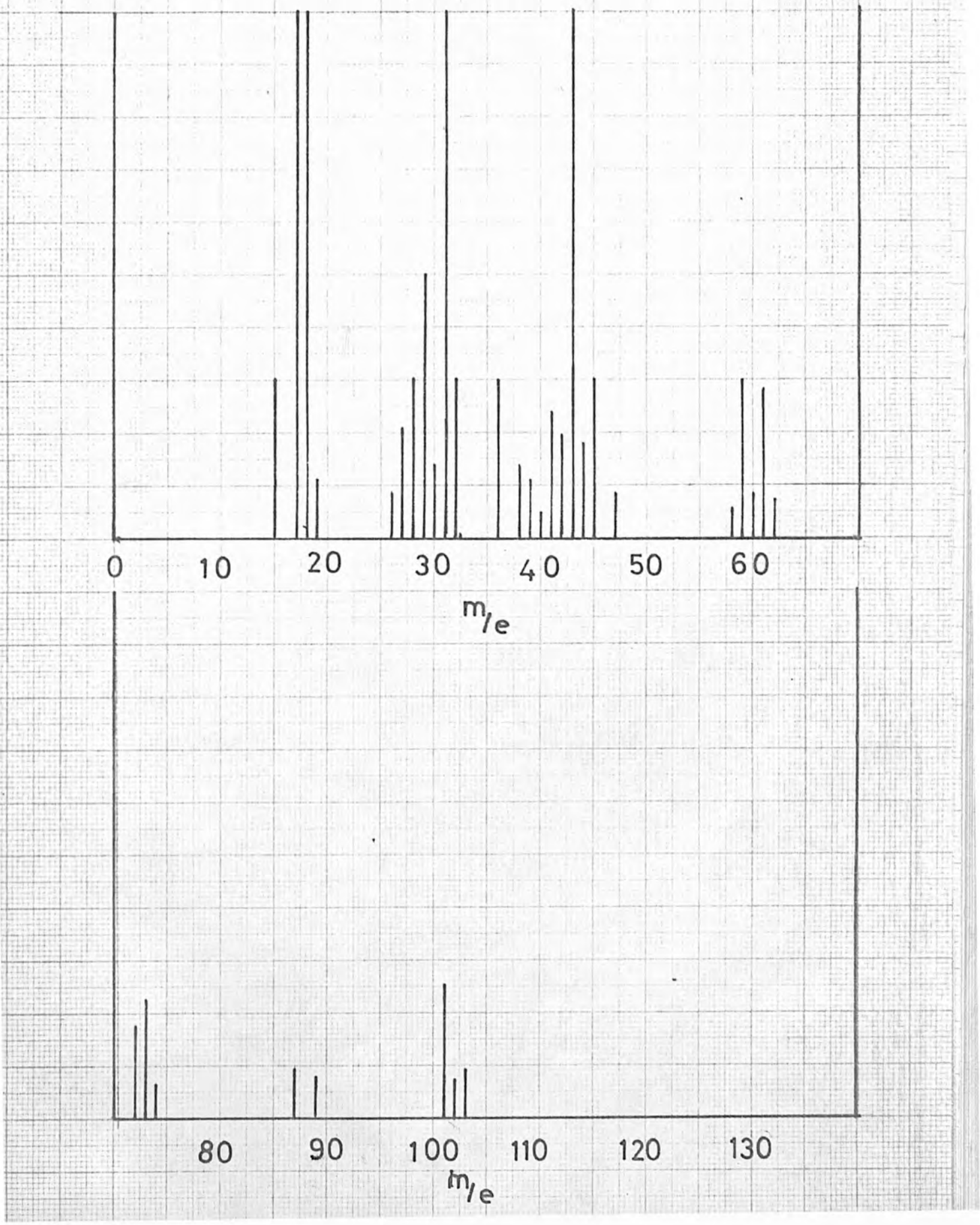
1,2;5,6-di-O-isopropylidene-D-Glucitol

3,4;5,6-di-O-isopropylidene-D-Glucitol

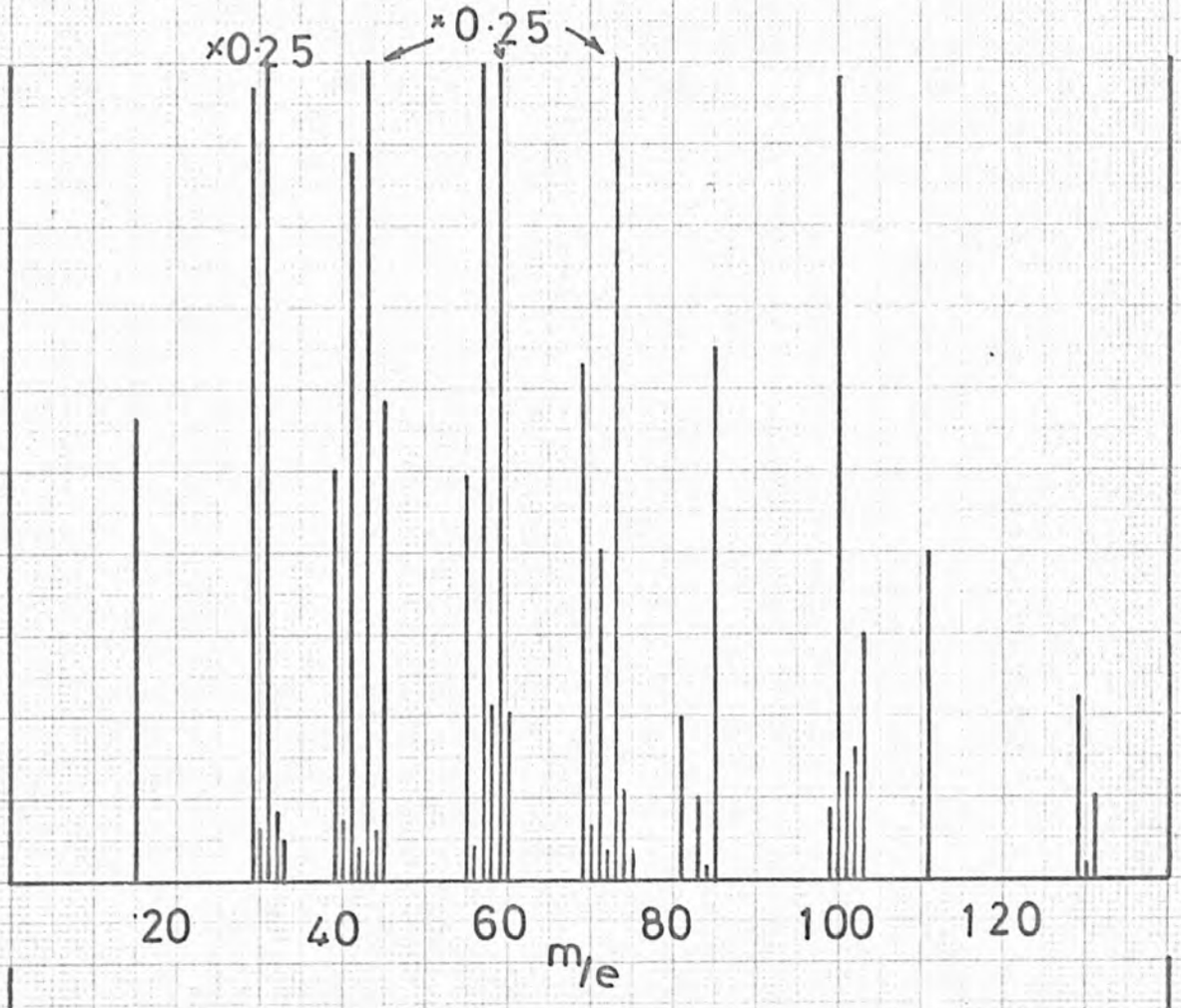
1,2;3,4;5,6-tri-O-isopropylidene-D-Glucitol

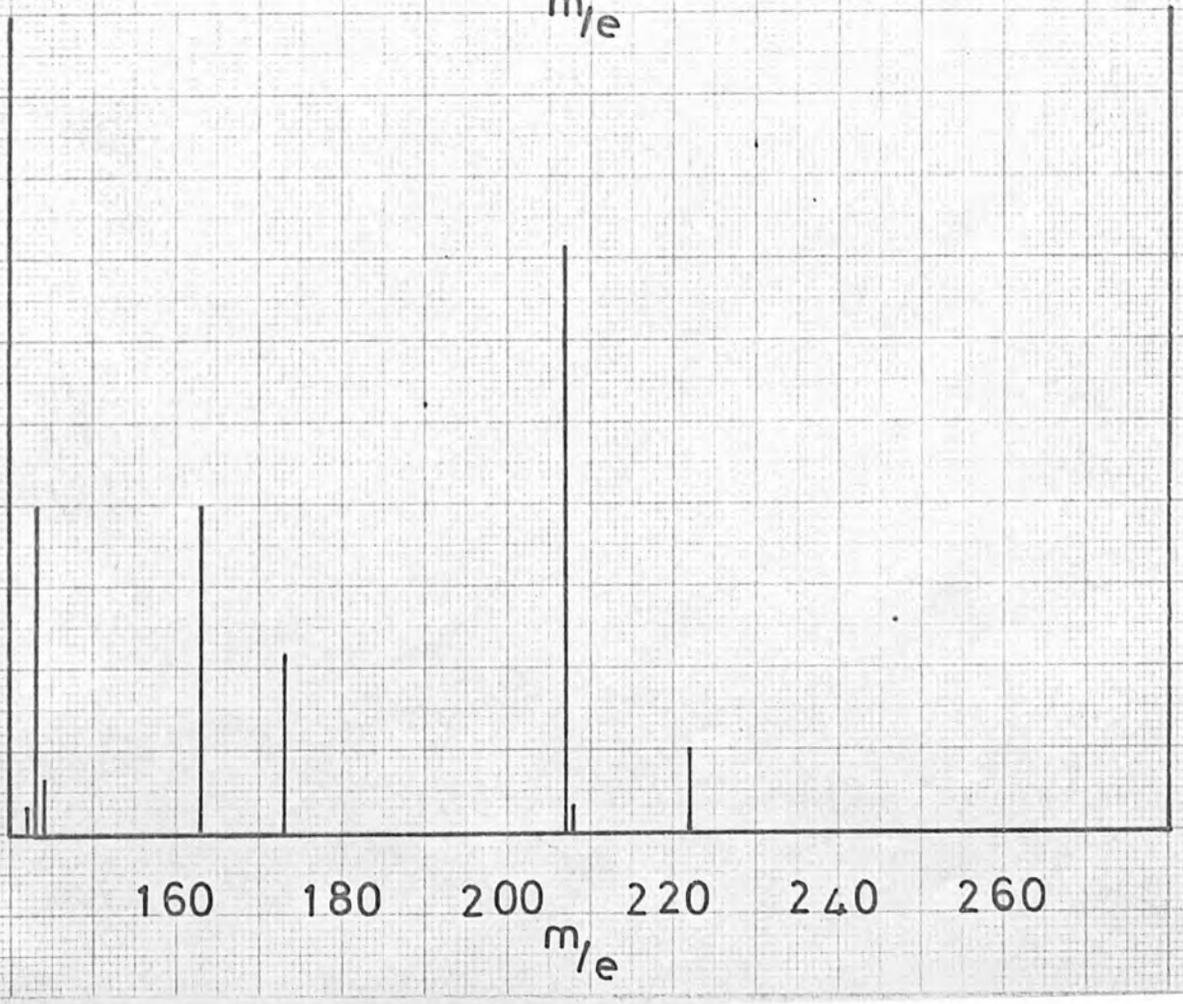
These syntheses have been described previously in Chapter 1, Experiments 1, 8, 13, 14.

2,2 Dimethyl Dioxolan

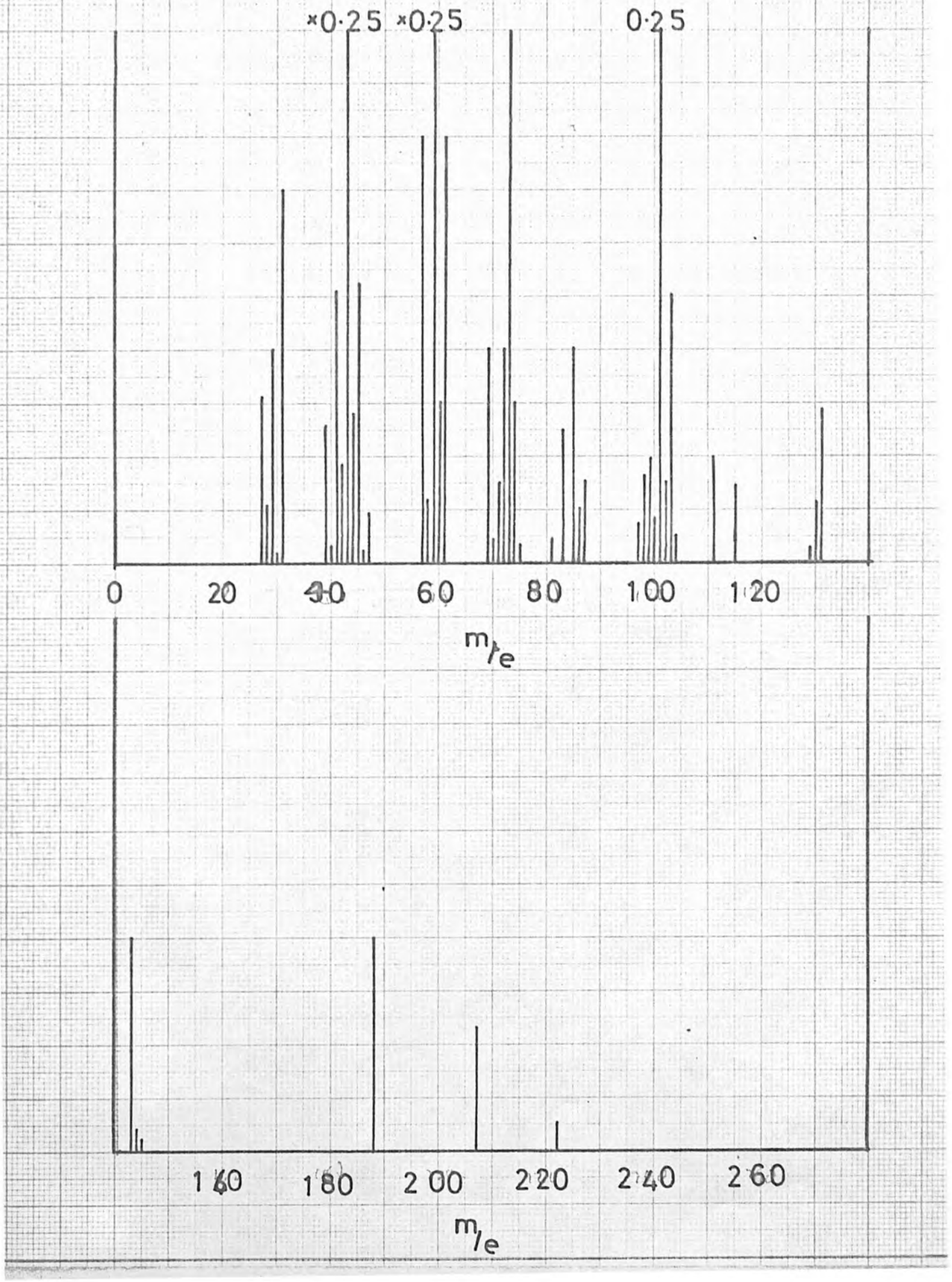


3,4-O-Isopropylidene-D-Glucitol

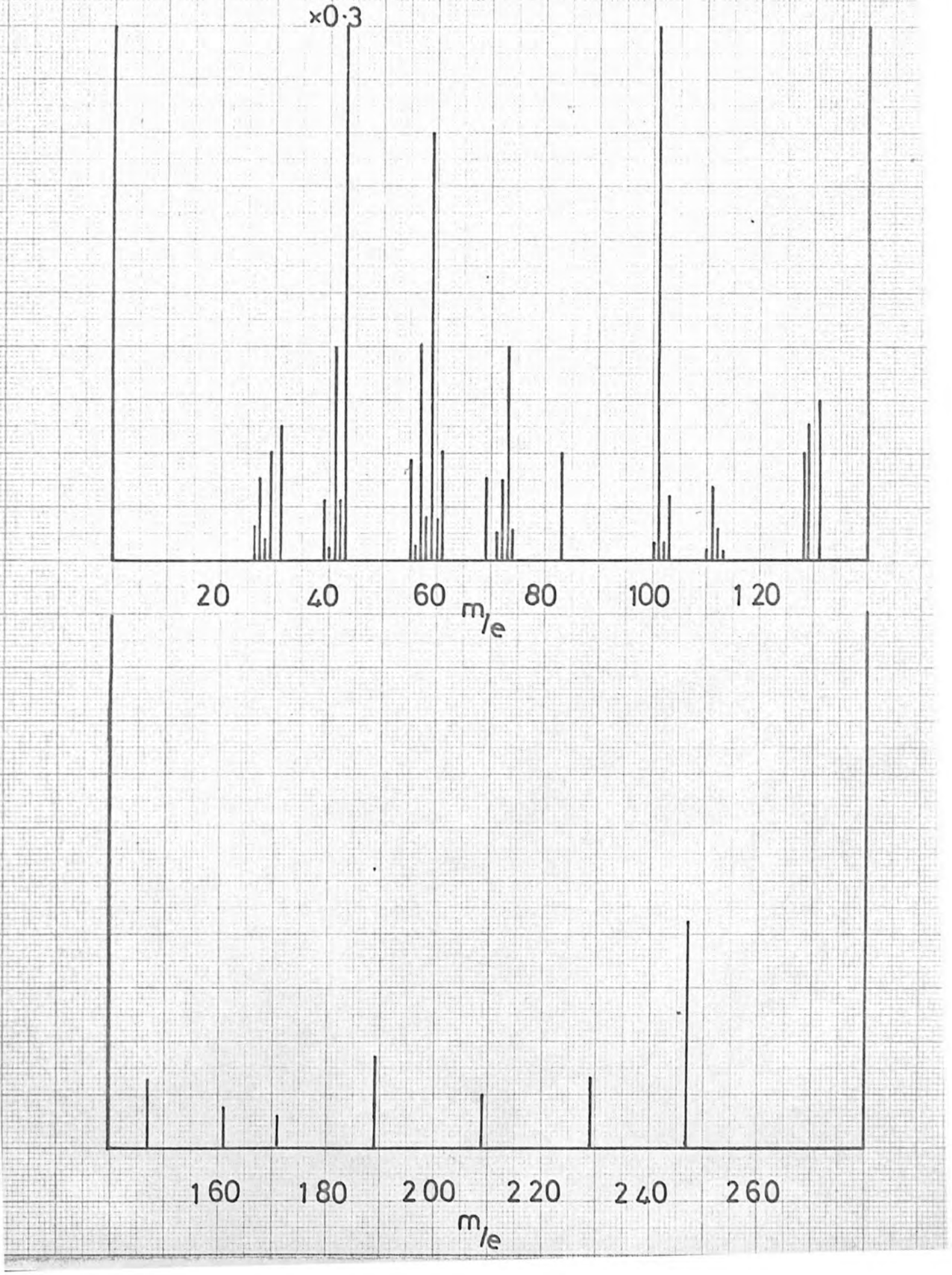




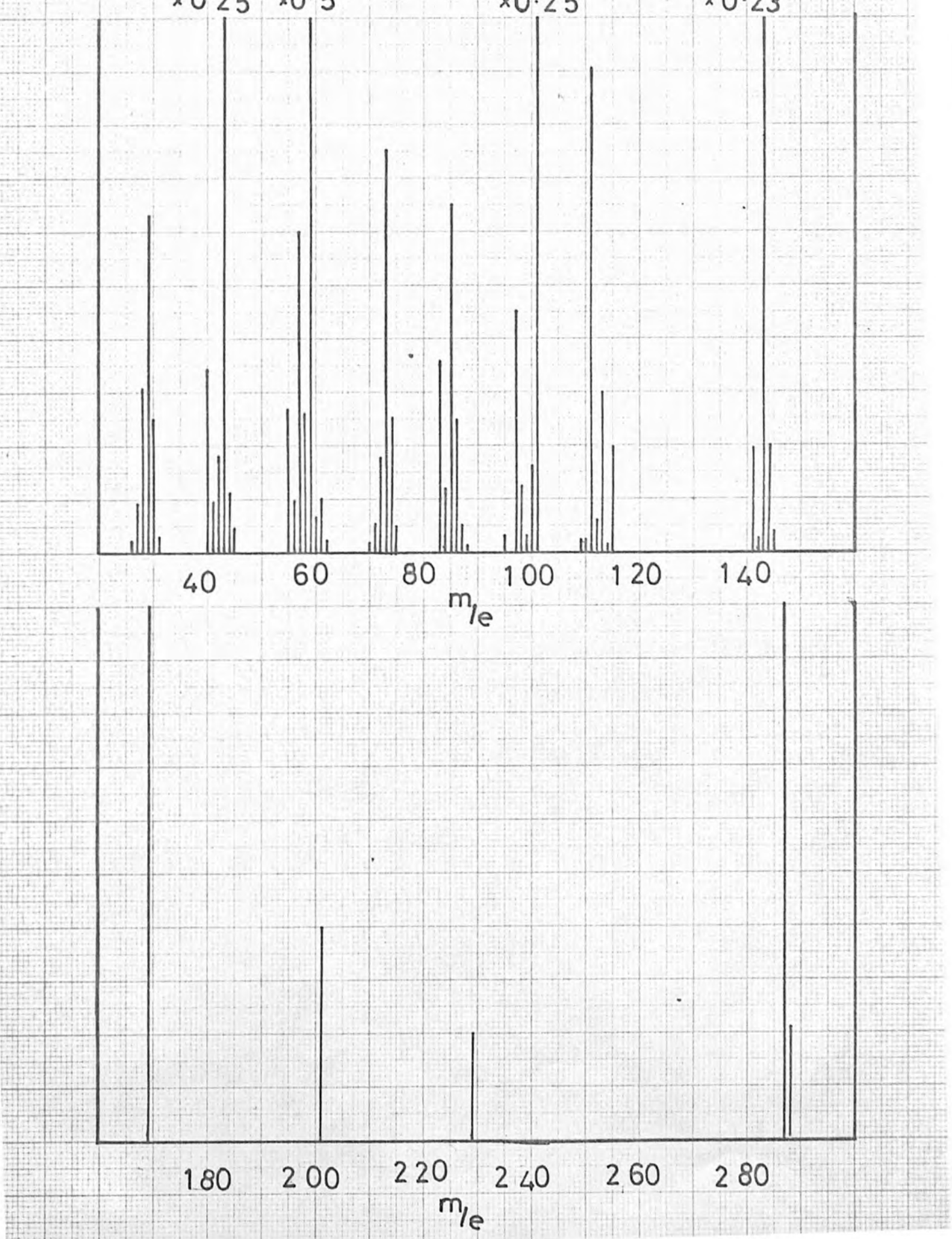
1,2-O-Isopropylidene-D-Glucitol



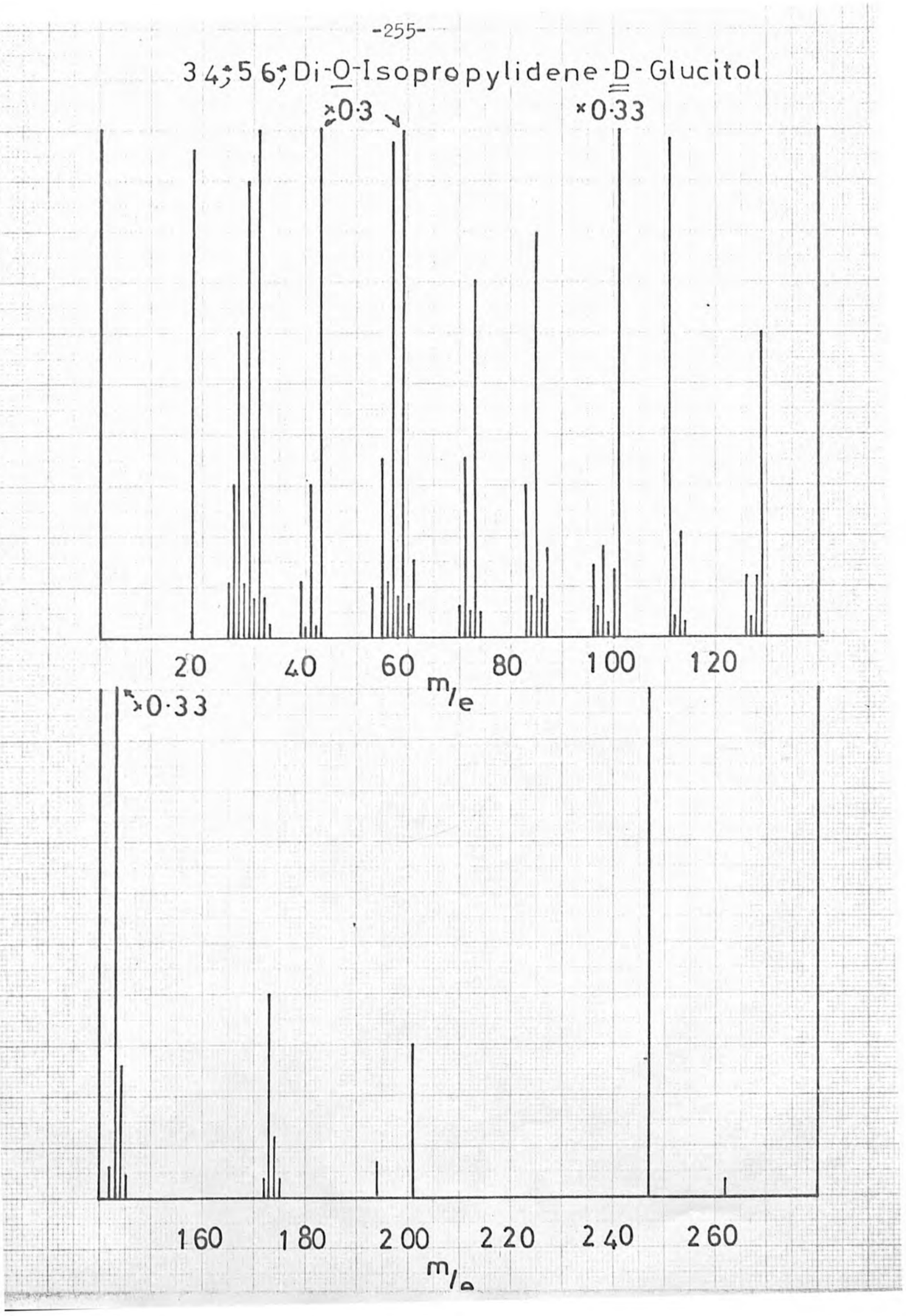
1,2:5,6; Di-O-Isopropylidene-D-Glucitol



1,2:3,4:5,6 - Tri-O-Isopropylidene D-Glucitol



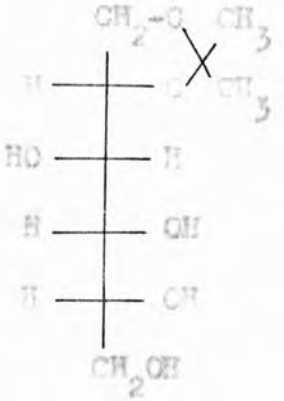
3 4; 5 6; Di-O-Isopropylidene-D-Glucitol



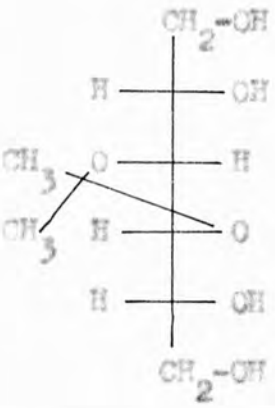
PROTON MAGNETIC RESONANCE SPECTRA OF

ISOPROPYLIDENE DERIVATIVES OF D-GLUCITOL

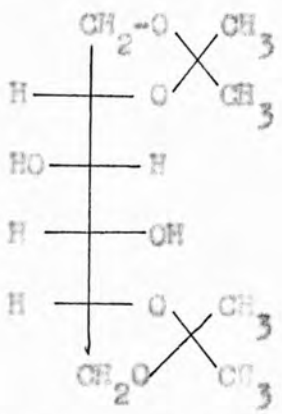
The ketals considered in this study were prepared as previously described in Chapter 7, with structures established by periodate oxidation. Therefore the structures considered are;



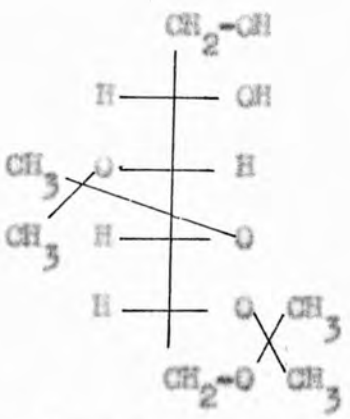
1,2-O-ISOPROPYLIDENE D-GLUCITOL



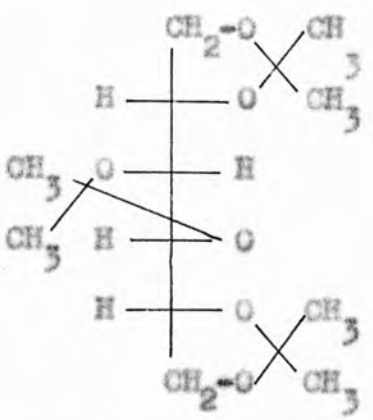
3,4-O-ISOPROPYLIDENE D-GLUCITOL



1,2:5,6-DI-O-ISOPROPYLIDENE D-GLUCITOL

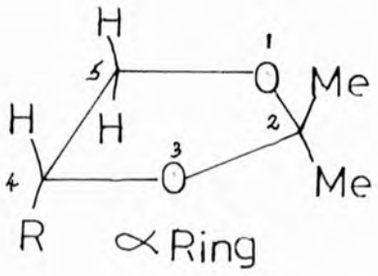


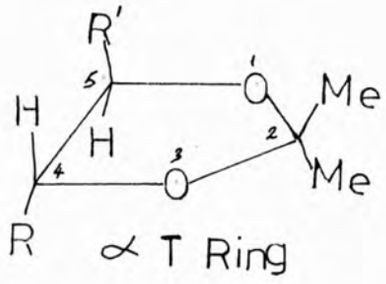
3,4:5,6 DI-O-ISOPROPYLIDENE D-GLUCITOL



1,2:3,4:5,6 TRI-O-ISOPROPYLIDENE D-GLUCITOLS

The rings present in isopropylidene derivatives of D-glucitol may be classified as α rings and α T rings by consideration of the Barker and Bourne rules[22].





An ∝ ketal has its Me groups in different environments, and thus $Me^{(a)}$ and $Me^{(b)}$ groups are, respectively, cis to H/H and H/R at the positions 4 and 5 of the 1,3-dioxolan ring, so that usually $Me^{(b)}$ is more effectively deshielded than $Me^{(a)}$ so that $Me^{(b)}$ protons appear at lover field[23].

Thus 1,2-O-isopropylidene D-glucitol exhibits equal signals at τ 8.74 and τ 8.72 which may be assigned to $Me^{(a)}$ and $Me^{(b)}$ respectively. Similarly 1,2;5,6-di-O-isopropylidene D-glucitol, since there are in both cases $Me^{(a)}$ and $Me^{(b)}$ in equal ratios.

The ∝ T ketal contains two $Me^{(b)}$ groups which results in a single sharp signal at τ 8.73 for 3,4-O-isopropylidene D-glucitol. 1,2;3,4;5,6 Tri-isopropylidene D-glucitol which has 2(a) and 4(b) had signals of relative strength 1:2 at τ8.73 and τ8.7 respectively, with the signal at τ 8.7 shouldered slightly at down field due to the different environment of the ∝ T ring methyls$^{(b)}$. The 3,4;5,6 di-O-isopropylidene D-glucitol had signals of relative strength 1:3 at τ7.4 and τ7.3 respectively due to one $Me^{(a)}$ and 3 $Me^{(b)}$, with the peak at τ 7.3 slightly shouldered up field due to the different environment of the ∝ ring methyl$^{(b)}$.

From the proton magnetic resonance spectra it is seen that the rings are equivalent with the methyls in equivalent environments which are slightly different to those of the 3,4-O-isopropylidene D-glucitol ∝ T ring methyls.

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SECTION 5

Preparative Work

CHAPTER 1

The synthesis of Butylidene acetals

DISCUSSION AND RESULTS

The mono-acetals of L-glucitol that were not previously known were the 1,2-acetal and the 5,6-acetal.

The synthesis of the 1,2-acetal involves a five step process. During these number of steps it might be expected that there was the possibility of acetal migration.

The tetrabenzoyl-D-glucitol prepared as the first step in the 1,2 acetal formation was shown to be the 3,4,5,6 benzoyl ester by its periodate uptake. The molar uptake was 1 mol with the liberation of 1 mol of formaldehyde. This was substantiated by the re-synthesis of the original ketal.

The 1,2-acetal structure was shown by the proton magnetic resonance spectrum of its tetra benzoyl ester and similarly the acetal itself was shown to have a 1,2-ring by its proton magnetic resonance spectrum as well as re-synthesis of its tetrabenzoyl ester. In addition to this the mass spectrum of the acetal tetrabenzoyl ester and the acetal itself showed the structure to be that which was expected.

The mass spectrum showed an ion at $\frac{m}{e}$ 115 which showed the dioxolan ring contained a primary hydroxyl rather than two secondary hydroxyls which would give an ion at $\frac{m}{e}$ 114.

The 5,6-acetals of D-glucitol have been prepared in a two stage synthesis, the periodate analysis shows a terminal dioxolan ring but the only evidence of a 5,6-ring is that its physical properties are substantially different to the 1,2-acetal.

EXPERIMENT 1

Synthesis of 3,4,5,6-tetra-benzoyl-D-Glucitol

1,2-O-Isopropylidene 3,4,5,6-tetrabenzoyl-D-Glucitol[1] (1 g) was dissolved in aqueous trifluoro acetic acid (9:1 V/V) and the mixture left at room temperature for fifteen minutes[2]. The solvent was then removed at reduced pressure keeping the water bath temperature below 50°C. The colourless syrup so formed was titurated with diethyl ether yielding an amorphous white solid which was crystallised from ethanol giving a white crystalline solid.

MP 212 - 214°

YIELD = 0.88 g = 96.7%

Analysis	Calculated for $C_{34}H_{30}O_{10}$	C 68.22%	H 5.05%	O 26.73%
	Actual	C 68.06%	H 4.93%	O 27.01%

Infra red spectra using a nujol mull showed two peaks at 3, 525cm^{-1} and 3460 cm^{-1}

EXPERIMENT 2

Periodate oxidation of the 3,4,5,6 tetrabenzoyl-D-Glucitol

The compound (0.0192 g) was dissolved in aqueous dimethyl formamide (3 ml H_2O + 15 ml dimethyl formamide). To this solution sodium meta periodate (0.0343 g) was added and the solution made up to 25 mls with water. The mixture was left in the dark for 6 hours and then the periodate uptake was determined by the Müller-Friedeberger Method[5]. Each sample was neutralised with analar sodium hydrogen carbonate (1 g) and 20% potassium iodate solution (2 ml) was added. The mixture was then left in the dark for 15 mins and titrated sodium arsenite (0.048 m) using sodium starch glycolate indicator.

SAMPLE	ORIGINAL WEIGHT OF SODIUM METAPERIODATE	WT. OF COMPOUND	MLS OF 0.048 M ARSENITE
1	0.0343 g	0.0192 g	3.20 ml
2	0.0343 g	0.0192 g	3.20 ml
3	0.0343 g	0.0192 g	3.20 ml

$$IO_4^{(-)} + 2I^{(-)} + H_2O \rightarrow IO_3^{(-)} + I_2 + 2OH^{(-)}$$

Mols of periodate taken up per mol of compound = 1.0 mols

The formaldehyde liberated was estimated spectrophotometrically in the normal way.

Mols of formaldehyde liberated/mol of compound = 1.0 mol.

EXPERIMENT 3

Acetonation of the Tetrabenzoyl D-Glucitol

The tetrabenzoate (0.5 g) was taken up in acetone (15 g) containing sulphuric acid (0.2 mls) and the mixture shaken, after 30 mins the mixture had formed a homogeneous solution which was left at room temperature for 24 hours. The mixture was then neutralised using sodium carbonate, filtered and evaporated to a syrup which was crystallised from ethanol giving a crystalline solid identical to the authentic 1,2-O-isopropylidene 3,4,5,6 tetrabenzoyl D-glucitol by melting point and mixed melting point.

MP = 97.5 - 98°

YIELD = 0.29 g = 55%

EXPERIMENT 4

Synthesis of Mixed 1,2-O-n-Butylidene 3,4,5,6 tetrabenzoyl D-Glucitol

3,4,5,6 Tetrabenzoyl D-Glucitol (1 g) was dissolved in n-butyraldehyde (10 ml) and concentrated sulphuric acid (0.5 ml) was added with stirring. The stirring was continued for 24 hours and the solutions was then neutralised with sodium carbonate, the mixture filtered and the filtrate evaporated under reduced pressure to a yellow syrup which was taken up in the minimum of ethanol and cooled to -5° for 48 hours when crystals separated out. The crystals were recrystallised to constant melting point from ethanol.

MP = 127.5 - 128°

YIELD = 1 g = 88.9%

Analysis	Calculated $C_{38}H_{36}O_{10}$	C 69.9%	H 5.56%	O 24.5%
	Actual	C 68.8%	H 5.59%	O 24.6%

N.M.R. in δ^6DMSO showed two overlapping triplets in the region of the acetal proton at 4.02 τ + 3.98 τ J = 4.0 cps

EXPERIMENT 5

Structural determination of the above Acetal

The acetal (0.3 g) was treated with aqueous trifluoroacetic acid (9:1 v:v) for ten minutes[2]. The acid was then evaporated off at reduced pressure below 50°C. The syrup so obtained gave a white solid on trituration with ether. The solid on recrystallisation from ethanol gave white crystals.

MP 212 - 214°

Mixed melting point with the authentic tetrabenzoate gave no depression.

YIELD = 0.26 g = 91%

EXPERIMENT 6

Saponification of the 1,2-O-Butylidene 3,4,5,6 tetrabenzoyl D-Glucitol

The acetal (2.0 g) was dissolved in the minimum of chloroform and sodium methoxide (1 M 0.5 ml) was added and the solution left at room temperature overnight. The sodium methoxide was then destroyed by the adding of carbon dioxide (CARDICE 2.0 g) and the solution evaporated to a syrup, which was extracted with ethanol. The sodium carbonate was filtered off and the filtrate set aside at -5°C when crystals were deposited. These were recrystallised from ethanol to constant melting point.

MP 129.5 - 131°C

$(\alpha)_D^{25°C}$ = 16.096 (c 356 in H_2O)

YIELD = 0.33 g = 46%

Analysis calculated $C_{10}H_{20}O_6$ C = 50.84% H = 8.53 O = 40.63%

Found C = 50.79% H = 8.42 O = 40.79%

EXPERIMENT 7

Benzoylation of the 1,2 Acetal

The acetal (0.2 g) was dissolved in pyridine (1 ml) and benzoyl chloride (0.5 ml) was added and the solution left overnight at room temperature. The mixture was then poured into ice water (1 ml) when a syrupy mass was deposited, which slowly crystallised. After recrystallisation from ethanol it was shown by melting point and mixed melting point to be identical with the authentic tetrabenzoate experiment 4.

MP = 127-128°C

MIXED MP = 127.5-128°C

YIELD = 0.27 g = 46.3%

EXPERIMENT 8

Periodate oxidation and determination of liberated formaldehyde for 1,2-O-Butylidene-D-Glucitol

This was carried out in the usual way using 0.0116 g of compound.

Periodate uptake = 3 mols/mol of compound after 4 hours

Formaldehyde liberated = 1 mol/mol of compound after 4 hours

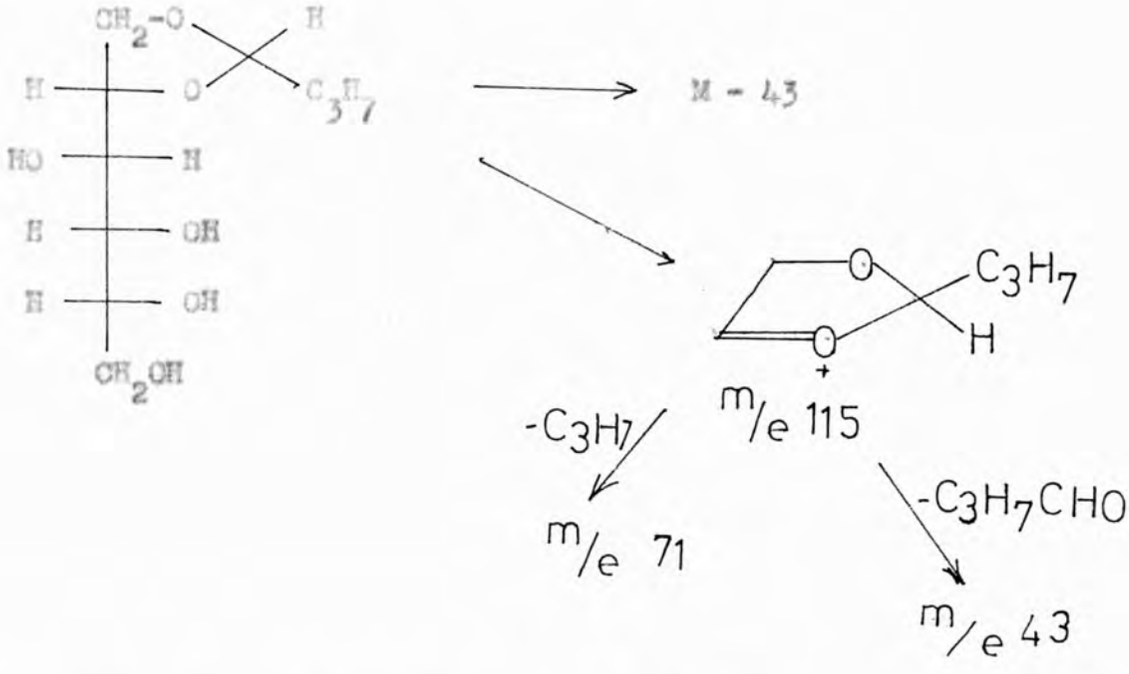
EXPERIMENT 9

MASS SPECTROMETRY OF THE 1,2 ACETALS AND ITS DERIVATIVES

Mass spectrum of 1,2-O-Butylidene-D-Glucitol

The mass spectrum showed a small peak at $\frac{m}{e}$ 236 which was equivalent to Mass ion M+ and also M-1 i.e. the loss of a proton.

Other significant peaks occur at $\frac{m}{e}$ 193; $\frac{m}{e}$ 115; $\frac{m}{e}$ 43; $\frac{m}{e}$ 71. Thus we can postulate the following fragmentation.

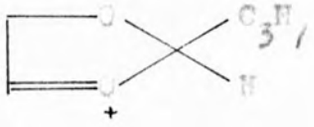


There are also peaks which are characteristic of loss of fragments from the carbon skeleton chain of the alditol.

1,2-O-butylidene-3,4,5,6 tetrabenzoyl-D-Glucitol

The mass spectrum of this compound shows a fairly simple fragmentation pattern giving evidence for its structure but with very few differences from the 1,2-acetal itself.

$\frac{m}{e}$ 653; $\frac{m}{e}$ 652 and $\frac{m}{e}$ 654 indicate the ions M, M-1 and M+1 as would be expected.

The molecule then shows fragmentation equivalent to the loss of $\frac{m}{e}$ 115 i.e.  as expected and also fragmentations of this ion.

The remaining fragmentation is due to the splitting off of $CH_2 - O - \overset{O}{\overset{\|}{C}} - \phi$ + $CH - O - \overset{O}{\overset{\|}{C}} - \phi$ fragments with further fragmentation.

EXPERIMENT 10

Preparation of a 3,4-O-Butylidene D-Glucitol[3]

(i) Preparation of Tricrotylidene-D-Glucitol

D-Glucitol (90 g) and crotonaldehyde (3-5 mols) were mixed and benzene (310-400 mls) were added followed by phosphoryl chloride catalyst (3 drops) and the mixture refluxed under a Dean and Stark head. After one hour a further 3 drops of catalyst were added and the reaction left for a further 24 hours when 15 mls of water had been collected.

The benzene solution was then decanted and evaporated to a syrup which was dissolved in ethanol (90 mls) followed by enough aqueous ammonia to destroy the catalyst. Water was then added until turbidity persisted. The mixture was cleared by careful addition of ethanol and the solution set aside at 5°C when crystals were deposited. Recrystallisation from 50% aqueous ethanol gave white crystals.

MP 105-108°C

LIT MP 105-1-8°C for tri acetal

YIELD 6.5 g = 3.8%

The liquors from the first crystallisation were evaporated yielding a syrup which distilled at 172°C 0.1 mm. Yielding a syrupy tri-O-butenylidene-D-Glucitol.

(ii) Hydrolysis of the syrupy acetal

The syrupy tri-acetal (13 g) was dissolved in ethanol and treated with 0.01N hydrochloric acid (107 ml) and left to stand at room temperature for 1 hour and then neutralised with sodium hydrogen carbonate (0.16 g)

in water and the solution evaporated to dryness. The resultant syrup was evaporated successively with ethanol and chloroform and then taken up in hot chloroform and set aside when a white solid was precipitated. This was filtered off and recrystallised from ethanol giving a white crystalline compound shown to be identical to an authentic sample of 3,4-O-but-2'-enylidene-D-glucitol.

MP AND MIXED MP = 168-170°

LIT MP = 169-170°

YIELD = 0.5 g = 6%

(iii) Hydrogenation of 3,4-O-But-2'-enylidene D-Glucitol

The 3,4-O-but-2'-enylidene D-glucitol (1 g) was dissolved in dry methanol and platinum black catalyst (1 g) was added and the mixture hydrogenated at low pressure (3-4 atm) until hydrogen uptake ceased.

The catalyst was filtered off under nitrogen and the filtrate evaporated to a white solid which was recrystallised from ethanol and shown to be a 3,4-O-butylidene-D-glucitol by comparison with an authentic sample.

MP = 111-113°,

LIT MP = 112-114°,

YIELD = 1 g = 98%

EXPERIMENT 11

Preparation of a 5,6-O-Butylidene-D-Glucitol

(i) 1,3; 2,4 di-O-benzylidene D-glucitol was prepared as described previously.

(ii) Preparation of 5,6-O-butylidene 1,3-2,4 di-O-benzylidene-D-Glucitol

1,3-2,4-di-O-benzylidene-D-glucitol (1 g)[4] was dissolved in n-butyraldehyde (5 ml) and freshly fused powdered zinc chloride (1 g) was added and the mixture stirred for 15 mins, when all the zinc chloride had dissolved and the solution had become warm. The stirring was continued for 4 hours. The mixture was then extracted with chloroform, the chloroform solution washed with bicarbonate solution and then water until neutral. The chloroform solution was then dried and evaporated to a syrup which was distilled under high vacuum.

BP = 150-154° 2.0 mm

Analysis Calculated $C_{24}H_{28}O_6$ C = 69.89% H = 6.84% O = 23.27%

Actual C = 69.9% H = 6.95% O = 23.15%

(iii) Preparation of a 5,6-acetal

The 1,3-2,4 di-O-benzylidene 5,6-O-butylidene D-glucitol (1 g) was dissolved in dry methanol (20 ml) and palladium catalyst (1 g) was added and the mixture hydrogenated at ~ 5 atmospheres until hydrogen uptake ceased. The palladium was filtered off under nitrogen and the filtrate evaporated to a greenish yellow syrup which was distilled under high vacuum yielding a pale yellow syrup.

BP = 125-130° 0.1 mm

t.lc silica gel/benzene 1.5% meOH showed Rf = 0.09; 0.55 and 0.97

V.P.C. of the trimethyl silyl ethers showed 3 peaks RV = 2.38, 4.21 and 4.3 relative to D-glucitol (185° 5% Apeizon K).

The syrup was separated on a silica gel column using toluene 5% MeOH as eluent, the syrup appeared in fractions 12-15 (20 mls each). The material Rf 0.09 RV 2.38 was obtained as a colourless syrup. The other materials were not isolated pure.

EXPERIMENT 12

Analysis of the 5,6-O-butylidene D-glucitol

The compound was treated with sodium metaperiodate and the periodate uptake and liberated formaldehyde were estimated spectrophotometrically in the normal way.

RESULTS

Amount taken	= 0.0117 g of compound
Periodate uptake	= 3.09 mols/mol of compound at 4 hours
Formaldehyde liberated	= 1.1 mols/mol of compound at 4 hours

This is identical to that for the 1,2-acetal but the other physical properties show it to be different.

EXPERIMENT 12

Preparation of 2 propyl dioxans and dioxolans[6]

The same method was used for the preparation of 2 propyl dioxan, 2 propyl dioxolan and 2 propyl 4 methyl dioxan.

(a) 2-propyl-dioxan

Propane 1,3-diol (76 ml) and n-butyraldehyde (200 ml) were mixed and concentrated sulphuric acid (3 mls) was added and the mixture stirred until homogeniety was attained. The mixture was then heated on a boiling water bath for six hours. The mixture was allowed to cool and extracted with ether. The ether extract was washed with sodium bicarbonate solution and then water until it was neutral. The ether solution was then dried over anhydrous magnesium sulphate and evaporated under reduced pressure to an oil.

Distillation at high vacuum gave a thin syrup,

BP 76-80° 1.5 mm

LIT BP 154° at 760 mm

Redistillation at atmospheric pressure BP 154°

IR showed the complete absence of aldehyde.

(b) 2-propyl-4-ethyl dioxolan from 1,2-propane diol

The same procedure was followed as above using exactly the same proportions. Distillation at atmospheric pressure gave a liquid

BP 139-141°

LIT BP 140-141° at 760 mm

(c) 2-propyl dioxolan

Ethone diol (90 ml) and n-butyraldehyde (200 ml) were treated as before. Distillation at atmospheric pressure gave a liquid

BP 132-134°

LIT BP 133-134° 760 mm

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CHAPTER 2

Synthesis of 4,6-O-Butylidene Gulose

EXPERIMENT 1

Preparation of 4,6-O-Butylidene Gulose

A. (i) Preparation of D-Gulono-γ-Lactone[1]

D-xylose (30 g) and ammonium chloride (10.7 g) were dissolved in water (100 mls) and ice (100 g) was added, followed by sodium cyanice (10 g) and the solution was kept at 0° for 2 days. Barium hydroxide octahydrate (63 g) were then added, followed by water (100 mls) and the mixture heated on a boiling water bath with stirring for two hours. The mixture was then stirred at 0° for 24 hours when barium gulonate and idonate separated out and was filtered off and the precipitate washed with ice cold water until it was chloride free. The barium salts were then suspended in water (200 ml) and the barium precipitated using 9 M sulphuric acid (12-14 ml) until pH remained at 1.5. The barium sulphate was filtered off and the filtrate evaporated under reduced pressure to a colourless syrup. The syrup was dissolved in hot methyl Cellosolve (50 ml) and ethyl acetate was added to turbidity and the mixture left at 0° until crystals formed (3 weeks). The crude product was filtered off and recr stallised from methyl Cellosolve which removed the idono-γ-lactone.

MP 181-183°

LIT MP 181-183°

YIELD 35% = 12.3 g

(ii) Preparation of D-Gulono-γ-Lactone tetrabenzoate[2]

Benzoyl chloride (17.5 g) and chloroform (17.5 mls) were mixed and cooled in an ice bath, to this was added slowly with stirring a

mixture of pyridine (21 ml) and chloroform (17.5 ml) followed by D-gulono -γ-lactone (5 g) and the mixture stirred for one hour and then left to stand overnight. The mixture was then extracted with a further amount of chloroform, washed three times with sodium bicarbonate solution followed by distilled water. The chloroform solution was dried over sodium sulphate and concentrated to a syrup. Toluene was added to the syrup, and removed under reduced pressure leaving a crystalline mass which was recrystallised from ethanol chloroform.

MP = 155-156°

L.IT MP = 155-156°

(iii) Preparation of DiBorane[3]

The preparation was carried out in an atmosphere of nitrogen with a continual stream of nitrogen passing through the apparatus which was baked at 150° for 4 hours before use. Sodium borohydride (4.31 g) in ether (114 mls) was placed in a flask equipped with a proficient magnetic stirrer and boron trifluoride etherate (10 ml) was added from a pressure equilised dropping funnel. The diborane passed over with the nitrogen, the ether vapour was removed by passing through a trap immersed in a cardice acetone bath and the diborane collected in anhydrous tetrahydrafuran cooled to 0°.

(iv) Analysis of the diborane solution

The diborane T.H.F. solution (1 ml) was pipetted into acetone (10 ml) to form diisopropoxy borane which was hydrolysed to boric acid by the addition of water (10 ml). Mannitol (0.7 g) was then added and the solution titrated with standard 0.01 N sodium hydroxide using

phenolpthalein indicator.

Titration value 48.6 ml = 2.43 molar B_2H_6

(v) Preparation of Disoamylborane[2]

Again the experiment was carried out under dry inert conditions using nitrogen.

In a flask equipped with a pressure equalised dropping funnel and a nitrogen inlet was placed 2-methyl-2-butene (25 ml) and the flask cooled to -10°. To this the borane solution (50 mls) was added with stirring. After 6 hours under a static pressure of nitrogen the solution was diluted to 100 ml with anhydrous tetrahydrofuran to give a solution of ~1.25 molar in disoamylborane.

(vi) Preparation of 2,3,5,6 Tetra-O-benzoyl D gulofuranose[2]

To tetrahydrofurane (75 ml) containing 0.125 mole of disoamylborane in a nitrogen atmosphere was slowly added the D gulono lactone tetrabenzoate (17.8 g) in tetrahydrofuran (50 ml). The mixture was left at room temperature overnight and then water (10 mls) was added dropwise and the mixture refluxed for half an hour. The solution was then cooled to 0° and 30% hydrogen peroxide (20 ml) was added dropwise keeping the pH between 7 and 8 by adding 3 N sodium hydroxide. The mixture was then concentrated under reduced pressure, extracted with chloroform and the chloroform washed with water and dried over calcium chloride. The chloroform was removed under reduced pressure yielding a syrup which was crystallised from ethanol.

MP 156-158°

LIT MP 156-157°

(vii) Preparation of D-gulose

The D-gulose tetrabenzoate was dissolved in methanol and sodium methoxide in methanol (0.5 N 1 ml) was added and the solution left at room temperature overnight. The sodium methoxide was then destroyed using carbon dioxide and the mixture evaporated yielding a syrup. This was taken up in ethanol and the sodium carbonate residue filtered off. The ethanol solution was evaporated to a colourless syrup which was shown to be gulose by comparison with an identical sample by paper chromatography (Butanol/Ethanol/Water 40:11:19).

(B) Alternative preparation of D-gulose

(i) Preparationof Ruthenium tetroxide

Ruthenium dioxide hydrate (10 g) was added to saturated sodium metaperiodate solution (70 ml) and carbon tetrachloride (70 ml) in a separating funnel. The mixture was shaken and the carbon tetrachloride layer run off and dried over calcium sulphate and used immediately. More carbon tetrachloride was added and also more saturated sodium metaperiodate until the carbon tetrachloride layer was colourless. At this stage all the ruthenium dioxide had been converted to ruthenium tetroxide.

(ii) Oxidation of 1,2: 5,6 di-O-isopropylidene α - D glucofuranose using Ruthenium Tetroxide

The diketal (15 g) was dissolved in carbon tetrachloride (350 ml) in a 2 litre conical flask equipped with a magnetic stirrer. To this was added freshly prepared ruthenium tetroxide (from 10 g of ruthenium dioxide hydrate). The mixture was then stirred for 2 hours and the

excess ruthenium tetroxide destroyed by the addition of iso-propanol (5 mls). The ruthenium dioxide was filtered off and the carbon tetrachloride removed under reduced pressure. The syrup so produced was distilled under high vacuum.

BP 103-106° 0.3 mm

(iii) Preparation of 1,2;5,6-di-O-isopropylidene ∝ D-ribo-3-hexulofuranose hydrate[5]

The ketone from (i) (10 g) was dissolved in ether (30 ml) saturated with water and warmed on a water bath for 15 mins. The mixture was then evaporated under reduced pressure (8 ml) and petroleum ether (BP 40-60 1 ml) was added causing turbidity. The turbid solution was set aside at 0°C until crystals appeared. This was recrystallised twice from ether; petroleum ether

MP 111-113°

LIT MP 112-114°

(iv) Preparation of 1,2;5,6-di-O-isopropylidene ∝-D ribo 3 hexulofuranose acetate[5]

The hydrate from (ii) (10 g) was dissolved in pyridine (30 ml) and acetic anhydride (20 ml) was slowly added, and the solution kept at 60°C for 16 hours. The solution was thencooled and poured into ice water, the syrup which was deposited was extracted which chloroform, the chloroform extract dried over anhydrous sodium sulphate and evaporated to a syrup which was crystallised from ethanol petroleum ether.

MP 60-62°

LIT MP 62-63°

(v) Preparation of 1,2; 5,6-di-O-isopropylidene α -D-gulofuranose and 5,6-O-isopropylidene α -D-gulofuranose[5]

The 1,2;5,6 di-O-isopropylidene α D-ribo-3-hexulo furanose acetate (5 g) was dissolved in dry methanol (20 ml) and sodium barohydride (1 g) was added slowly to the cooled solution. When effervescence had ceased the solution was heated at 60° for 24 hrs, allowed to cool and the solution neutralised with resin. The resin was filtered off and the methanol evaporated off. After successive evaporations of ethanol all the boron had been removed as volatile methyl borate, leaving a syrup which was crystallised from ligroin. Two crops of crystals were produced.

MP = 118-120° - 1,2-O-isopropylidene-D-gulose

Analysis	Found	C 58.2%	H 6.10%	O 35.61%
	Calc.	C 58.20%	H 6.01%	O 35.79%

MP = 105-106 -1,2;5,6 di-O-isopropylidene D-gulose

Analysis	Found	C 67.39%	H 5.64%	O 26.97%
	Calc.	C 67.41%	H 5.66%	O 26.93%

(vi) De-acetalisation using aqueous trifluoro acetic acid[6]

Both the preceeding compounds were treated in a similar manner. The compound (1 g) was taken up in aqueous trifluoro acetic acid (9:1 vv THF:: water) (10 ml) and left at room temperature for 20 mins. The mixture was then evaporated to a syrup below 50°C. This was triturated with ether and reevaporated four times, removing the last traces of trifluoro acetic acid, and leaving a syrup which was shown by paper chromatography (Butanol/Ethanol/Water 40:11:19) to be identical

to an authentic sample of D-gulose.

(C) Preparation of the 4,6-O-butylidene D gulose[7]

D-gulose (0.5 g) was shaken with an ether, n butyraldehyde mixture (1:1 vv)(2 ml) containing concentrated sulphuric acid (1 drop) until solution was complete (1 hr). The mixture was then left for 24 hrs at room temperature. Ethyl ether was then added until a slurry was formed, solid potassium carbonate (0.1 g) was then added and the suspension stood at room temperature for 4 hrs. The mixture was filtered. The solid was extracted with acetone and cooled in ice until crystals appeared. The filtrate was evaporated under reduced pressure which was extracted with boiling acetone (2 ml) and cooled in ice to give a second crop of crystals.

MP 120-123°

Analysis	Calculated	C	51.27%	H 7.75%	O 40.98%
	Found	C	51.17%	H 7.71%	O 41.12%

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CHAPTER 3

The Synthesis of Bromoethylidene Acetals of D-Glucitol

DISCUSSION AND RESULTS

The acid catalysed condensation of bromo-acetaldehyde with D-mannitol yields the three possible isomers of 1,2; 5,6-di-bromoethylidene D-glucitol, the cis, cis; trans, trans; and the trans cis isomers.

The reaction between bromo-acetaldehyde dimethyl acetal and D-glucitol was carried out in an attempt to product the 1,2-mono-acetal. When an equi-molar reaction was carried out a mono-acetal was isolated. When periodate oxidation was carried out the periodate uptake was 1 mol per mol of compound, with the liberation of 1 mol of formaldehyde instead of the expected 3 mols of periodate uptake and 1 mol of formaldehyde. The di-acetal which was isolated on hydrogenation gave the known 1,3;2,4-di-O-ethylidene D-glucitol and therefore the original di-acetal must have the same structure.

Therefore D-glucitol and bromo-acetaldehyde react in the normal way giving the 2,4 mono-acetal and the 1,3; 2,4 di-acetal instead of the 1,2 acetal and the 1,2; 5,6 di-acetal which would be expected by comparison with D-mannitol.

EXPERIMENT 1

Condensation of D-Glucitol and Bromoacetaldehyde dimethyl acetal under acid catalysis

1:1 Molar quantities of D-Glucitol and Bromoacetaldehyde dimethyl acetal. D-Glucitol (4 g) was added to a mixture of water and concentrated sulphuric acid (1:1 8 mls) and Bromoacetaldehyde dimethyl (4.5 g) was added with stirring, stirring was continued until homogeneity was attained. The solution was left to stand for 24 hours then exactly neutralised with sodium hydroxide. The solution was evaporated to a syrupy solid which was extracted with ethanol. The ethanolic extract was evaporated under reduced pressure yielding a syrup.

Thin layer chromatography using ethyl methyl ketone saturated with water showed three spots

Rf = 0.01

Rf = 0.42

Rf = 0.74

The syrupy mixture was subjected to column chromatography using silica gel, eluting with ethyl methyl ketone saturated with water, yielding a syrup Rf 0.42 which was crystallised from ethanol, compound D.

MP 167.5-168.5°

Analysis Calculated for $C_8H_{15}O_{10}Br$ C% 33.47 H% 5.27 Br% 27.830 % 33.44

Observed C% 33.25 H% 5.31 Br% 27.910 % 33.53

Also a syrup Rf = 0.74, compound E.

Analysis Calculated for $C_{10}H_{16}O_6Br_2$ C% 30.25 H% 4.06 Br% 24.180 % 40.25

Observed C% 30.19 H% 4.11 Br% 24.190 % 41.51

EXPERIMENT 2

Periodate oxidation of compounds D and E and determination of liberated formaldehyde

The periodate oxidation and formaldehyde determination were carried out in the normal way.

Weight of Compound	Molar uptake periodate	Mol Formaldehyde liberated
Compound D 0.0082 g	1.1 mols	0.96 mols
Compound E 0.0091 g	1.07 mols	1.03 mols

EXPERIMENT 3

Preparation of the acetate of Compound D

Compound D (0.5 g) was dissolved in dry pyridine (3 mls) and acetic anhydride (2 mls) was added and the solution left at room temperature for 24 hours after which it was poured into ice water. A syrup was deposited which slowly crystallised and was recrystallised from ethanol.

MP 125-125.5°

Analysis Calculated for $C_{16}H_{23}O_{10}Br$ C% 42.21 H% 5.09 Br% 17.53 O% 35.14

C% 42.31 H% 5.00 Br. 17.49 O% 35.10

EXPERIMENT 4

Hydrogenolysis of Compounds D and E[1]

(i) Compound D

The compound (1.0 g) was dissolved in 95% ethanol (20 ml) containing potassium hydroxide (0.32 g) and 5% Pd/c (0.4 g). The mixture was subjected to hydrogenation at ~ 5 atmospheres until no further hydrogen was taken up. The mixture was then filtered and the filtrate exactly neutralised with hydrochloric acid (1.0 M). The mixture was evaporated to a syrup and extracted with ethanol. The ethanol extract yielded a syrup which crystallised as was recrystallised from ethanol/ether.

MP 146-147°

2,4-O-Ethylidene D-glucitol LIT MP 146°

The mixed MP was not depressed

(ii) Compound E

The above procedure was repeated using Compound E (1.0 g); 95% ethanol (40 ml); potassium hydroxide (0.64 g); and 5% Pd/C (0.8 g)

On work up a solid which was recrystallised from ethanol was produced.

MP 212-214°

1,3;2,4-di-O-Ethylidene-D-glucitol LIT Mp 212-214°

The mixed MP was not depressed

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CHAPTER 4

Synthesis of 3,4,5,6 tetra benzyl D-glucitol

EXPERIMENT 1

Synthesis of 1,2-O-Isopropylidene 3,4,5,6-tetra benzyl D-Glucitol using silver oxide catalyst[1]

1,2-O-Isopropylidene D-Glucitol (1 g) was dissolved in dry dimethyl formamide and benzyl bromide (5 ml) was added followed by dry silver oxide (3 g). The mixture was shaken in the dark for 3 days. The silver oxide was filtered off and the filtrate evaporated to a semi-solid which was extracted with chloroform, the chloroform extract was washed with water and dried over anhydrous sodium sulphate. The benzylation procedure was repeated four times to complete benzylation (as shown by infra-red spectroscopy). A dark brown syrup was obtained which was distilled at 0.5 mm yielding a pale yellow syrup, BP 185-190°.

$$[\alpha]_D^{15.5^\circ} = -29.59$$

Yield = 0.52 g = 20%

EXPERIMENT 2

Synthesis of 1,2-O-Isopropylidene 3,4,5,6 tetra-benzyl D-Glucitol using sodium hydride catalyst[2]

1,2-O-Isopropylidene D-glucitol (3 g) was dissolved in dry dimethylformamide and ether washed sodium hydride (9.6 g) was added to the stirred mixture under nitrogen. The mixture was then cooled in an ice bath and benzyl bromide (25 ml) was dripped in. The stirring was continued for one hour with the reaction cooled in ice, and then for a further 48 hours at room temperature. The mixture was again cooled in an ice bath and the excess sodium hydride destroyed by adding dry methanol until effervescence ceased. Stirring was continued for ½ hour and the mixture filtered. The filtrate was evaporated to a brown syrup at reduced pressure, the residue from filtration was extracted with chloroform and the chloroform extract evaporated to a syrup. Infra-red showed both syrups to be identical. The syrup was distilled giving a distillate at 0.5 mm, BP 187-193°C.

$$[\alpha]_D^{18} = -29.63$$

Yield = 1.96 g = 25%

EXPERIMENT 3

Synthesis of 1,2-O-Isopropylidene 3,4,5,6 tetra benzyl D-Glucitol using potassium hydroxide catalyst[3,4]

1,2-O-Isopropylidene D-glucitol (1 g) was dissolved in benzyl chloride (50 ml) and powdered potassium hydroxide (10 g) was slowly added with the reaction vessel cooled in ice. The potassium hydroxide was added so that the temperature did not rise above 130°. After addition of the potassium hydroxide, (3 hours), the temperature was maintained at 130° for 2 hours. Distilled water (100 mls) were added and the solution extracted with chloroform (250 ml). The chloroform extract was washed with water three times and dried over magnesium sulphate. The chloroform was removed under reduced pressure, the benzyl chloride and dibenzyl ether were removed under high vacuum 0.5 mm, BP 39-54°. A pale yellow solid remained which distilled at 0.5 mm 188-192°.

$$[\alpha]_D^{20} = -29.7$$

Yield = 1.39 g = 53%

Analysis	Required for $C_{37}H_{42}O_6$	C 76.26%	H 7.26%	O 16.48%
	Found	C 77.5%	H 7.19%	O 15.31%

EXPERIMENT 4

Hydrogenolysis of the syrup from Experiment 5^3

The compound (1.27 g) was dissolved in dry methanol (60 ml) and palladium black (2.75 g) in dry methanol (30 ml) saturated with hydrogen was added. The mixture was hydrogenated at 1.5 atmospheres for 6 days.

Uptake adjusted to N.TP = 249.5 ml

Calculated uptake at N.TP = 205.44 ml

The palladium was filtered off under nitrogen and the filtrate evaporated to a syrup, which was crystallised from ethanol.

YIELD = 0.34 g

MP = 165-166°

Mixed MP with authentic 1,2-O-isopropylidene D-glucitol = 166-167°

Therefore no migration had occurred on benzylation.

EXPERIMENT 5

Hydrolysis of 1,2-O-Isopropylidene 3,4:5,6 tetra benzyl D-Glucitol

1,2-O-isopropylidene 3,4:5,6 tetra benzyl D-glucitol (1.25 g) was taken up in aqueous ethanol (50% 10 ml) and 1R 120H$^+$ resin (1.0 g) was added and the mixture heated on a boiling water bath for two hours. The resin was filtered off and the filtrate evaporated to a pale yellow syrup. Thin layer chromatography on silica gel using benzene containing 1.5% methanol as developing agent showed a spot at Rf = 0.12 in comparison with the starting material Rf = 0.53.

The syrup was taken up in hot ethanol but would not crystallise, other solvents, methanol ethyl acetate and ethyl acetate petroleum ether mixtures were attempted without success.

Analysis	Required for $C_{34}H_{38}O_6$ =	C = 75.25%	H = 7.06%	O = 17.69%
	Found	C = 75.31%	H = 7.11%	O = 17.58%

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GENERAL TECHNIQUES

1. Polarimetry:-

Polarimetric measurements were carried out on three instruments.

(a) Hilger Watts M. 511 photoelectric polarimeter at Mercury 5461 line

(b) Bellingham and Stanley polarimeter at Sodium D line

(c) Perkin Elmer 141 at 365 nm; 436 nm; 546 nm; 578 nm and 589 nm.

A jacketed polarimeter tube connected to a thermostat was used in conjunction with the Hilger Watts M. 511 and Perkin Elmer 141.

2. Spectrophotometry:-

(a) Kinetic runs were carried out using the Perkin Elmer 137 UV spectrophotometer and a 1 cm constant temperature cell.

(b) Other spectrophotometric determinations were carried out using the Unicam SP. 500 spectrophotometer, using 1 cm cells.

It was noted that n-butyraldehyde obeyed Beer's Law at 281 nm over a period of 8 hours without appreciable photodecomposition.

3. Thin Layer Chromatography:-

This was normally carried out using Kieselgel G nach Stahl on glass plates, with the spots brought up in an iodine vapour tank.

The plates were developed with saturated aqueous methyl ethyl ketone, which was found to be especially useful for separation of isomeric mono-acetals as well as the mono-, di and tri acetals and ketals.

4. Column Chromatography:-

This was carried out using Watman CF 11 and Kieselgel 0.2-0.5 mm and Alumina chromatography grade, eluting with the solvents mentioned in the particular experiments.

5. Paper Chromatography:-

Whatman No 1. chromatography paper was used, with the following solvent systems, for descending chromatography.

(a) Methyl Ethyl Ketone - saturated with water:-

The stationary phase was water and the mobile phase was methyl ethyl ketone.

Similar to thin layer chromatography this was useful for separation of configurational isomers of mono-acetals.

(b) Butanol/Ethanol/Water[1] (40/11/19):-

A stationary phase of water with a mobil phase containing n-butanol ethanol and water in the above proportions.

This was useful for general separations of mixtures of acetals and hexitols.

(c) Butanol/Pyridine/Water (6/4/3):-

A stationary phase of water with a mobile phase containing n-butanol pyridine and water in the above proportions, useful for separation of pentoses.

The compounds were located as follows:-

(i) The papers were dried in the oven at excess of 80° .

(ii) Sprayed lightly with saturated sodium meta-periodate solution[2].

(iii) Dipped in saturated aqueous solution of silver nitrate consisting of silver nitrate (2.5 ml) in acetone (490 ml) with water (10 ml). The paper was allowed to dry at room temperature.

(iv) The paper was then dipped in ethanolic sodium hydroxide (sodium hydroxide (2 g) in aqueous ethanol (2 ml H_2O + 98 ml Ethanol)). This brought compounds up as brown spots.

(v) The chromatograms were finally preserved by 'fixing' in a solution of aqueous sodium thiosulphate (2.5% w/v).

This method was suitable for sugars and polyhydric alcohols together with the mono and di-acetals of hexitols.

Mobilities were generally measured relative to the solvent front Rf.

6. Paper Ionophoresis:-

Ionophoresis was carried out on Whatman No 3 paper using a Shandon High Voltage Electrophoresis Apparatus using the following electrolytes.

(a) Sodium borate (Boric acid (14.9 g) and sodium hydroxide (8 g) in water (2 l) pH adjusted to pH 9.8-10), 2,3,4,6-Tetra-O-methyl-D-glucose was used as non migrating marker.

(b) Sodium molybdate[3] (Sodium molybdate dihydrate (25 g) in water (1200 ml) adjusted to pH5 with concentrated sulphuric acid) Glycerol was used as non migrating marker.

(c) Sodium meta vanadate; an aqueous solution of sodium meta vanadate[4,5] (1.5% w/v).

The same locating reagents were used for borate and molybdate buffers as in paper chromatography, while sodium metavanadate was used only to distinguish hexitols in the purity check on D-glucitol, and

here it was sufficient to heat the ionophoretograms to c 100°C for 10 min in order to locate the compounds as bluish spots on a yellow background.

7. Vapour Phase Chromatography:-

(a) A Pye Argon Chromatograph, with - ionisation detector and glass column (4 ft x 4 mm), was used, with argon as the carrier gas at a rate of 70-80 ml/min.

(b) Perkin Elmer Fractometer modified with a flame ionisation detector and all glass columns (4 ft x 4 mm).

Stationary phases employed in both cases were:-

P.P.E. - 10% (w/w) m-bis (m-phenoxy phenoxy) benzene on silicone treated celite.

S.E. - 30 (A methyl silicone) 3% (w/w) on Gas Chrom P; Apeizon K - (5% w/w) on celite.

With the exception of fully substituted derivatives all samples were injected as their trimethylsilyl ethers (T.M.S. derivatives) which were prepared according to Sweeley et al.[7]

The substance (c 10 mg) was dissolved in anhydrous pyridine (1 ml) and hexamethyldisilazane (0.2 ml) and trimethyl-chlorosilane (0.1 ml) were added). After shaking for 30 secs. the mixture was allowed to stand for 20 mins at room temperature and then centrifuged. The clear liquid was decanted from the white precipitate and rotary evaporated to low bulk, and taken up in diethyl ether (1 ml). This solution was injected into the column. Retention volumes (RV) were recorded relative to the T.M.S. derivative of D-Glucitol (RV = 1)

8. Infrared Spectroscopy:-

These were carried out on the Perkin Elmer 337 Grating Infrared Spectrophotometer and the Pye Unicam SP 100 using Nujol Mulls or thin films between Potassium Bromide Plates.

9. Proton Magnetic Resonance Spectroscopy:-

The Varian 60 Spectrometer.

10. Elemental Analysis:-

All analyses were carried out by Alfred Bernhardt (Mülheim (Ruhr) Germany).

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