Synthesis, Structure and NMR Spectroscopy of Some Deoxy Carbohydrate Polyol Derivatives and their Mono-O-Butylidene Acetals.

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ABSTRACT

I The reactions between some deoxy polyol derivatives and n-butyraldehyde have been studied in aqueous hydrochloric acid and the initial rate coefficients of the deoxy polyols determined.

1. 2-Deoxy-D-arabino-hexitol yielded a 1,3-acetal as a kinetic phase and a 4,6-acetal as a thermodynamic phase.

2. 2-Deoxy-D-lyxo-hexitol yielded a 1,3-acetal as a kinetic phase. It also gave 4,5 and 4,6-acetals as a combined thermodynamic phase.

3. 2-Deoxy-D-erythro-pentitol yielded a 1,3-acetal as a kinetic phase and a 3,5-acetal as a thermodynamic phase.

4. 3-Deoxy-D-ribo-hexitol yielded a 2,4-acetal only.

5. 4-Deoxy-D-xylo-hexitol yielded diastereoisomeric 2,3-acetals as a kinetic phase with a 1,3-acetal as a thermodynamic phase.

6. 3-Deoxy-3-fluoro-D-glucitol yielded a 4,6-acetal as a kinetic phase and a 2,4-acetal as a thermodynamic phase.

7. 6-Deoxy-6-fluoro-D-galactitol yielded diastereoisomeric 4,5-acetals, there was also evidence suggesting the presence of 1,3 and 2,3-acetals.

II A carbon-13 n.m.r. spectral analysis has been undertaken for some deoxy polyols and acetals derived therefrom.

1. The carbon-13 chemical shifts of the deoxy polyols were assigned by consideration of substituent effects upon the appropriate non deoxy polyols and deuterium substitution.

2. The structures of the acetals of the deoxy polyols have been ascertained by consideration of carbon-13 chemical shift changes associated with acetalation.

III Proton n.m.r. spectroscopy has been used for further structural and conformational analysis of the acetals of the deoxy polyols.

IV Fluorine-19 n.m.r. spectroscopy was used to investigate the conformation and structure of the deoxy fluoro polyols and their acetals.

CONTENTS

I INTRODUCTION

A cyclic acetal is the condensation product formed when a diol or higher polyhydric alcohol reacts with an aldehyde. The product of reaction with a ketone is often called a ketal. The chemistry of cyclic acetals and ketals has been widely studied since Wurtz[1] first condensed ethylene glycol with acetaldehyde yielding 2-methyl-1,3-dioxolane (Fig. I-1).

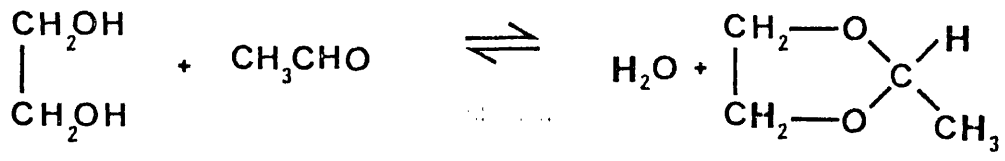


Fig. I-1

Acetal formation was subsequently shown by Meunier[2] to be catalysed by acidic substances, the commonest acids being mineral acids and the Lewis acids such as phosphorous pentoxide and zinc chloride. Recently, however, certain sugar acetals have been prepared without the use of an acid catalyst.[3] The nature of the acid catalyst can sometimes govern the products formed from a given pair of reactants. For example, von Vargha[4] found that the reaction between 1,2-O-isopropylidene-D-mannitol and acetone yielded 1,2:5,6-di-O-isopropylidene-D-mannitol with cupric sulphate as catalyst. However, when the catalyst was changed to concentrated sulphuric acid the product was 1,2:3,4:5,6-tri-O-isopropylidene-D-mannitol. Another example is the reaction between 1,6-di-O-benzoyl-galactitol. Haskins, Hann and Hudson[5] found that two

isomeric dibenzylidene acetals could be obtained by variation of the acid catalyst.

The mechanism for cyclic acetal formation is usually depicted as below[6] (Fig. I-2).

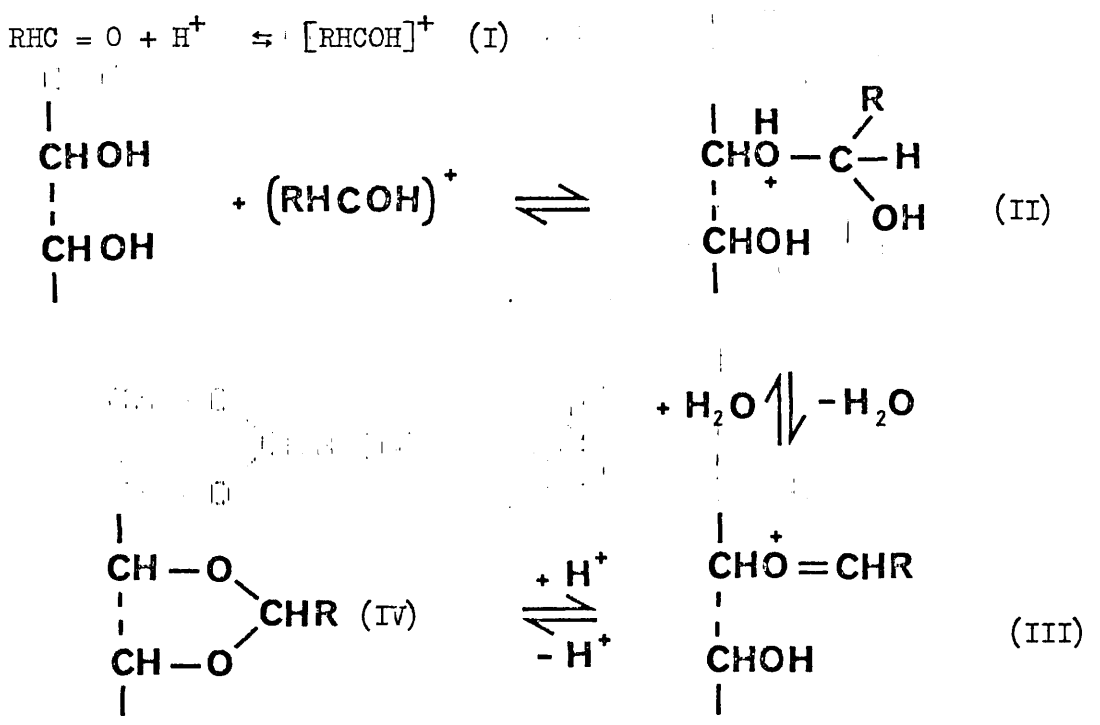


Fig. I-2

The aldehyde species reacts with a proton to form its conjugate acid (I), the conjugate acid then attacks one of the hydroxyl oxygen atoms to yield a hemiacetal (II). The hemiacetal then loses a molecule of water to give the oxocarbonium ion (III). Finally, the oxocarbonium ion reacts with the other hydroxyl oxygen with loss of the catalytic proton to give the cyclic acetal (IV). Considerable work has been done on the mechanisms of acetal hydrolysis and formation. Bell et al[7] propose a mechanism for the formation of acyclic acetals which has the

formation of the oxocarbonium ion as the rate determining step. The acid catalysed hydrolysis of acetals has been extensively studied. It may be the case that the rate determining step in hydrolysis is different for cyclic and acyclic acetals. It was generally thought that the rate determining step in hydrolysis is unimolecular (A-1) decomposition of a protonated species to the products.[8] Recent studies on cyclic acetals however have concluded that the rate determining step in hydrolysis is bimolecular attack of water on an oxocarbonium ion[9,10] (Fig. I-3).

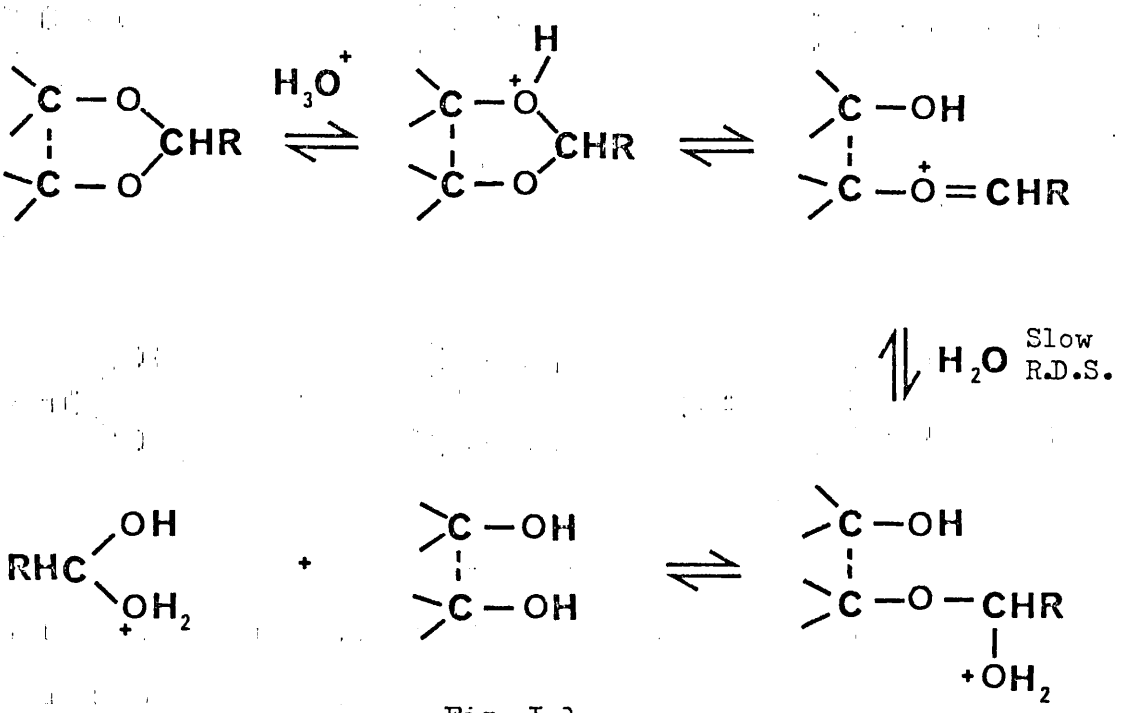


Fig. I-3

For the polyols, the hydroxyl function first attacked by the conjugate acid is either primary or secondary. Available evidence for diols[11] and methyl glycosides[12,13] seems to suggest that the primary hydroxyl is preferentially attacked in hemiacetal formation. Cyclic monoacetal formation results in the blocking of two hydroxyl groups on the polyol. It is readily seen that for a common polyol such as D-glucitol the number of theoretical structural isomers is

large, fifteen to be precise. The size of the acetal ring in these isomers can vary from a five membered ring to a nine membered ring. When the acetalation of the polyol is carried out and the products isolated however, it is found that the number of products formed is much less than the theoretical number. In practice eight and nine membered acetal rings are never formed and seven membered only rarely observed.

The most commonly observed acetal rings are the six membered, which are derivatives of 1,3-dioxane (Fig. I-4).

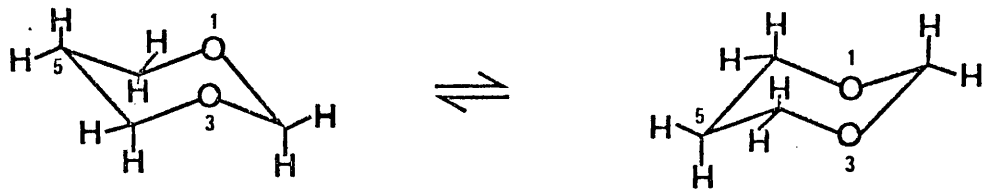


Fig. I-4

Quite common, but not so common as the six membered are the five membered rings, they are derivatives of 1,3-dioxolane (Fig. I-5).

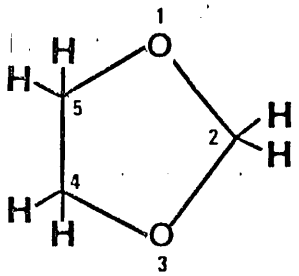


Fig. I-5

That a given polyol and aldehyde react together to form a limited specific set of products has already been mentioned. Hann and Hudson[14] proposed a set of empirical rules to account for this behaviour. They based their rules on the available data for the known methylene acetals of D-glucitol, galactitol and D-mannitol together with the benzylidene acetals of some other polyols. They demonstrated that there was a relationship between the configuration of the hydroxyl groups of the polyol and the acetals formed from it in condensation with an aldehyde. Barker and Bourne[15] later extended the initial rules of Hann and Hudson encompassing all the relevant information that had come to light since the inception of Hann and Hudson's rules. The Barker-Bourne rules were based on the information regarding the condensations of the polyhydric alcohols with acetaldehyde, benzaldehyde and formaldehyde. Barker and Bourne[15] also introduced a code system whereby the position and size of the acetal ring were defined. If the acetal is formed between hydroxyl groups on adjacent carbon atoms then it is an α ring; if formed between hydroxyl groups on carbon atoms with one intervening carbon atom then it is a β ring etc. Furthermore, the configuration of the hydroxyl groups involved are shown relative to the Fischer projection formula of the polyol. If the involved hydroxyl groups are on the same side of the Fischer projection formula the ring is a cis-ring (C). If the involved hydroxyl groups are on opposite sides of the projection formula the ring is a trans-ring (T). If one of the hydroxyl groups is in a terminal hydroxymethyl function then no cis or trans notation is required. The cis, trans notation was subsequently changed to erythro and threo respectively.[16] The Barker-Bourne rules are

summarised below.

(i) First preference is for β-erythro ring.

(ii) Second preference is a β-ring.

(iii) Third preference is α-, α-threo, β-threo, and γ-threo rings.

These preferences are illustrated in Fig. I-6.

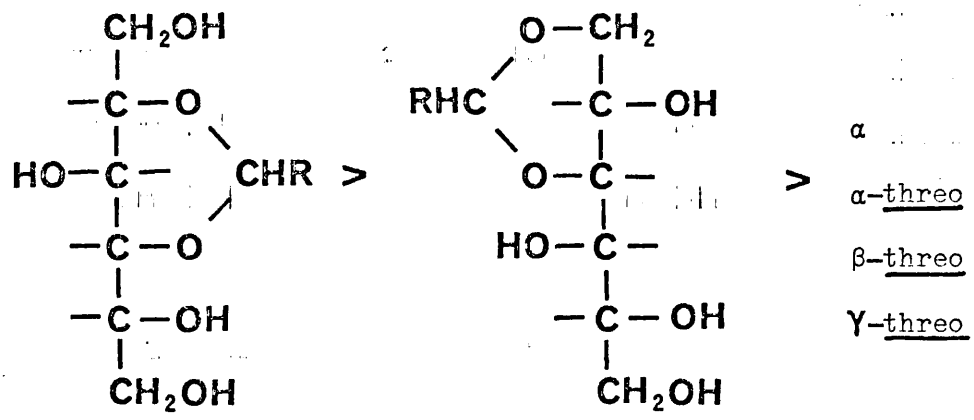


Fig. I-6

Before proceeding it is worth pointing out that the Hann-Hudson rules and the Barker-Bourne rules are only meant to be applied to the acetal(s) formed under thermodynamic conditions i.e. at equilibrium in the acetalation reaction. In the early stages of the reaction less preferred acetals may be formed more rapidly than the theoretically predicted most stable acetal(s).

After the publication of the Barker-Bourne rules there were two different proposals forthcoming to explain the preferred structures. Barker, Bourne and Whiffen[17] based their explanation

on the conformation of the polyol, whilst Mills[18] based his explanation on a conformational analysis study of the acetals themselves.

Barker, Bourne and Whiffen assumed that the most stable conformation and likely adopted one for a polyol was the planar zig-zag.[19] The planar zig-zag is illustrated for D-arabinitol (Fig. I-7).

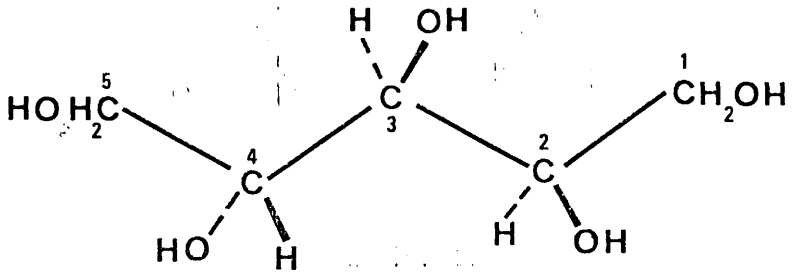


Fig. I-7

—— represents bonds in the plane of the paper.

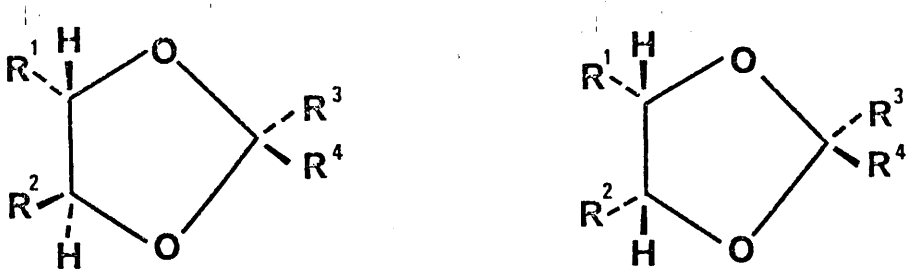
▬▬ represents bonds above the plane of the paper.

- - - represents bonds receding away from the plane of the paper.

From accurate models, Barker, Bourne and Whiffen measured the O-C-O distance between two oxygen atoms through space and found it to be 2.34Å. The principle of their explanation is that the more preferred a ring is then the easier it is to bring two oxygen atoms to the required 2.34Å distance. In order to orientate two oxygen atoms to the required distance, the conformation, and sometimes some O<C>C bond angles of the polyol have to be changed. There will be energy barriers for these changes but the

most preferred structure will have the lowest energy barrier. When Barker, Bourne, and Whiffen applied this theoretical approach to the acetals and polyols which formed the basis for the rules they found agreement between theoretically predicted and experimentally observed acetals.

Returning now to the explanation of Mills[18] using a conformational approach to the acetals themselves. The explanation is aided with Figs. I-8 and I-9.

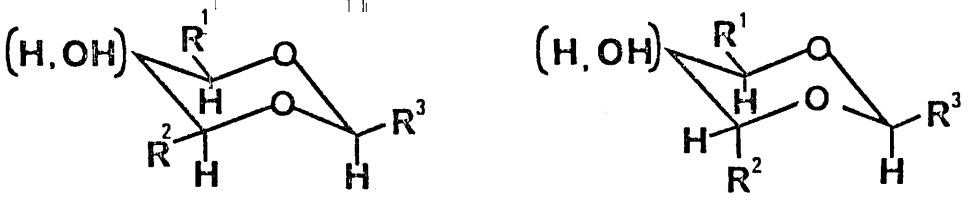


α-threo α-erythro

Fig. I-8

Mills assumed the 1,3-dioxolane ring to be very nearly planar. The α-threo ring shown in Fig. I-8 has the substituent groups R^1 and R^2 in a staggered position whereas the α-erythro ring has the substituent groups R^1 and R^2 eclipsed. The eclipsed interaction of R^1 and R^2 destabilises the α-erythro ring relative to the α-threo ring. For an α-ring R^1 or R^2 is hydrogen and the α-threo ring will be preferred over the α-ring because it is more

symmetrically substituted.[17]



β-erythro β-threo

Fig. I-9

Mills assumed the conformation of the six membered 1,3-dioxane ring to be a chair. The β-erythro ring has the substituents R^1 and R^2 both equatorial whereas the β-threo ring has either R^1 or R^2 axial. This axial disposition of the substituent was Mills' explanation of the lower preference of the β-threo rings. A β-ring has R^1 or R^2 as hydrogen and the less symmetrically substituted β-ring is not as stable as the more highly symmetrically substituted β-erythro ring as was the case for the 1,3-dioxolane derivatives.[17] Generally acetals of the polyols with β- or β-erythro rings have all large substituents in equatorial positions.

In the twenty years or more that have elapsed since Barker, Bourne, and Whiffen and then Mills explained preferred acetal ring structures, a wealth of information has appeared concerned with cyclic acetals. Not all of this has direct bearing on polyols and their acetals but some quite important findings have come to

light. A lot more is known about the conformation of the acetals and polyols both in the solid state and solution. Also free energy differences between equilibrating acetals have been measured and in some cases explained.

The conformations of the polyols were assumed by Barker, Bourne, and Whiffen[17] to consist of an extended planar zig-zag structure. This has been shown to be an erroneous assumption for some polyols by x-ray crystallography for the crystal state and by n.m.r. in solution.

Jeffrey and Kim[20] have shown that in the solid state the polyols adopt an extended planar zig-zag provided there are no eclipsed C-O bonds on alternating carbon atoms. This type of interaction is commonly called a 1,3-interaction. When such an interaction is present rotation about a C-C bond occurs in order to relieve the interaction. The resulting conformation of the polyol has been called "bent" or "sickle". This can be illustrated with reference to D-glucitol (Fig. I-10).

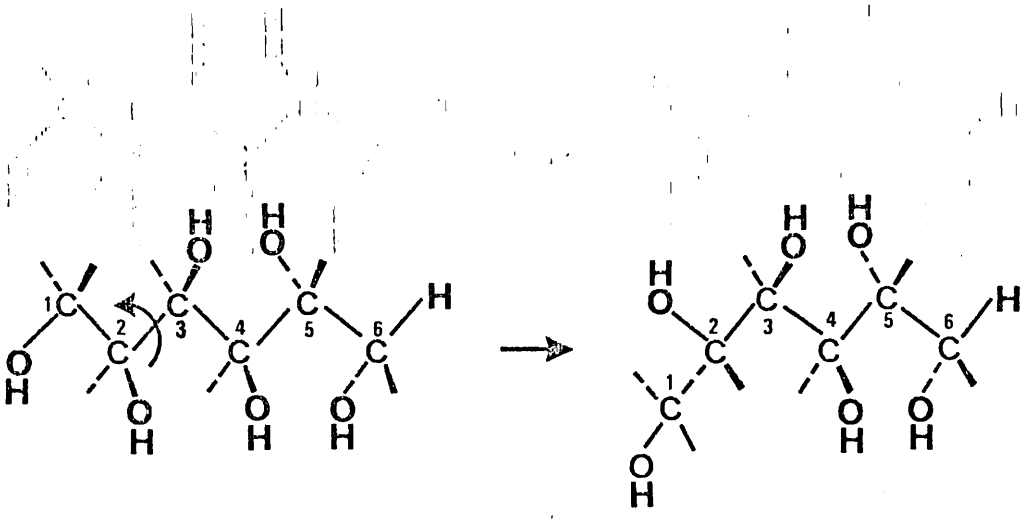


Fig. I-10

There is a 1,3-interaction between the hydroxyl functions on C-2 and C-4 for an extended planar zig-zag conformation of D-glucitol. This interaction is relieved by a 120° rotation about the C-2-C-3 bond as shown in Fig. I-10. The other polyols which exhibit this property are those having a ribo or xylo configuration of hydroxyl groups. The illustrated example was taken from work by Jeffrey and Kim[20] on the solid state conformation. The same situation has been found in solution by n.m.r. Horton has shown that ribo and xylo configurations containing acyclic sugar derivatives adopt "sickle" or "bent" conformations in solution whereas the lyxo configuration adopts an extended planar zig-zag. The results of Horton and Wander were taken from n.m.r. studies of peracetylated aldose dithioacetals[21] and diethyl and diphenyl aldose dithioacetals[22] with unsubstituted hydroxyl groups. Angyal has also found the same situation operating for peracetylated alditols[23] and alditols in the presence of lanthanide shift reagents[24] and calcium ions.[25] Similar work to that of Angyal has also been done by Kieboom et al[26] with polyols and lanthanide shift reagents with similar results. However, Kieboom et al also propose slightly modified conformations for the planar zig-zag and "sickle" conformations on the basis of intramolecular hydrogen bonding. Their proposals are illustrated for the case of galactitol (Fig. I-11).

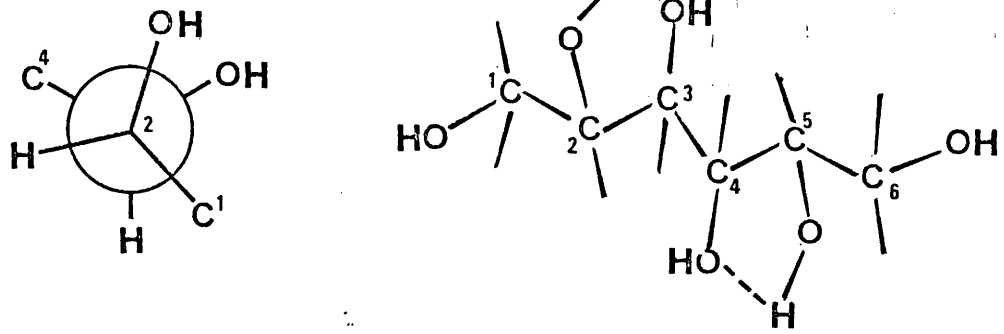


Fig. I-11

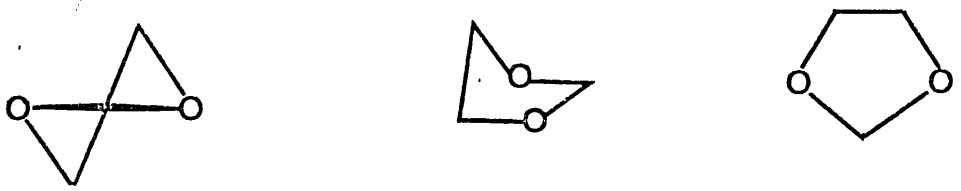
The dihedral angle between the hydroxyl functions on C-2 and C-3 is diminished to 40° from the expected 60° hence, so is the C-4 C-5 hydroxyls dihedral angle. This is supposedly due to intramolecular hydrogen bonding and results in a planar zig-zag bent by rotation around the C-2 - C-3 and C-4 - C-5 bonds. These considerations were applied by the same people to various other polyols with similar results.[26]

The last word here on polyol conformation is left to Mills who has proposed a set of rules and system of nomenclature which give the conformation of each hydroxymethyl and hydroxymethylene group of a polyol relative to its neighbouring groups.[27] He bases his system on the Cahn, Ingold, Prelog rules for specification of molecular chirality[28] with the uses of the letters A, M, P and G, K, U to specify certain orientations.

Conformational studies on the cyclic acetals can be divided into two convenient groups. Work dealing with 1,3-dioxolane plus

derivatives and also 1,3-dioxane plus derivatives.

Mills assumed the 1,3- dioxolane ring to be very nearly planar when explaining preferred acetal structures. This was subsequently shown to be an erroneous assumption. There are three types of conformation for a 1,3-dioxolane ring (Fig. I-12).



A B C

Fig. I-12

One is the half chair (A) where two atoms are displaced from the plane of the three remaining ring atoms, one above the plane, the other below. Another form is the envelope (B) where only one atom is out of the plane of the ring. The third form is the planar ring (C). Raman and infra-red spectroscopy[29] on 1,3-dioxolane suggest that the ring is non-planar. This has been further supported by n.m.r. which has shown 1,3-dioxolane[30] and 4-substituted 1,3-dioxolanes[31] to exist as envelope and half chair conformers. This is not to say that specific half chair and envelope structures are always found. Eliel[32] has suggested that 1,3-dioxolane and some of its derivatives exist as interconverting half chair and envelope conformers in a rapid state of conformational flux. This phenomenon has been given the name pseudorotation. The substitution of 1,3-dioxolane can affect the

pseudorotational itinerary of the ring. However only the most bulky substituents show a tendency to anchor the ring in a particular conformation. Small and medium substituents on 1,3-dioxolanesstill permit some conformational changes between energy minima conformations.

There is a great deal of evidence that 6-membered acetal rings which are derivatives of 1,3-dioxane (Fig. I-4) exist as chair conformers. However, the C-O bond is 10% shorter than a C-C bond so the chair conformers of 1,3-dioxane derivatives are puckered in the O_1-C_2-O_3 region and flattened in the C_4-C_5-C_6 region. This has been substantiated by n.m.r.[33] and x-ray crystallography.[34] Much of the published work on 1,3-dioxane and its derivatives has been carried out by two groups of workers. Anteunis[35] has carried out an extensive n.m.r. study of many different derivatives of 1,3-dioxane and related the n.m.r. to conformation. Eliel[36] has looked at free energy differences between isomers present in an equilibrium mixture for a wide range of acetals. An interesting point arising from Eliel's work is that electronegative substituents such as fluorine at C-5 prefer the axial orientation rather than the sterically expected equatorial position[36] (Fig. I-13).

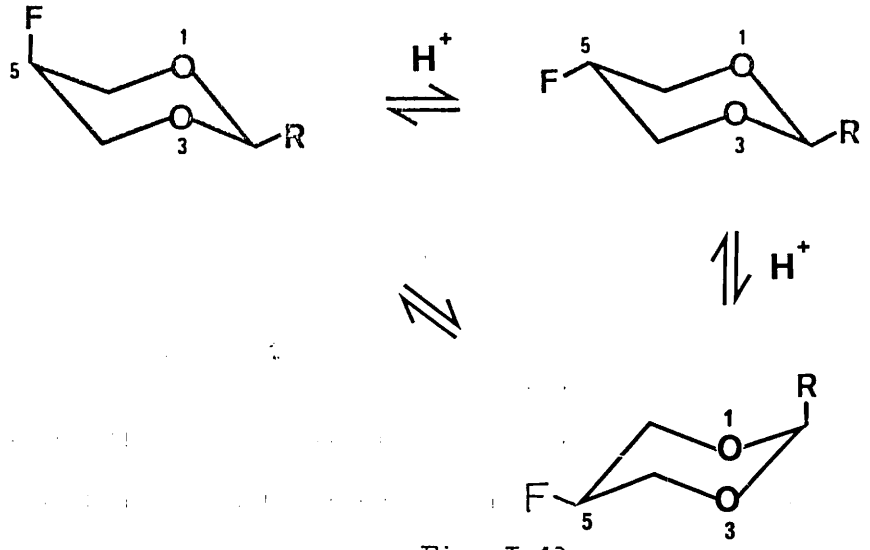


Fig. I-13

The above equilibrium lies to the left. This has been found not only for fluorine but a range of other electronegative substituents.

Acetal formation creates the possibility of diastereoisomerism[37] about the acetal carbon atom. For the butylidene acetals which are derivatives of 1,3-dioxane this diastereoisomerism does not occur when the acetals are formed under acid catalysis. This is because the propyl side chain prefers the equatorial environment rather than axial on steric grounds. Steric repulsions are greater for the axial n-propyl group in 1,3-dioxane compared to cyclohexane because of the nature of the ring puckering. The n-propyl group would be tilted towards axial substituents or hydrogen atoms on C-4 and C-6 in 1,3-dioxane whereas in cyclohexane it would be in a perfect axial orientation.[38] Butylidene acetals that are derivatives of 1,3-dioxolane commonly occur as a diastereoisomeric mixture. This is not surprising in view of the fact that the n-propyl side chain has much less of a steric requirement in a five membered ring compared to a six membered ring.

The empirial rules predict a 2,4-acetal to be most favoured for D-glucitol. It has been found however that in the early stage of the reaction of D-glucitol with aldehydes the 2,3-acetal is the predominant isomer.[39] At equilibrium, the 2,4-acetal is the predominant isomer.[39] The reaction is thus operating under kinetic control. The 2,3-acetal is a kinetically controlled product and the 2,4-acetal is a thermodynamically controlled product. Kinetic control is not limited to D-glucitol nor to 2,3-cyclic acetals. There are several examples of other acetalation reactions operating under kinetic control.[6,40]

The kinetic control for an acetalation raises the question of what the source of the thermodynamic product is. It can be formed from the polyol or the kinetically controlled product via an intramolecular rearrangement (Fig. I-14).

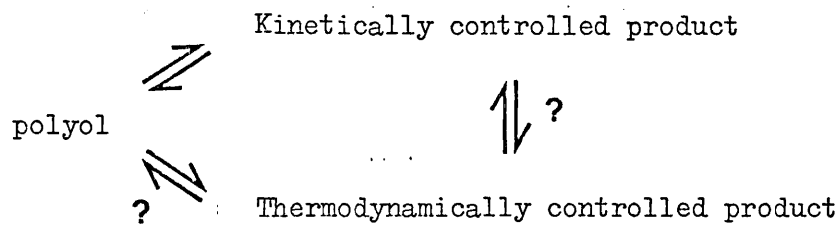


Fig. I-14

It has been suggested that the thermodynamically controlled acetal is formed from the polyol on the basis of some hydrolysis studies.[39] Capon[41] however queries this assessment by saying the experiment as carried out does not show which side of the equilibrium the thermodynamically controlled acetal originates.

Let us now consider structural elucidation of the cyclic acetals of polyols. There are several methods available for such structure determinations. One of the older techniques is periodate

oxidation[42] of the acetal, measuring the periodate uptake and the liberation of formic acid and formaldehyde (Fig. I-15).

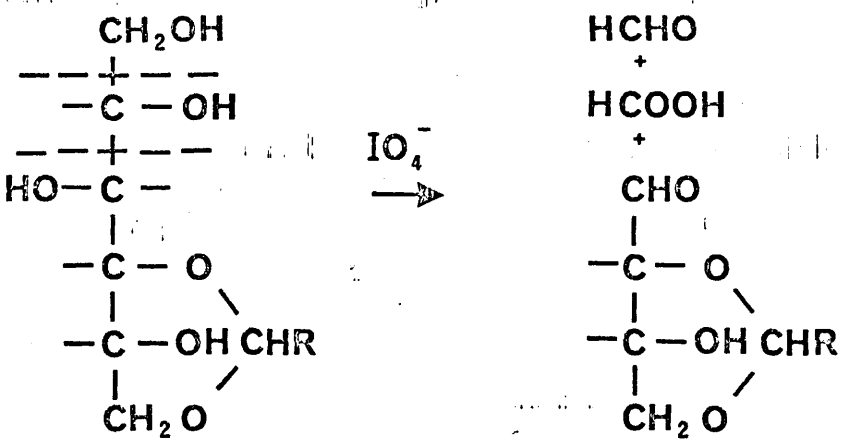


Fig. I-15

The periodate ion cleaves between vicinal diol groups as shown above. Spectrophotometric determination of periodate uptake, formic acid and formaldehyde liberation[43] give insight into the structure.

The number of free hydroxyl groups in an acetal can be determined by acetate formation followed by estimation of the acetate content. The primary hydroxyl functions can be tested for by tritylation with triphenylmethyl chloride.

More modern techniques are n.m.r. and mass spectrometry. The ring size of an acetal can be determined from certain features of its n.m.r. spectrum associated with the acetal proton.[44] The acetal protons in five, six, and seven membered rings have different chemical shifts characteristic of the particular ring size.[44]

Mass spectrometry has found increasing use in the structure elucidation of cyclic acetals of polyols. One particularly elegant method is the methylation of the free hydroxyl groups, hydrolysis of the acetal ring then acetylation[45] (Fig. I-16).

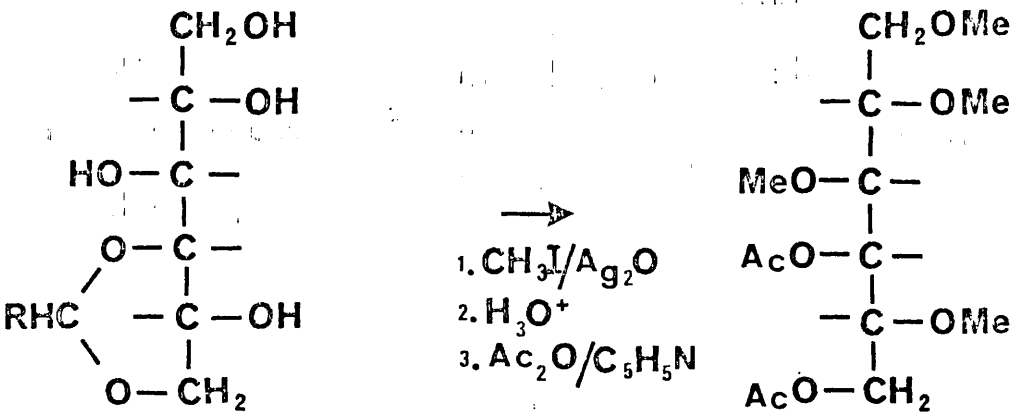


Fig. I-16

The methylated alditol acetate obtained will have a breakdown pattern characteristic of the distribution of methyl and acetyl groups[46] hence the original position of the acetal ring may be ascertained.

The further use of n.m.r. as a structural tool for cyclic acetals will be mentioned later on in the n.m.r. section of this thesis. It will suffice to say here that the n.m.r. technique is invaluable to structure elucidation for a range of nuclei such as hydrogen, carbon and fluorine.

After discussing historical and modern topics of importance to the cyclic acetal field, a few words would not be out of place regarding the origin of the work described in this thesis.

After the discovery of kinetic control in the acetalation of D-glucitol[39] further work was carried out on derivatised D-glucitols.[6] 1-Deoxy-D-glucitol was found to exhibit kinetic control in its acetalation as was 2-deoxy-D-glucitol. However, the original structural analysis of the cyclic acetals revealed that 2-deoxy-D-glucitol yielded a five membered ring as a thermodynamically controlled product and a 6 membered ring as a kinetically controlled product (Fig. I-17).

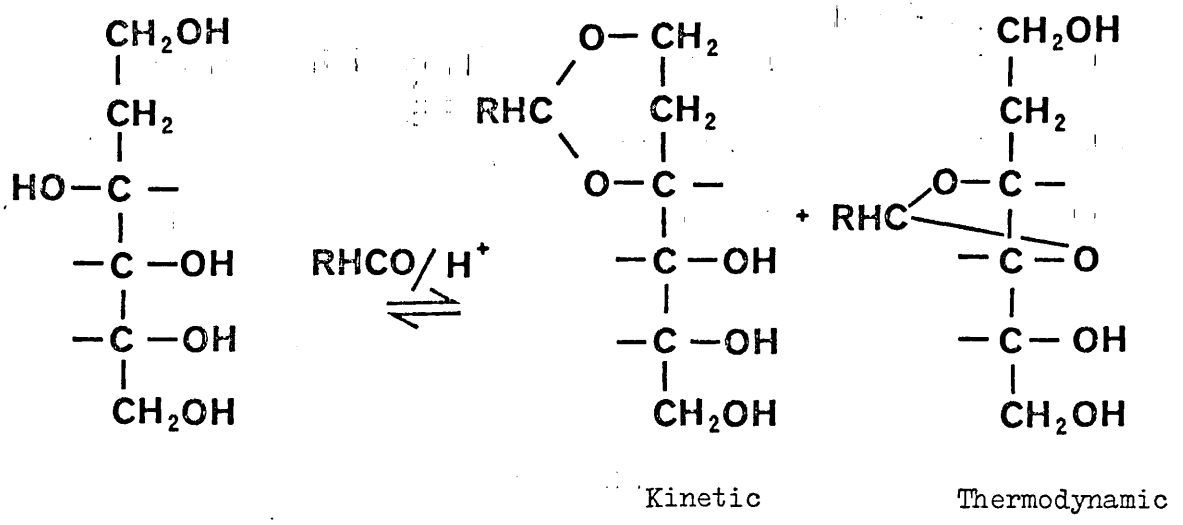


Fig. I-17

The results of the experiment could not be explained by the Barker-Bourne rules and it seemed as though the 2-deoxy-D-glucitol was behaving as an exception. The 1-deoxy-D-glucitol however behaved normally in its acetalation. Hence it was decided to pursue the matter further by a programme of research into the acetalation of deoxy polyols having secondary deoxy groups and other derivatives such as their fluoro analogues. The work presented in this thesis is a result of some of these investigations.

II Monobutylidene Acetals of Some 2-Deoxy Polyols

II-A 2-Deoxy-D-arabino-hexitol

1. Introduction

Although the solid state structure and conformation in solution have not been investigated the carbon chain of 2-deoxy-D-arabino-hexitol is expected to adopt a planar zig-zag conformation (Fig. II-1). This is inferred from a lack of any 1,3-interactions between hydroxyl functions.

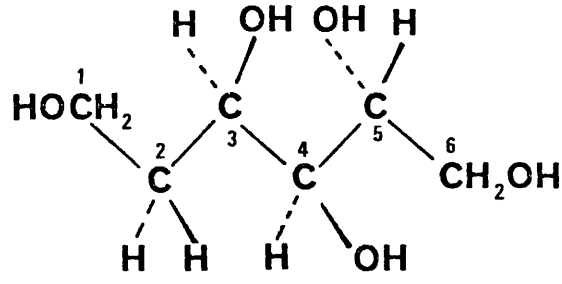


Fig. II-1

The Barker-Bourne rules predict the most favoured cyclic acetal of the polyol as that having a β-ring. There are two such β-rings possible, namely the 1,3 and 4,6-rings. The butylidenation of 2-deoxy-D-arabino-hexitol has been previously studied under conditions yielding monoacetals[6] and diacetals.[47] The monoacetalation study concluded that a 1,3-monoacetal was formed as a kinetically controlled product with a 3,4-monoacetal as a thermodynamically controlled product. The diacetalation study

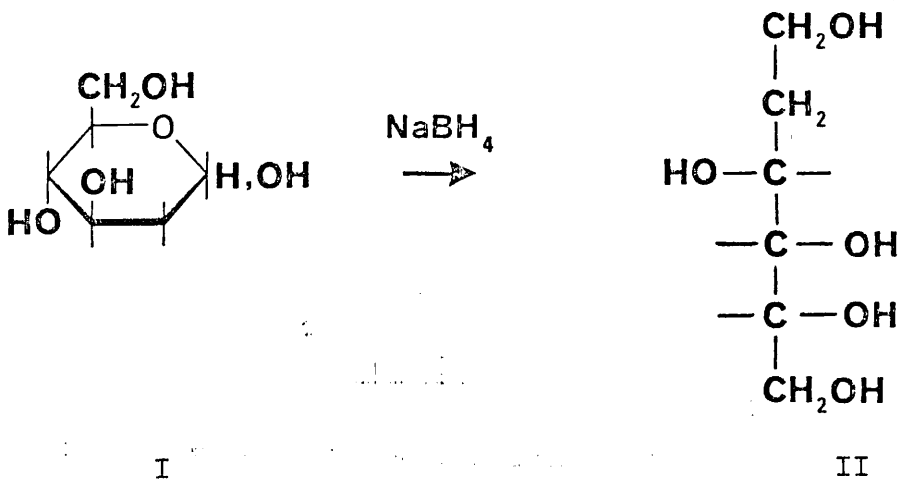
showed the presence of several diacetals. One of these, a 1,3:4,6-diacetal was present as a thermodynamic phase, the remaining diacetals, all of unknown structure were present as a kinetic phase.

The terms kinetically and thermodynamically controlled products or phases have been used previously in describing acetalation reaction products by this research school. Their continued use has been adopted in this thesis for this reason. Briefly, the kinetic phase is thought of as that product which is formed quickest in the early stages of the reaction. The thermodynamic phase is the product with the slowest initial rate of formation but is the predominant product at the reaction equilibrium.

Returning to the acetalation studies of 2-deoxy-D-arabino-hexitol[6,47] one may see a contradiction in the structures of the thermodynamic phases. The diacetalation product conforms to the Barker-Bourne rules whereas the monoacetalation product does not. The only other reported acetals of 2-deoxy-D-arabino-hexitol are dimethylene[48] and di-(m-nitrobenzylidene)[49] derivatives, both of unknown structure. A lack of any other acetalation studies which might clarify the position prompted a reinvestigation of the monoacetalation studies.

2. Results and Discussion

2-Deoxy-D-arabino-hexitol (Fig. II-2, II) was obtained by borohydride reduction of commercially available 2-deoxy-D-arabino-hexose (Fig. II-2,I).



I II

Fig. II-2

The reaction between 2-deoxy-D-arabino-hexitol and n-butyraldehyde (both 0.1M) in 0.5M-hydrochloric acid was monitored by polarimetry and gas liquid chromatography. These studies were visually the same as those previous[6] in that they indicated the presence of kinetically and thermodynamically controlled products. The polarimetric study (Fig. II-3) showed an initial decrease of optical rotation followed by an increase to a constant value. The rotation minimum corresponded to a maximum concentration of the kinetic phase. The increase to a maximum value represented the formation of the thermodynamic phase and attainment of the reaction equilibrium.

The gas liquid chromatography study showed a set of three main peaks corresponding to the deoxy polyol and its two acetals (Fig. II-4). By taking chromatograms at known time intervals it

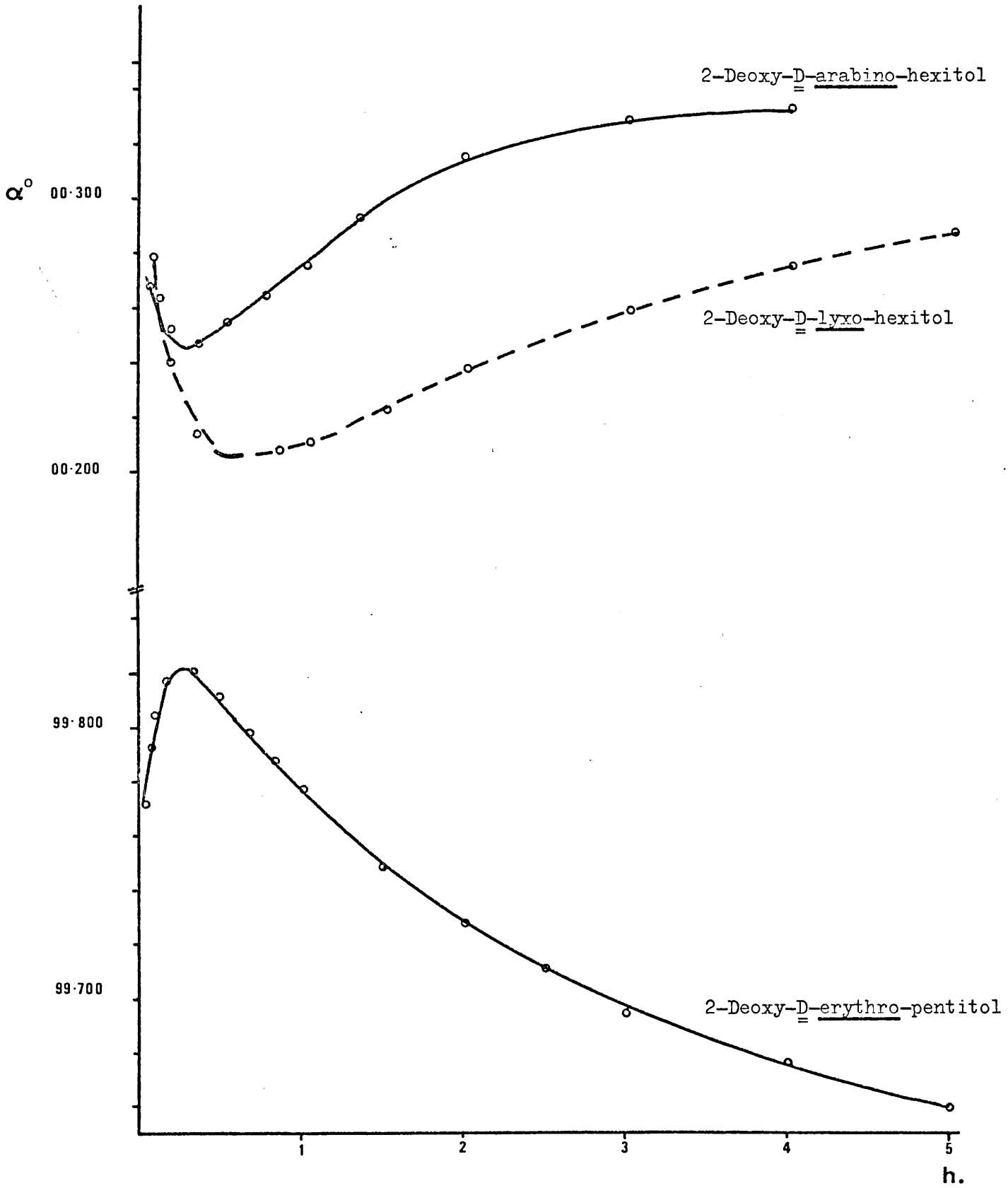


Fig. II-3 Optical Rotation versus Time for the Reactions between n-Butyraldehyde and Some 2-Deoxy Polyols.

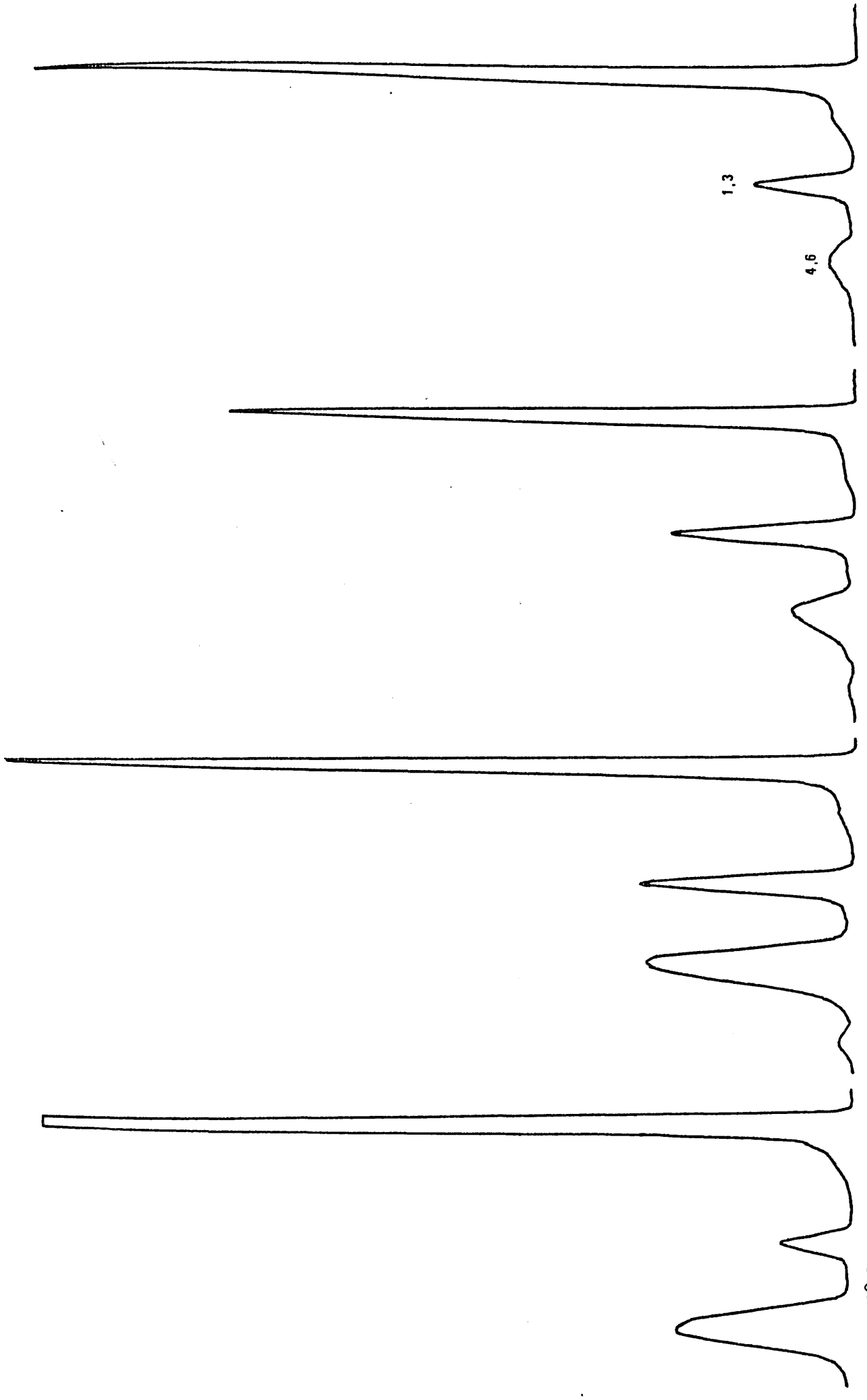


Fig. II-4 Gas Liquid Chromatograms of the Reaction between n-Butyraldehyde and 2-Deoxy-D-arabino-hexitol.

proved possible to measure the change in concentration of reactant and products with time. This is illustrated in Fig. II-5. The concentration of any one component of the reaction mixture at a given time was obtained relative to the sum of all the components of the mixture by the ratio of its peak area to the sum of all the peak areas. The areas of the various peaks were given by an electronic peak integrator. The absolute concentrations of components were not determined. The method described enabled the initial rate coefficient of 2-deoxy-D-arabino-hexitol to be measured. This was done by plotting the reciprocal of the deoxy polyol concentration against time. This treatment is based upon the simplification of the reaction to a second order reaction of a single component A i.e.;

$$2A \xrightarrow{k_1} C + H_2O$$

$$2A \xrightarrow{k_2} D + H_2O$$

This simplification can be made from the actual case

$$A + B \xrightarrow{k_1} C + H_2O$$

$$A + B \xrightarrow{k_2} D + H_2O$$

as the initial concentrations of A and B at time t_o are equal.[50] A corresponds to the deoxy polyol, B to the n-butyraldehyde, C and D to the kinetic and thermodynamic phases. The initial slope of the above mentioned plot yielded the initial rate coefficient k of the reaction of the deoxy polyol with n-butyraldehyde. This rate coefficient k is a composite rate coefficient of k_1 and k_2 which are shown above. In the present case this was found to be

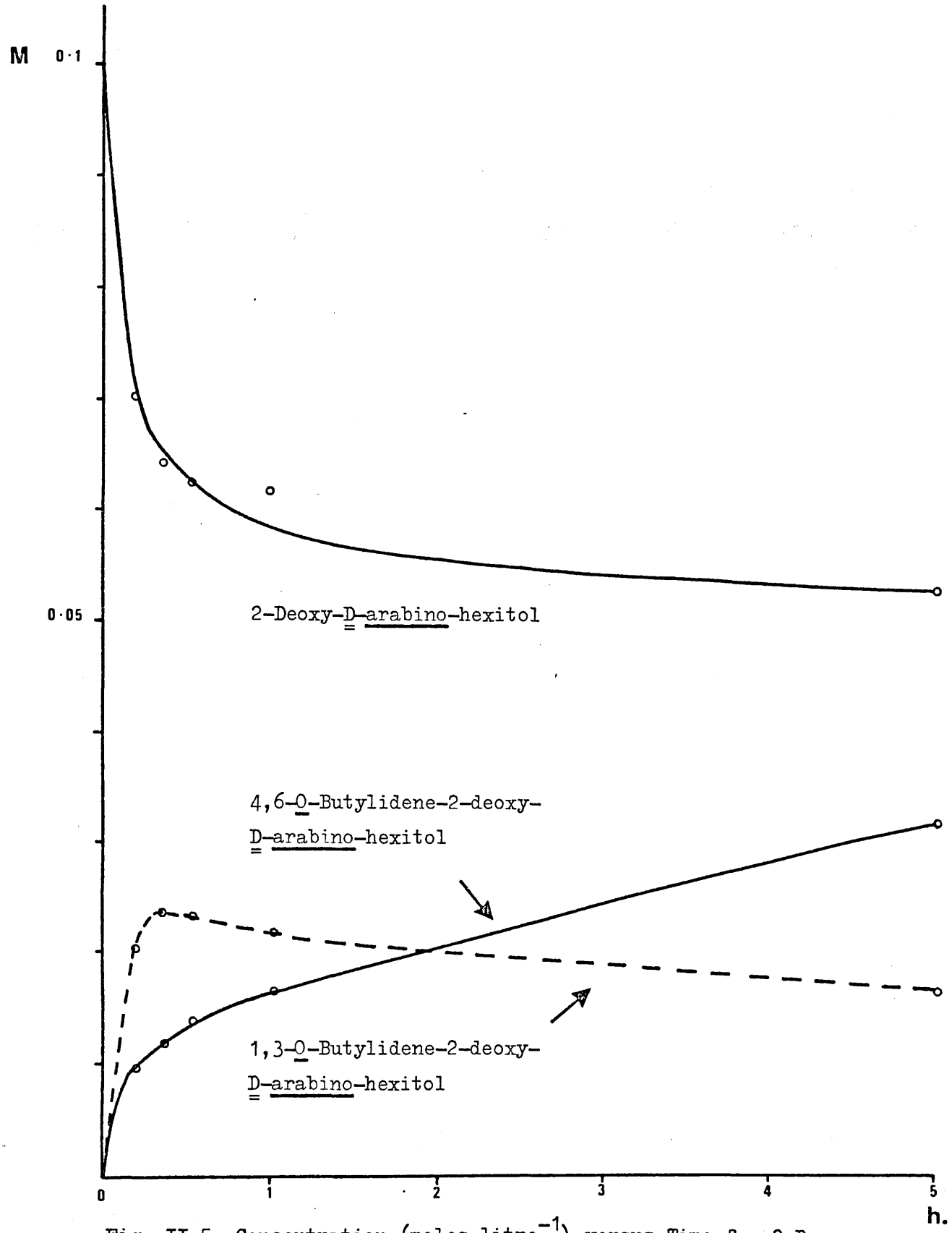
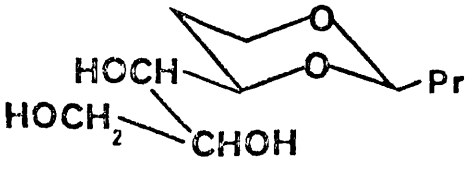
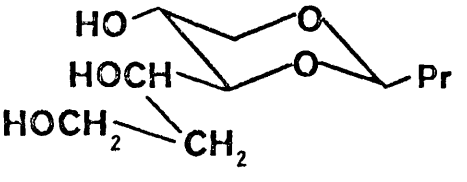


Fig. II-5 Concentration (moles litre^{-1}) versus Time for 2-Deoxy -D-arabino-hexitol and its Acetals in the Reaction with n-Butyraldehyde

5.7×10^{-3} litres $moles^{-1} sec^{-1}$. This compares favourably with the initial rate coefficient of 5.5×10^{-3} litres $moles^{-1}$ sec^{-1} found previously by spectrophotometric methods under comparable conditions of concentration and acid strength.[6] The agreement between the two initial rate coefficients seems to indicate that the gas liquid chromatography method is a reasonable one for measurement of changes in concentration with time for these acetalation studies.

Subsequent isolation (experiment 3) of the two monoacetals showed 1,3-O-butylidene-2-deoxy-D-arabino-hexitol (Fig. II-6,I) to be the kinetic phase. The thermodynamic phase was shown to be 4,6-O-butylidene-2-deoxy-D-arabino-hexitol (Fig. II-6,II).





I II

Fig. II-6

The presence of the 1,3-acetal as a kinetic phase agrees with the earlier work on the deoxy polyol.[6] The thermodynamic phase was previously postulated as being a 3,4-acetal. The present studies

disagree with those findings. Moreover, the isolation of a 4,6-acetal as a thermodynamic phase is in agreement with that predicted by the Barker-Bourne rules and is complementary to the diacetalation study.[47]

Both the kinetic and thermodynamic phases of the reaction contain β-ring systems yet there is a differentiation between them as to which is the kinetic phase. The ratio of the 4,6-acetal to the 1,3-acetal at equilibrium is approximately 2.5:1 corresponding to a free energy difference between the isomers of only 0.5 Kcal $mole^{-1}$. This distinction between the types of β-ring systems is common to the other 2-deoxy polyols studied and will be further elaborated upon later when the acetalation studies of these polyols have been discussed.

3. Structural Analysis of 1,3-O-Butylidene-2-deoxy-D-arabino-hexitol (Fig. II-6,I).

The structure of this acetal was elucidated quite thoroughly in the previous investigation.[6] A comparison between the presently isolated specimen and an authentic sample (thin layer chromatography, gas liquid chromatography, melting points and mixed melting point) showed no cause to assume disparity between the two. For this reason the structural investigation was confined to a spectroscopic study (n.m.r.).

^1H n.m.r. spectroscopy (section V-B) showed an acetal proton triplet centred at 4.53δ with a vicinal ($^3J_{HH}$) coupling of 5.0 Hz, both features being consistent with a six membered acetal ring.[31,44] The presence of one primary and two secondary hydroxyl functions was also detected by running the ^1H n.m.r. spectrum in D.M.S.O. (d^6)

before and after D_2O exchange. The only possible monoacetals having a six membered ring system with the above distribution of hydroxyl functions were the 1,3-acetal and 4,6-acetal. ^{13}C n.m.r. spectroscopy (section V-A) indicated that C-1 and C-3 experienced substantial chemical shift deshieldings in the acetal compared to their chemical shifts in the deoxy polyol. This indicated that C-1 and C-3 were carbons bearing acetal ring oxygens. Hence the n.m.r. spectroscopy studies gave no cause to doubt the previously determined 1,3-ring structure.

4. Structural Analysis of 4,6-O-Butylidene-2-deoxy-D-arabino-hexitol (Fig. II-6,II).

The monoacetal did not consume any periodate ion thus the structure was lacking any vicinal diol groups. The only possible monoacetals consistent with this were the 3,5, 4,5, and 4,6-acetals. The 220 MHz ^1H n.m.r. spectrum of the acetal (section V-B) in D.M.S.O. (d^6) showed an acetal proton triplet centred at 4.43δ with a ^3J coupling of 5.1 Hz, both facts consistent with a six membered ring system.[31,44] This eliminated the 4,5-ring as a possibility. One primary and two secondary hydroxyl functions were detected by re-running the ^1H n.m.r. spectrum after D_2O exchange then observing which of the original peaks were absent. This excluded the 3,5-ring and also the previously eliminated 4,5-ring leaving the structure as the 4,6-acetal.

^{13}C n.m.r. spectroscopy (section V-A) confirmed the above findings. Both C-4 and C-6 of the acetal showed substantial chemical shift deshieldings relative to the deoxy polyol. These deshieldings were consistent with C-4 and C-6 bearing acetal ring oxygens.

II-B 2-Deoxy-D-lyxo-hexitol

1. Introduction

In the solid state galactitol has been shown to adopt a planar zig-zag conformation of the carbon chain.[20] The same conformation is thought to exist in solution.[24] It seems safe to assume therefore that its 2-deoxy derivative will also exist as a planar zig-zag (Fig. II-7).

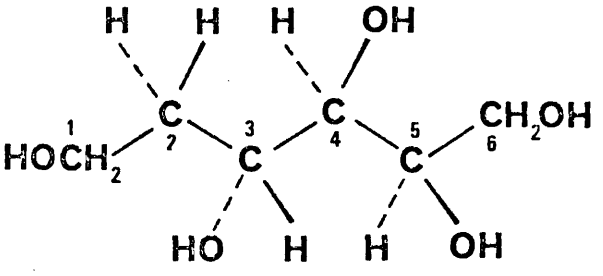


Fig. II-7

The reaction of 2-deoxy-D-lyxo-hexitol with n-butyraldehyde is expected to be more complicated than that of galactitol.[45] This is because the deoxy function removes the reflection plane of symmetry present in galactitol, thereby rendering the possibility of more structural isomers. The situation is similar to that of 1-deoxy-D-galactitol where an increase in the number of monoacetals is found compared to galactitol.[40] The only recorded acetal or ketal of 2-deoxy-D-lyxo-hexitol is a di-O-isopropylidene derivative of unknown structure.[51] From the

disposition of the hydroxyl groups (Fig. II-7) the predicted most stable acetal rings are both β-rings namely 1,3 and 4,6-rings.

2. Results and Discussion

2-Deoxy-D-lyxo-hexitol was prepared by sodium borohydride reduction of commercially available 2-deoxy-D-lyxo-hexose (Fig. II-8).

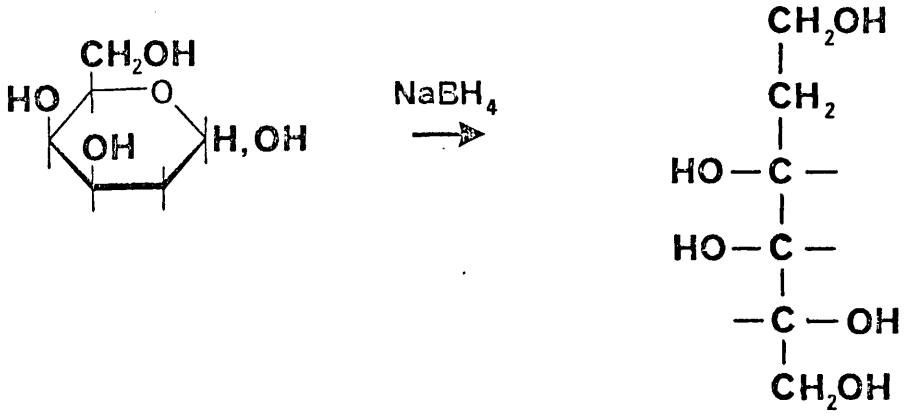
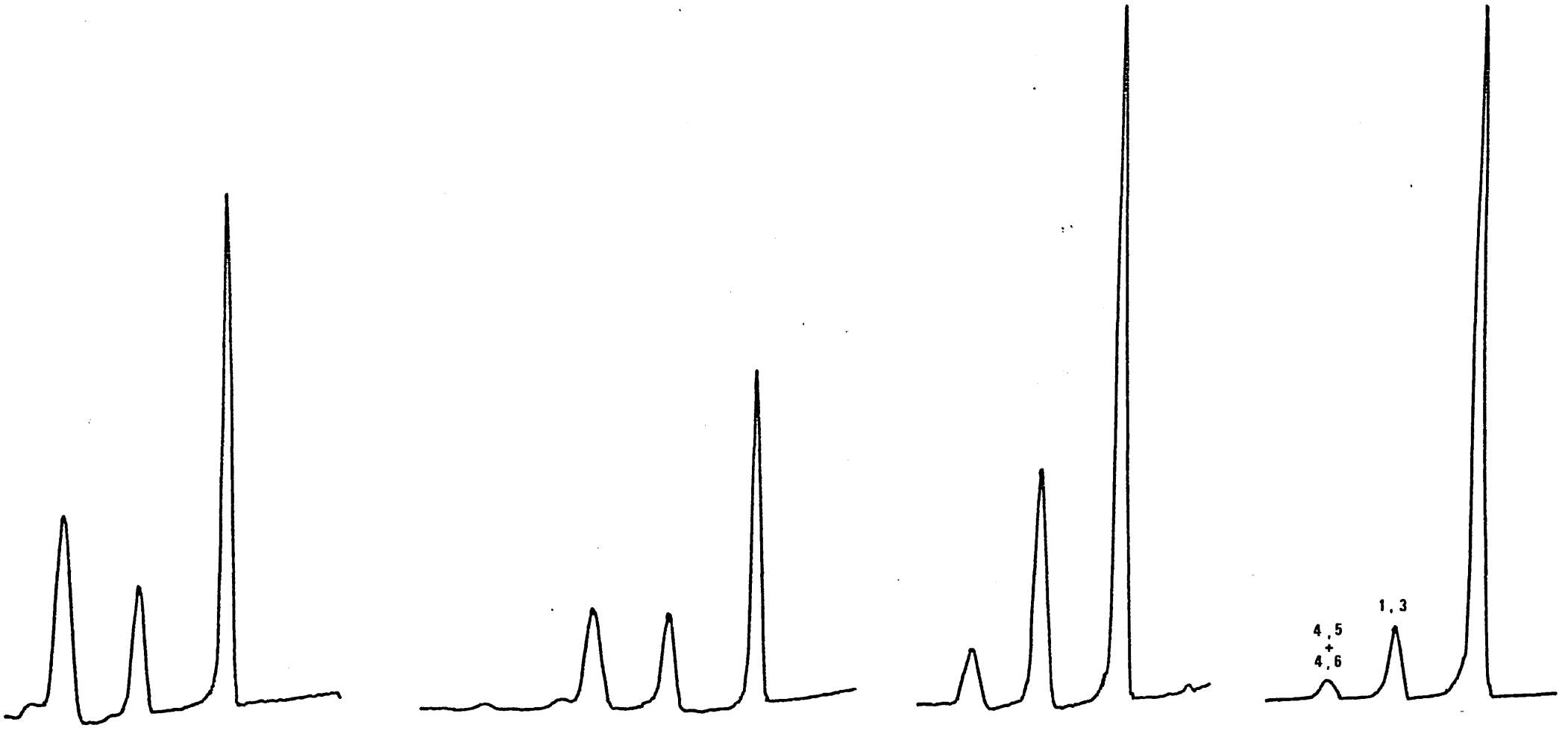


Fig. II-8

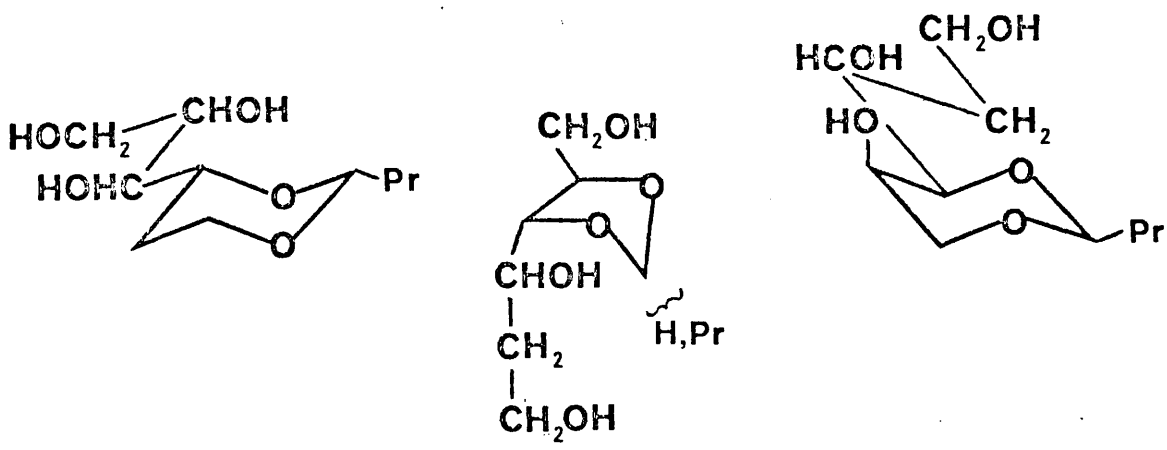
The reaction between 2-deoxy-D-lyxo-hexitol and n-butyraldehyde was monitored under identical conditions to those described previously (section II-A). The polarimetric (Fig. II-3) and gas liquid chromatography (Fig. II-9) studies indicated the presence of both kinetic and thermodynamic phases. The gas liquid chromatography study can however be misleading as it shows only two major monoacetal peaks when in fact there are three major monoacetals. The situation is further complicated by the fact that thin layer chromatography of the reaction mixture at equilibrium indicates only two monoacetal components.



24 hours 4 hours 25 minutes 5 minutes

Fig. II-9 Gas Liquid Chromatograms of the Reaction between n-Butyraldehyde and 2-Deoxy-D-lyxo-hexitol

Isolation of three monoacetals (experiments 5 and 6) followed by individual investigation of their thin layer and gas chromatographic behaviour clarified the situation. The gas liquid chromatography peak representing the kinetic phase was due only to 1,3-O-butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10,I). The gas liquid chromatography peak representing the thermodynamic phase was due to two monoacetals, 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10,II) and 4,6-O-butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10,III).



I II III

Fig. II-10

By recording gas chromatograms at known time intervals it proved possible to measure the changes in concentration of the deoxy polyol and its acetals with time as plotted in Fig. II-11. The initial rate coefficient of the deoxy polyol was also obtained by plotting the reciprocal of its concentration against time. This was found to be 5.35×10^{-3} litres moles^{-1}sec^{-1}.

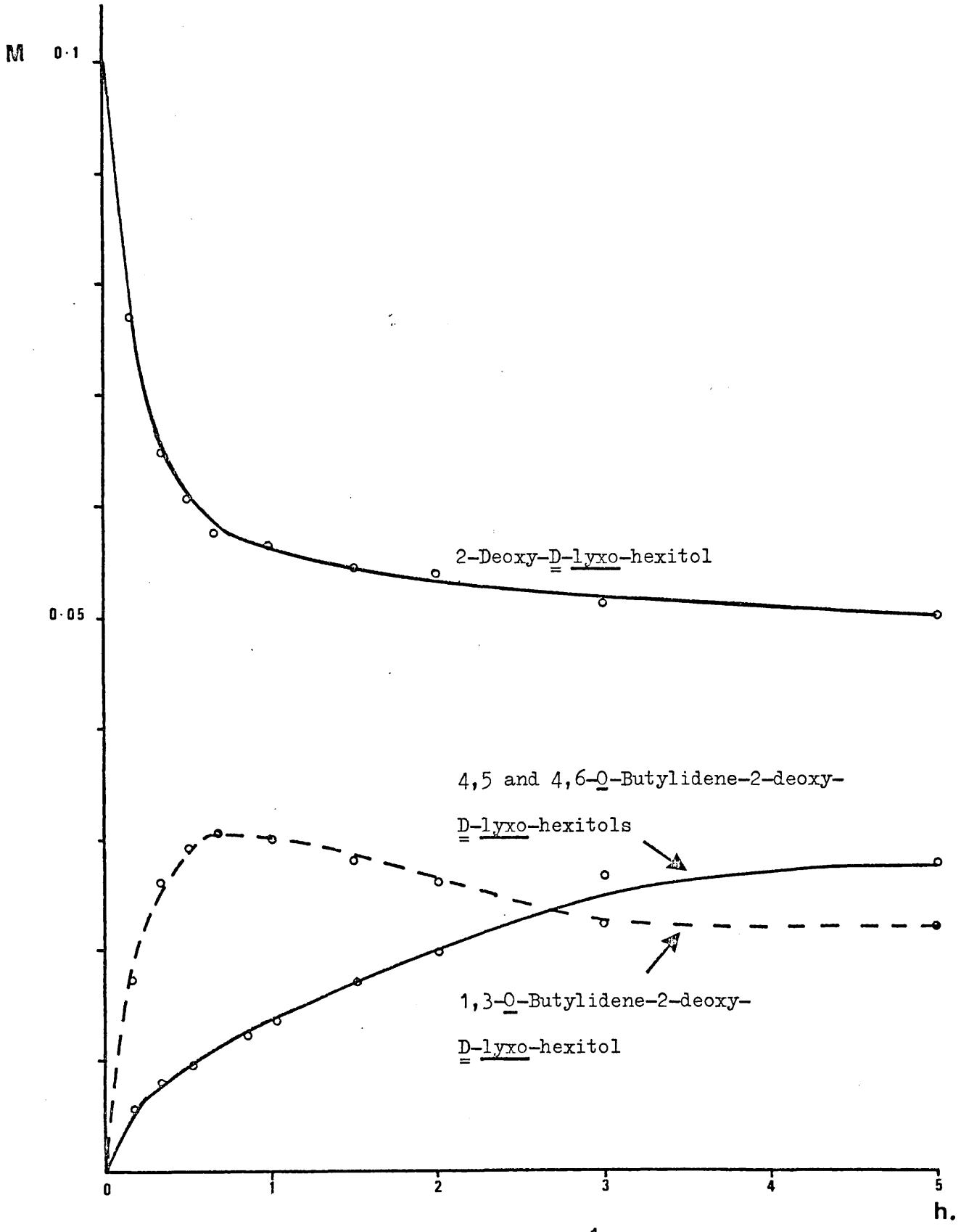


Fig. II-11 Concentration (moles litre^{-1}) versus Time for 2-Deoxy-D-lyxo-hexitol and its Acetals in the Reaction with n-Butyraldehyde.

The coincidental gas liquid chromatography peaks for the 4,5 and 4,6-monoacetals cause complications when trying to understand the acetalation behaviour of 2-deoxy-D-lyxo-hexitol. The complication arises through not being able to get the ratio of the 4,5 and 4,6-acetals to one another and of each to the 1,3-acetal. The reaction is deemed to have kinetic and thermodynamic phases as the concentration of the monoacetals represented by the thermodynamic phase gas liquid chromatography peak is 2.4 times the concentration of the monoacetal represented by the kinetic phase peak at equilibrium.

The existence of the 1,3-acetal as a kinetic phase with the 4,6-acetal as a thermodynamic phase is in line with the previous findings for 2-deoxy-D-arabino-hexitol (section II-A). The role of the 4,5-acetal is what may be called the bone of contention. A 1,3-ring as a kinetic phase with a 4,5-ring as a thermodynamic phase is contrary to the Barker-Bourne rules. However, as the ratio of the respective acetals is unavailable from the gas liquid chromatography study it may be presumptious to call the 4,5-acetal a thermodynamic phase with respect to the 1,3-acetal.

Inspection of the quantity of 4,5 and 4,6-acetals isolated from the equilibrium mixture shows the 4,5-acetal to be the predominant isomer by a 1.4:1 ratio. This may suggest that the thermodynamic phase gas liquid chromatography peak represents a predominance of the 4,5-acetal. If this is true then the 4,5-acetal is a thermodynamic phase with respect to the 1,3-acetal. Butylidenation studies on related systems[40,45] however have shown the β- (i.e. 4,6) acetal to predominate over the α-threo-4,5-acetal a situation opposite to that found here. This introduces the possibility

of a loss of the 4,6-acetal in the work up procedure, thereby altering its ratio with respect to the 4,5-acetal. A possible consequence of this would be that the 4,5-acetal is not a thermodynamic phase with respect to the 1,3-acetal.

It was not possible to measure the ratio of the 1,3 and 4,5-acetals by their quantities isolated from the reaction at equilibrium. Attempts at this resulted in a loss of the 1,3-acetal presumably through hydrolysis or isomerisation on the alumina column used to separate the monoacetals from unreacted polyol. This loss was detected from gas liquid chromatographic analysis of the organic fractions before and after elution through the alumina column. Weighing up the pros and cons of the situation it is perhaps safest to leave the role of the 4,5-acetal open to speculation. Apart from the 4,5-acetal, 2-deoxy-D-lyxo-hexitol is behaving as predicted as both favoured β-ring systems i.e. 1,3 and 4,6-rings are found. The existence of the 4,5-acetal may also be predicted from previous studies on related systems[40,45] in which α-threo acetals were found.

3. Structural Analysis of 1,3-O-Butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10,I).

The acetal consumed 1.98 moles of periodate ion with liberation of 0.98 moles of formaldehyde and 0.99 moles of formic acid. The only possible ring system arising from acetalation of 2-deoxy-D-lyxo-hexitol giving this result was a 1,3-ring.

Supporting evidence for a 1,3-acetal comes from ^{1}H and ^{13}C n.m.r. spectroscopy. The ^{1}H n.m.r. spectrum (section V-B) showed

an acetal proton triplet centred at 4.47δ with a ^{3}J value of 5.0 Hz, both facts consistent with a six membered ring system. One primary and two secondary hydroxyl functions were detected using the D_2O exchange technique. The only acetals fitting the above ^{1}H n.m.r. spectroscopic observations were 1,3 and 4,6-acetals. ^{13}C n.m.r. spectroscopy (section V-A) showed the C-1 and C-3 chemical shifts of the acetal to be deshielded relative to their chemical shifts in the deoxy polyol. The magnitude of this deshielding suggested that C-1 and C-3 of the acetal were bearing acetal ring oxygens thereby suggesting a 1,3-ring system.

4. Structural Analysis of 4,5-O-Butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10, II).

The acetal did not consume any significant amount of periodate ion (0.2 mol) hence there is an absence of any vicinal diol groups. The only possible acetals resulting from this observation were the 3,5, 4,5 or 4,6-acetals.

The ^{1}H n.m.r. spectrum in D.M.S.O. (d^{6}) showed an acetal proton triplet centred at 4.95 δ with a ^{3}J value of 4.6 Hz, both facts favouring a five membered ring. The ^{1}H n.m.r. spectrum in pyridine (d^{5}) showed two overlapping acetal proton triplets in the 5.3 δ region. These two acetal proton triplets indicated the presence of diastereoisomers commonly found for five membered acetal rings (section V-B). Of the three above mentioned possibilities, the 4,5-acetal was the only one containing a five membered ring therefore by elimination the structure was accorded to it. ^{13}C n.m.r. spectroscopy also indicated the presence of a five membered ring

from the lower field chemical shift of the acetal carbons (section V-A shows how a distinction can be made between five and six membered rings on the basis of the acetal carbon chemical shift). Also, the presence of two diastereoisomeric acetal carbon signals indicated a five membered ring.

5. Structural Analysis of 4,6-O-Butylidene-2-deoxy-D-lyxo-hexitol (Fig. II-10,III).

The acetal did not consume any periodate ion hence the possible structures were as outlined for the 4,5-acetal above, the 4,5-structure being impossible in retrospect.

The ^{1}H n.m.r. spectra in D.M.S.O. (d^{6}) and D_2O revealed an acetal proton triplet at 4.50 δ with a ^{3}J value of 5.2 Hz, both facts consistent with a six membered ring. The spectra also indicated one primary and two secondary hydroxyl functions. The only six membered cyclic acetal consistent with all these facts was the 4,6-acetal. ^{13}C n.m.r. spectroscopy supported the 4,6-structure. Both C-4 and C-6 of the acetal were deshielded relative to their chemical shifts in the deoxy polyol. The magnitude of the deshielding indicated that they were bonded to acetal ring oxygens thereby giving further evidence for the 4,6-acetal ring.

II-C 2-Deoxy-D-erythro-pentitol

1. Introduction

In the absence of any 1,3-interactions between hydroxyl functions the carbon chain of 2-deoxy-D-erythro-pentitol is expected to exist as a planar zig-zag conformation (Fig. II-12) in solution.

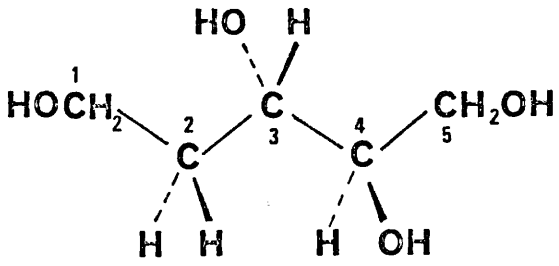


Fig. II-12

From the hydroxyl configuration shown above the predicted most stable monoacetals are the 1,3 and 3,5-acetals, both being β-ring systems. The only reported acetal of 2-deoxy-D-erythro-pentitol is a monobenzylidene derivative of unknown structure.[52]

2. Results and Discussion

2-Deoxy-D-erythro-pentitol was prepared by sodium borohydride reduction of commercially available 2-deoxy-D-erythro-pentose (Fig. II-13).[53]

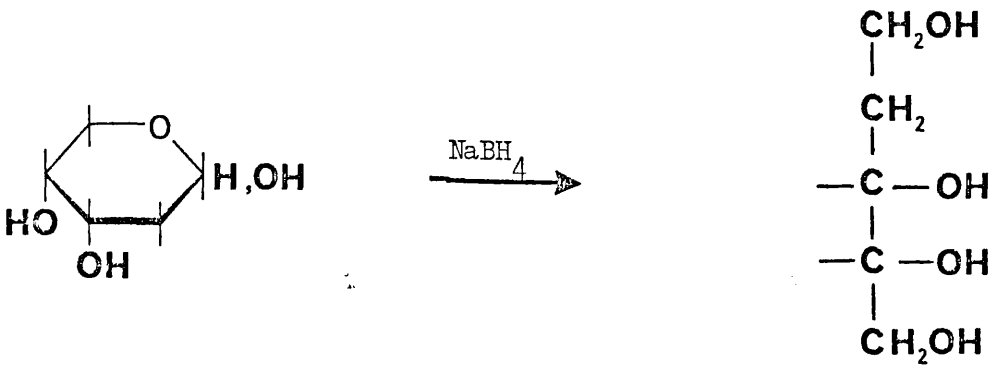


Fig. II-13

The reaction between 2-deoxy-D-erythro-pentitol and n-butyraldehyde was monitored under identical conditions to those previously described (section II-A). Both polarimetric (Fig. II-3) and gas liquid chromatography studies indicated the presence of kinetic and thermodynamic phases. Subsequent isolation (experiment 8) of two monoacetals showed the kinetic phase to be 1,3-O-butylidene-2-deoxy-D-erythro-pentitol (Fig. II-14,I) with 3,5-O-butylidene-2-deoxy-D-erythro-pentitol (Fig. II-14,II) as the thermodynamic phase.

I II

Fig. II-14

The proportion of the two monoacetals at equilibrium was found to be 1.2:1 in favour of the 3,5-acetal. This corresponds to a free energy difference between the isomers of only 0.12 Kcal mole^{-1}. Again there is a distinction between the two β-rings as regards which is the kinetic phase. Apart from this the deoxy polyol is behaving as predicted in its acetalation.

Let us now consider this differentiation between the β-ring systems found in these three 2-deoxy polyols. Assuming the 2-deoxy-D-lyxo-hexitol acetals follow the trend observed for the two other 2-deoxy polyols then in each case the kinetic phase has no ring hydroxyl function. The thermodynamic phase on the other hand has an acetal ring hydroxyl function. A consequence of the deoxy function in each polyol could be to give enhanced reactivity towards acetal formation on those carbons bearing hydroxyls adjacent to the deoxy function. This enhanced reactivity may be explained as follows.

The rate determining step in acetal formation has been proposed as formation of the oxocarbonium ion.[7] The easier it is formed then the quicker the acetalation will proceed. The mechanism for acetal formation illustrated in Fig. I-2 shows an initial attack on the hydroxyl function by a protonated aldehyde species to form a protonated hemiacetal. Subsequent loss of water from the protonated hemiacetal leads to the oxocarbonium ion. Let us envisage this process as happening at the relevant hydroxyl functions of the deoxy polyols to give kinetic and thermodynamic phases (Fig. II-15).

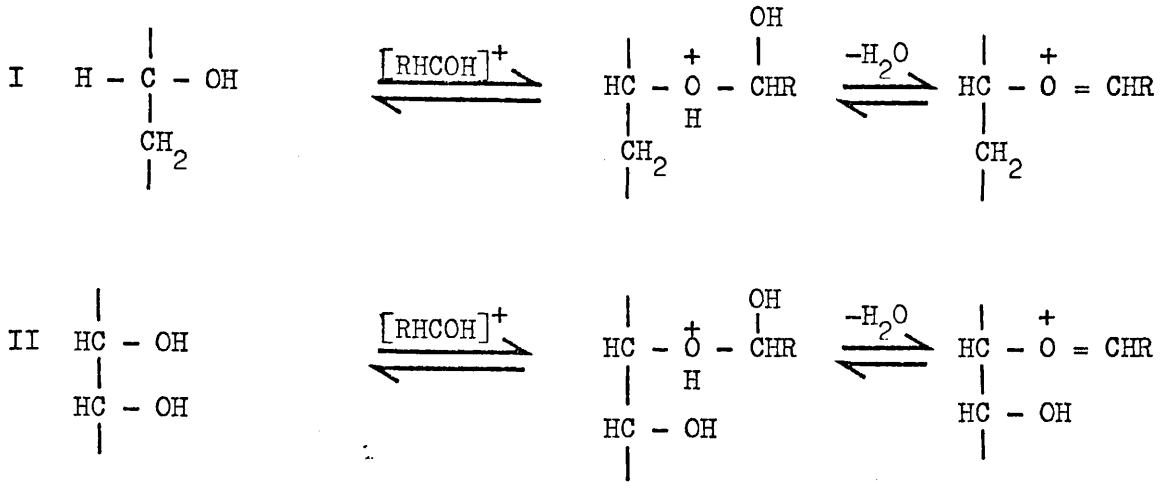


Fig. II-15

The electron withdrawing hydroxyl function on the adjacent carbon to that involved in oxocarbonium ion formation will tend to hinder this process (Fig. II-15,II) relative to that where there is no such adjacent hydroxyl (Fig. II-15, I). This hindrance is brought about because in scheme II above there is less electron density at the hydroxyl involved in oxocarbonium ion formation than in scheme I. The deoxy function thereby increases the nucleophilicity of the adjacent hydroxyls to attack by the protonated aldehyde species and subsequent oxocarbonium ion formation.

The discussion above may account as to why the 1,3-acetals of the 2-deoxy polyols are formed quickest in the early stages of the reaction. It does not however explain why that β-ring containing a ring hydroxyl function is formed to the greater extent, i.e. to a predominance at equilibrium. The equilibrium position of each acetal with respect to the deoxy polyol is a measure of its free energy content. The acetal with the lowest free energy will predominate in such circumstances. The free energy differences

between the kinetic and thermodynamic phases as gauged from their concentrations at equilibrium varies between 0.12 and 0.5 Kcal $mole^{-1}$ for the two measured cases. This is quite a small free energy difference and may be caused by some subtlety the nature of which is not apparent at present.

3. Structural Analysis of 1,3-O-Butylidene-2-deoxy-D-erythro-pentitol (Fig. II-14,I).

The monoacetal was isolated as a syrup which could not be induced to crystallise. It was derivatized as its di-O-tosyl derivative. The monoacetal itself consumed 0.97 moles of periodate ion with liberation of 0.92 moles of formaldehyde. This indicated vicinal diol groups, one of which was primary the other secondary. The only possible monoacetal of 2-deoxy-D-erythro-pentitol consistent with these observations was the 1,3-acetal. Supporting evidence for this structure came from n.m.r. spectroscopy.

The ^{1}H n.m.r. spectrum of the acetal showed an acetal proton triplet centred at 4.47 δ with a ^{3}J value of 5.5 Hz, both facts consistent with a six membered acetal ring. The D_2O exchange technique indicated a primary and a secondary hydroxyl function. The only six membered acetal rings with this type of hydroxyl functions were 1,3 and 3,5-rings. The ^{1}H n.m.r. spectrum of the di-O-tosyl derivative of the acetal was fully analysed and then computer simulated (section V-B) on the basis of a 1,3-acetal. The simulated spectrum showed good agreement with the experimental spectrum thereby giving further confidence towards a correct structure analysis.

The ^{13}C n.m.r. spectrum of the acetal showed C-1 and C-3 to be substantially deshielded compared to their chemical shifts in the deoxy polyol. This observation was consistent with C-1 and C-3 being carbons with acetal ring oxygens attached to them, again proposing a 1,3-ring structure.

4. Structural Analysis of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol (Fig. II-14, II).

The monoacetal did not consume any periodate ion thereby indicating a lack of vicinal diol groups. Possible monoacetals consistent with this observation were 1,4, 3,4, 3,5 and 4,5-acetals.

The ^{1}H n.m.r. spectra of the acetal in D.M.S.O. (d^6) and D_2O indicated the presence of one primary and one secondary hydroxyl function thereby excluding a 3,4-ring. The spectra also showed an acetal proton triplet centred at 4.43 δ with a ^{3}J value of 5.1 Hz indicating a six membered ring. The only possibility from the above mentioned acetals with a six membered ring was the 3,5-acetal. ^{13}C n.m.r. spectroscopy also supported the 3,5-ring structure. Both C-3 and C-5 in the acetal showed the expected chemical shift deshieldings relative to the deoxy polyol.

III Monobutylidene Acetals of Other Secondary Deoxy Polyols

III-A 3-Deoxy-D-ribo-hexitol

1. Introduction

The conformation of the carbon chain in 3-deoxy-D-ribo-hexitol is expected to be a "sickle" (Fig.III-1). The planar zig-zag conformation is destabilized due to a 1,3-interaction between eclipsed hydroxyl functions on C-2 and C-4.

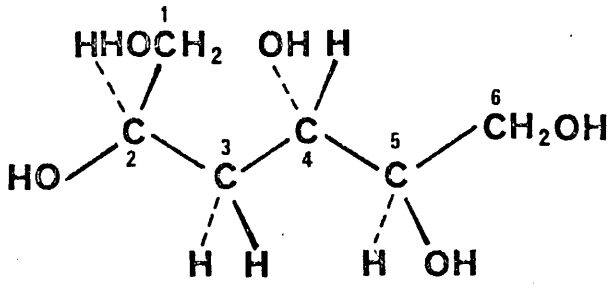


Fig. III-1

The previously described work on the 2-deoxy polyols (section II) indicated extra stability may be inferred to a six membered β-ring containing a hydroxylated ring carbon. The comparison for stability was made with a six membered β-ring without such a carbon, i.e. a deoxy ring carbon. The aim of the present study was to see if a similar effect was operating between two different types of six membered rings. 3-Deoxy-D-ribo-hexitol offers the possibility of these two types of six membered rings in the 2,4 and 4,6-rings.

The 2,4-ring is a β-*erythro* ring, the highest preferred monoacetal structure. The 4,6-ring is a β-ring the second highest preferred structure on the basis of the Barker-Bourne rules. Butylidenation of the related 3-*O*-methyl-*D*-glucitol yields only the 2,4-acetal;[6] at first sight therefore one may expect 3-deoxy-*D*-*ribo*-hexitol to form a 2,4-acetal. However, the 2,4-acetal would contain a deoxy ring carbon whereas the 4,6-acetal would have a hydroxylated ring carbon. This may result in a reversal of the preferred ring structures or the appearance of the 4,6-acetal as well as the 2,4-acetal in the same reaction. The reported acetals and ketals of 3-deoxy-*D*-*ribo*-hexitol are a 1,5,6-tri-*O*-acetyl-2,4-*O*-methylene derivative[54] and a 5,6-*O*-isopropylidene derivative.[55]

2. Results and Discussion

3-Deoxy-*D*-*ribo*-hexitol was prepared in seven stages starting from 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose (experiments 10 to 14). The synthetic scheme is illustrated below (Fig. III-2).

The reaction between 3-deoxy-*D*-*ribo*-hexitol and *n*-butyraldehyde was monitored under identical conditions to those described previously (section II-A). The polarimetric study (Fig. III-3) showed a steady decrease in optical rotation to a constant value. The gas liquid chromatography study showed only one major monoacetal peak, the intensity of which increased with time. By taking a series of gas chromatograms at known time intervals the initial rate coefficient of the deoxy polyol was found using the method described previously (section II-A). This was found to be 4.31×10^{-3} litres moles^{-1} sec^{-1}.

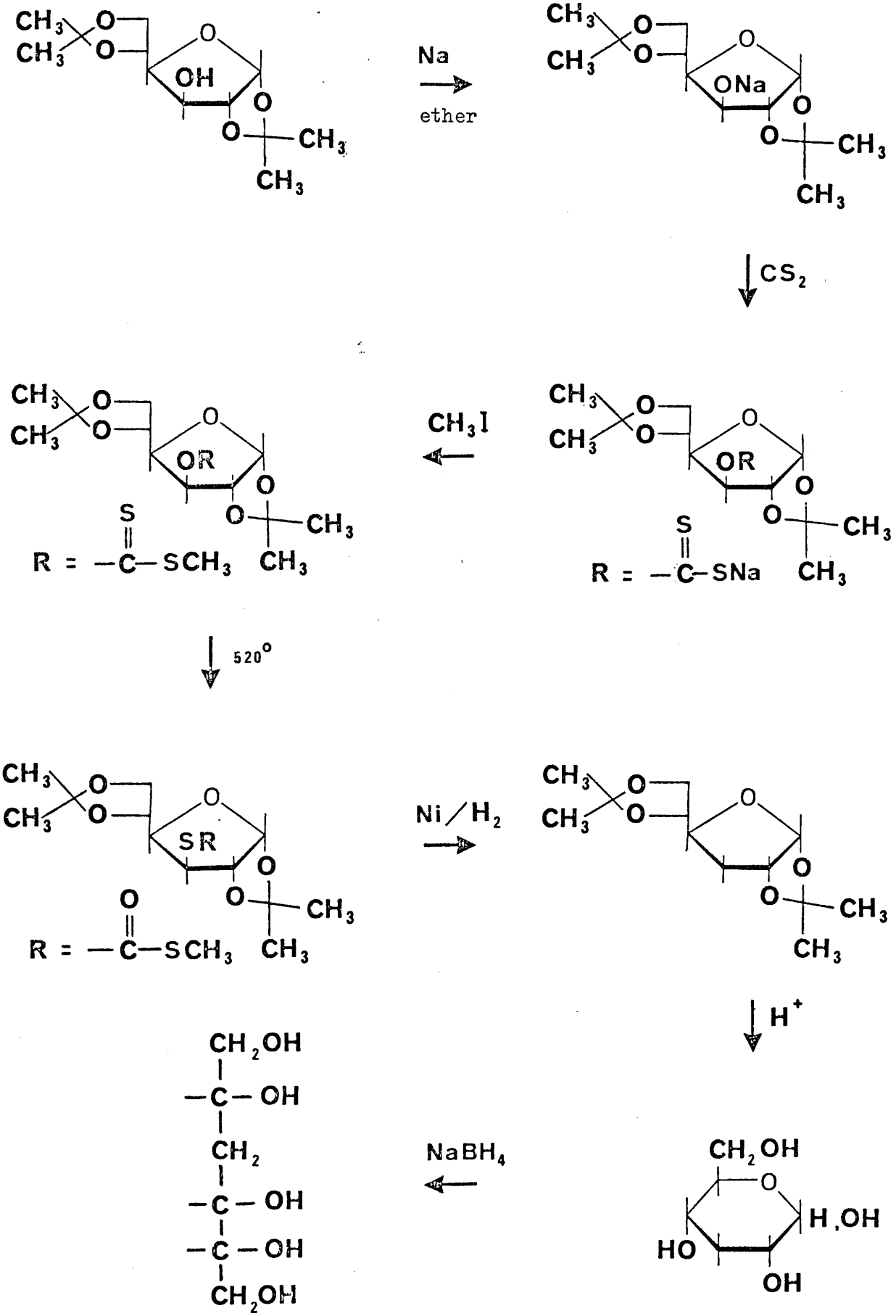


Fig. III-2

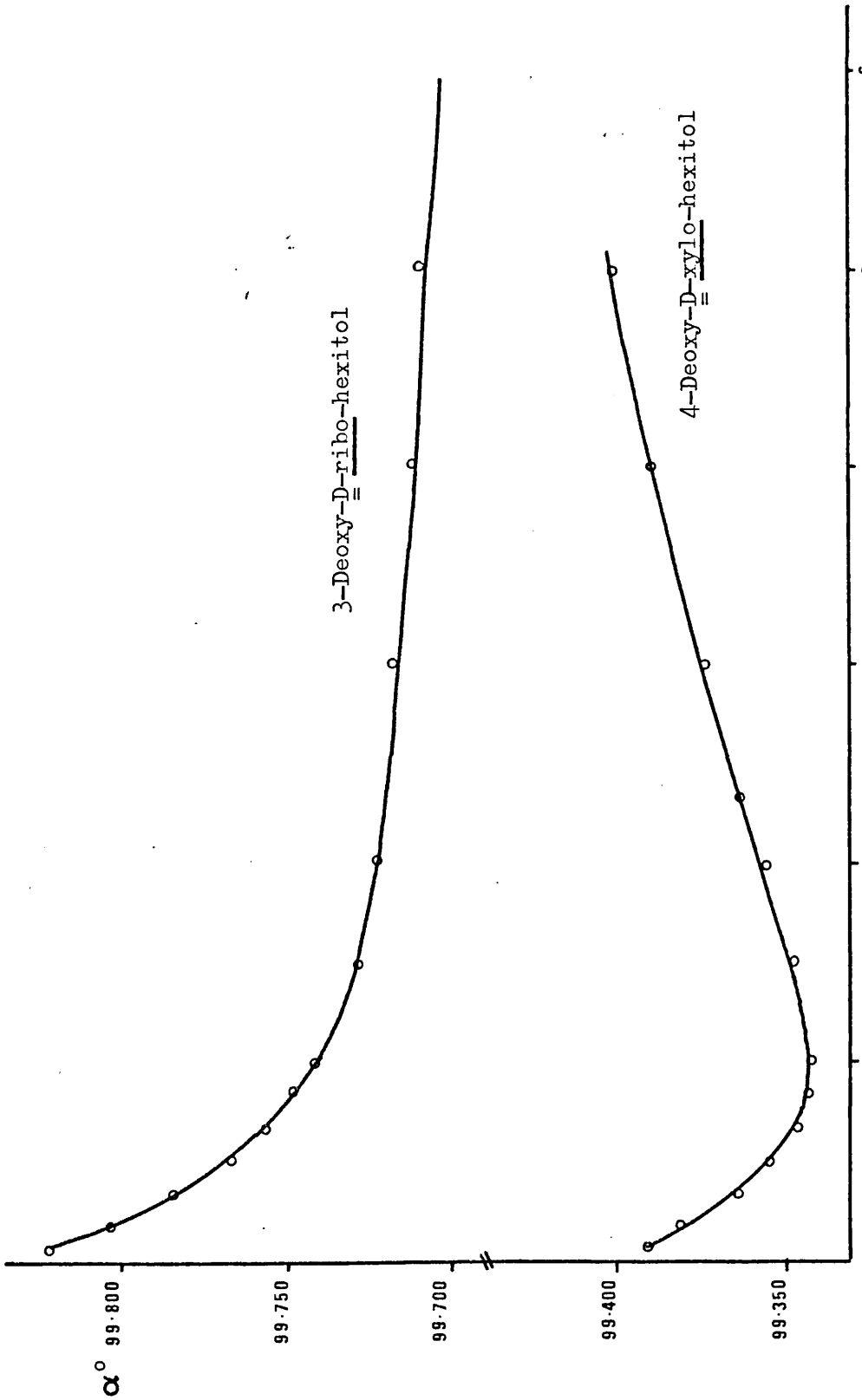


Fig. III-3 Optical Rotation versus Time for the Reactions between n-Butyraldehyde and Some Secondary Deoxy Polyols.

There was no evidence of a kinetic phase in the reaction, work up of the reaction mixture at equilibrium yielding one monoacetal only (experiment 16). The structure of the acetal was shown to be 2,4-O-butylidene-3-deoxy-D-ribo-hexitol (Fig. III-4).

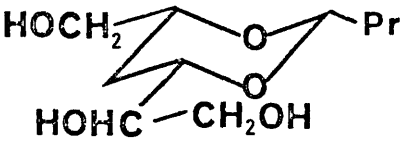


Fig. III-4

The absence of a 4,6-acetal shows that the extra stability conferred by a hydroxylated ring carbon compared to a deoxy ring carbon is restricted to rings of the same type, i.e. both β-rings. The extra stability is not enough to cause a reversal of ring preferences, or permit the formation of a β-ring in a system able to form a β-erythro ring.

Both 3-O-methyl-D-glucitol and 3-deoxy-D-ribo-hexitol yield a 2,4-butylidene acetal as the only major product of their acetalations. A comparison of the time scale required for attainment of reaction equilibrium shows the deoxy system to be much quicker. The deoxy system takes 24 hours whereas the 3-O-methyl polyol system does not reach equilibrium even after 96 hours.[6] These different times taken to attain equilibrium may be accounted for by the argument

presented in section II-C for the 2-deoxy polyol acetals. The hydroxyl functions of the 3-deoxy-polyol will have enhanced nucleophilicity when compared to the same hydroxyl functions of the 3-O-methyl polyol.

3. Structural Analysis of 2,4-O-Butylidene-3-deoxy-D-ribo-hexitol (Fig. III-4)

The acetal was derivatized as its tri-O-tosyl compound. The monoacetal itself consumed 1.17 moles of periodate ion with liberation of 1.08 moles of formaldehyde. This indicated the presence of vicinal diol groups one of which was primary the other secondary. Possible structures were limited to the 1,4, 2,4, 4,5, 4,6 and 5,6-acetals.

^{1}H n.m.r. spectroscopy showed an acetal proton triplet centred at 4.49 δ with a ^{3}J value of 5.0 Hz, both facts consistent with a six membered ring. This eliminated the 1,4, 4,5 and 5,6-structures. The D_2O exchange technique indicated one secondary and two primary hydroxyl functions, thereby eliminating the 4,6-structure and leaving only the 2,4-acetal. ^{13}C n.m.r. spectroscopy supported these findings, both C-2 and C-4 showing the expected chemical shift deshieldings compared to their shifts in the deoxy polyol.

III-B 4-Deoxy-D-xylo-hexitol

1. Introduction

The conformation of the carbon chain in 4-deoxy-D-xylo-hexitol in solution is predicted to be a planar zig-zag (Fig. III-5) in the absence of any 1,3-interactions.

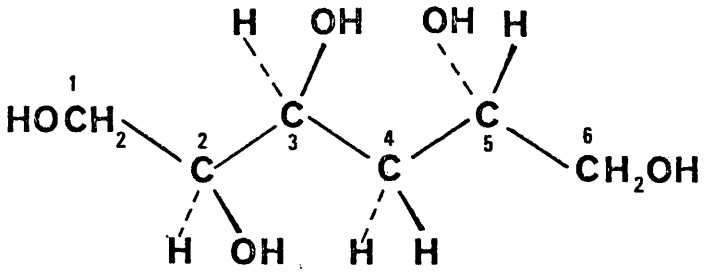


Fig. III-5

Acetalation studies on D-glucitol have shown a 2,3-acetal as a kinetic phase with a 2,4-acetal as a thermodynamic phase.[56] The 4-deoxy polyol is still able to form a 2,3-acetal but not a 2,4-acetal. The highest preferred acetal possible for 4-deoxy-D-xylo-hexitol is the 1,3-acetal, i.e. a β-ring. One may expect to see therefore both the 2,3 and 1,3-rings formed in the acetalation of the deoxy polyol. At present there are no reported acetals of 4-deoxy-D-xylo-hexitol.

2. Results and Discussion

4-Deoxy-D-xylo-hexitol was prepared in eight stages starting from D-galactose (experiments 18 to 25) by the scheme illustrated below (Fig. III-6).

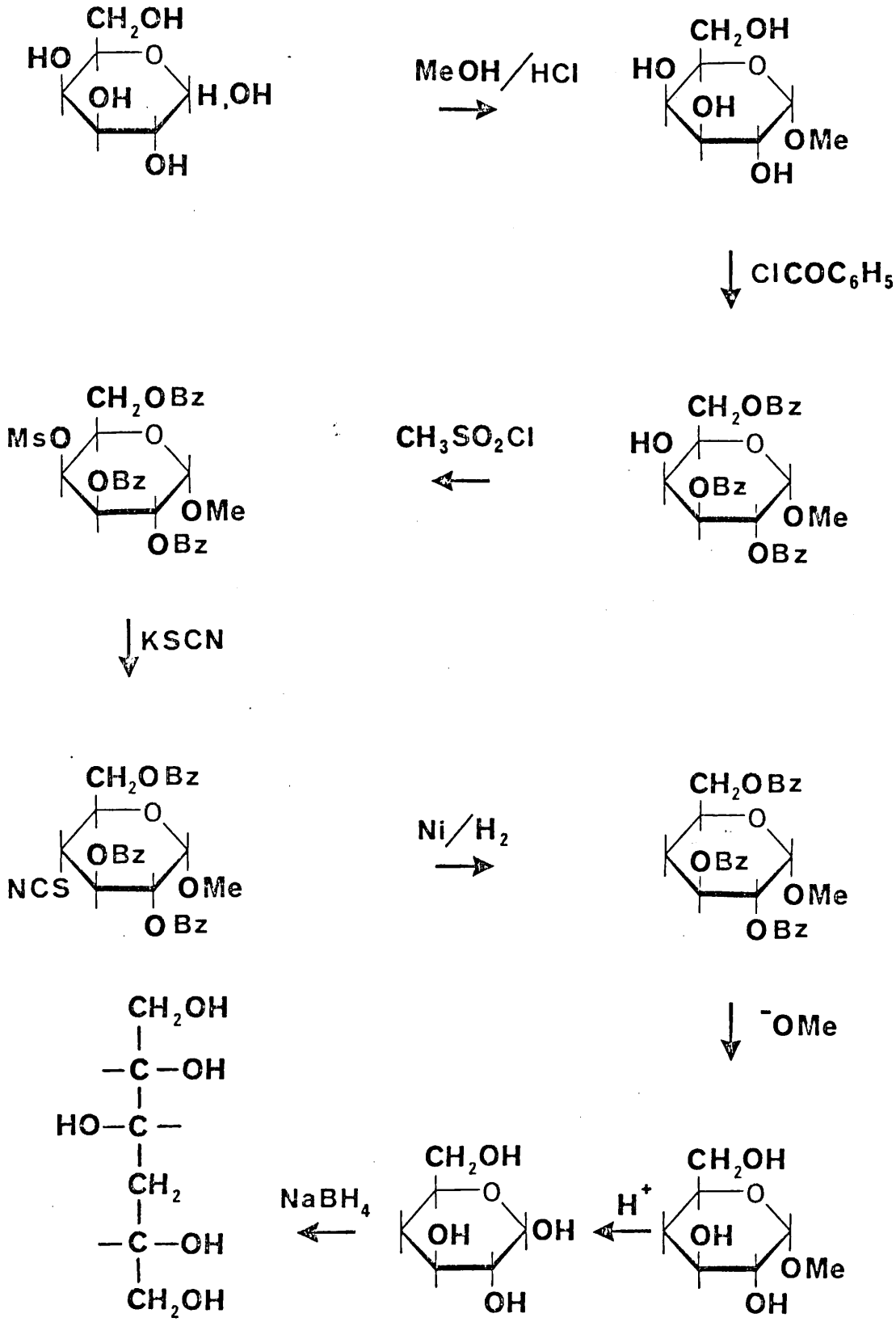
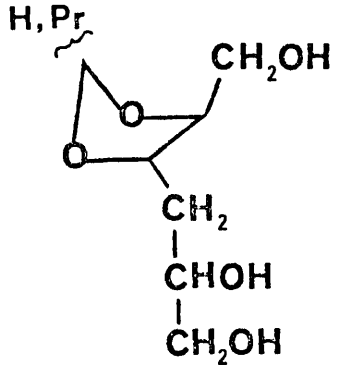

CH2OH
HO
O
OH
H,OH
OH
MeOH/HCl
CH2OH
HO
O
OH
OMe
OH
ClCOC6H5
CH2OBz
MsO
O
OBz
OMe
OBz
CH3SO2Cl
CH2OBz
HO
O
OBz
OMe
OBz
KSCN
CH2OBz
NCS
O
OBz
OMe
OBz
Ni/H2
CH2OBz
O
OBz
OMe
OBz
-OMe
CH2OH
C
OH
HO
C
CH2
C
OH
CH2OH
NaBH4
CH2OH
O
OH
OH
OH
H+
CH2OH
O
OH
OMe
OH

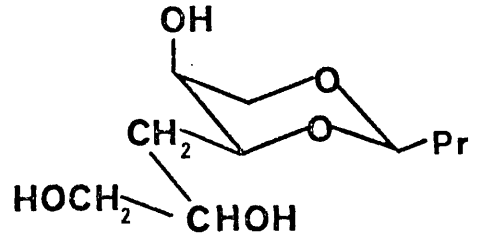
Fig. III-6

The reaction between 4-deoxy-D-xylo-hexitol and n-butyraldehyde was monitored under identical conditions as previously described (section II-A). The polarimetric study (Fig. III-3) showed an initial decrease of optical rotation followed by an increase to a constant value, a feature associated with the presence of both kinetic and thermodynamic phases. Gas liquid chromatography showed the presence of two monoacetals, one of which was a kinetic phase the other a thermodynamic phase. Gas chromatograms were taken at known time intervals in order to ascertain the change in concentration of reactants and products with time (Fig. III-7). From these studies the initial rate coefficient of the deoxy polyol was measured to be 1.88×10^{-3} litres $moles^{-1}$ sec^{-1}.

Isolation (experiment 27) and structure elucidation of the monoacetals revealed the kinetic phase as 2,3-O-butylidene-4-deoxy-D-xylo-hexitol (Fig. III-8,I) with 1,3-O-butylidene-4-deoxy-D-xylo-hexitol (Fig. III-8,II) as the thermodynamic phase.



I



II

Fig. III-8

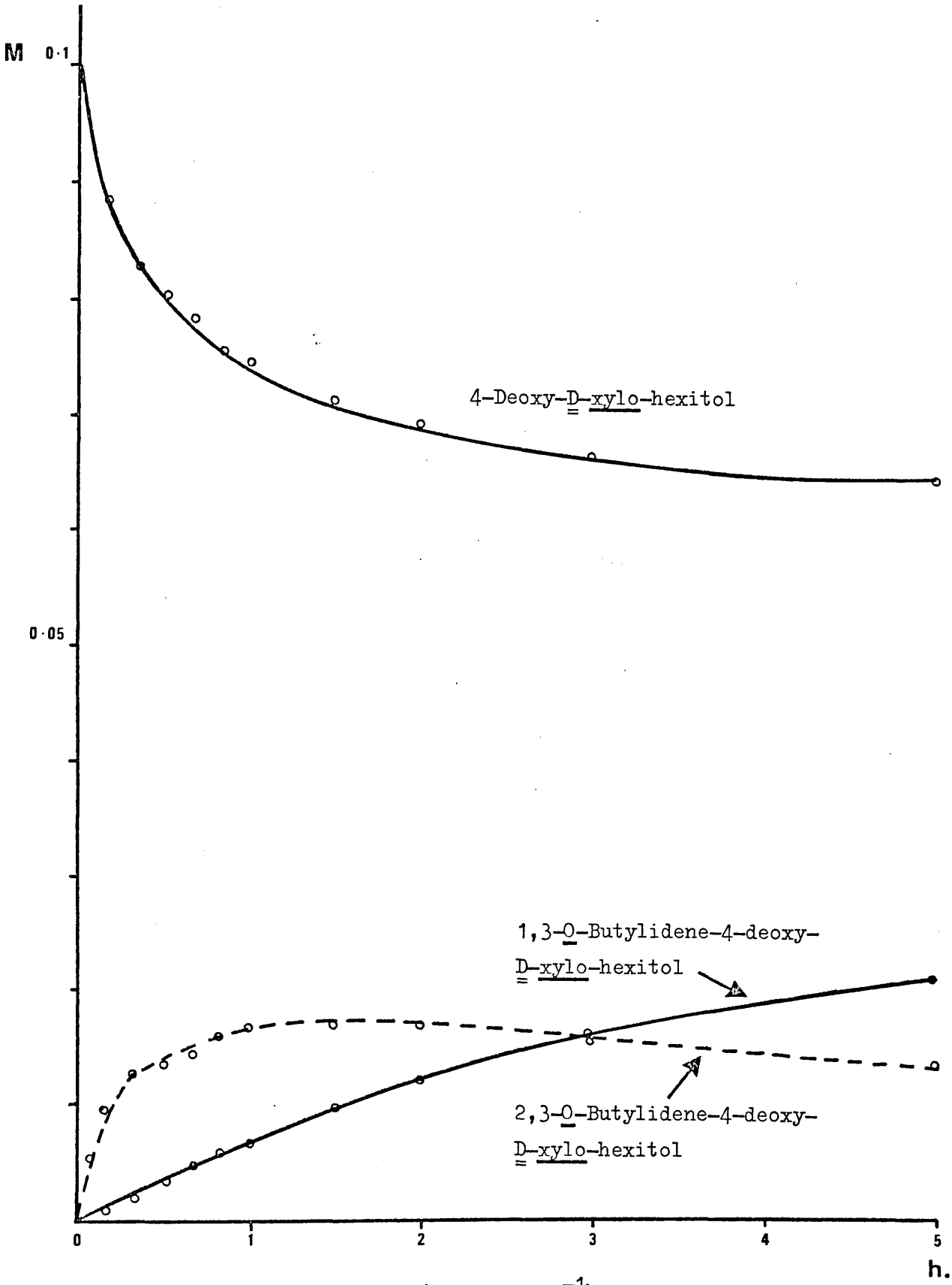


Fig. III-7 Concentration (moles litre^{-1}) versus Time for 4-Deoxy-D-xylo-hexitol and its Acetals in the Reaction with n-Butyraldehyde.

The deoxy polyol is behaving exactly as predicted in its acetalation. The 2,3-acetal is the kinetic phase as was the case for D-glucitol, and the highest possible preferred acetal, i.e. the 1,3-acetal is found as a thermodynamic phase. The ratio of the 1,3 to 2,3-acetals at equilibrium was found to be 2.8:1 corresponding to a free energy difference of approximately 0.6 Kcal $mole^{-1}$ between the isomers.

3. Structural Analysis of 2,3-O-Butylidene-4-deoxy-D-xylo-hexitol (Fig. III-8,I).

The acetal consumed 1.04 moles of periodate ion with liberation of 1.04 moles of formaldehyde. These observations indicated the presence of vicinal diol groups, one of which was primary the other secondary. Possible acetals of the deoxy polyol consistent with these facts were the 1,2, 1,3, 2,3, 3,5 and 3,6-acetals.

^{1}H n.m.r. spectroscopy of the acetal showed an acetal proton triplet centred at 4.90 δ indicating a five membered ring. This left only the 1,2 and 2,3-acetals as possibilities. ^{13}C n.m.r. spectroscopy of the acetal showed two acetal carbon resonances. The appearance of two such resonances is usually associated with diastereoisomeric acetal carbons arising from a five membered acetal ring. The chemical shift of these resonances was also indicative of a five membered ring (section V-A) both facts supporting the ^{1}H n.m.r. spectroscopy observation. ^{13}C n.m.r. spectroscopy also showed C-2 and C-3 of the acetal to be deshielded compared to their chemical shifts in the deoxy polyol.

The magnitude of this deshielding indicated C-2 and C-3 as bearing acetal ring oxygens. On this basis the acetal was accorded the 2,3-structure.

4. Structural Analysis of 1,3-O-Butylidene-4-deoxy-D-xylo-hexitol (Fig. III-8,II).

The acetal consumed 1.00 moles of periodate ion with liberation of 0.98 moles of formaldehyde. This gave the same possibilities for the acetal structure as previously discussed for the 2,3-acetal. The 2,3-ring being impossible in retrospect.

^{1}H n.m.r. spectroscopy showed an acetal proton triplet centred at 4.52 δ with a ^{3}J value of 5.4 Hz thereby indicating a six membered ring. Of those acetals consistent with the periodate/formaldehyde observations only the 1,3 and 3,5-acetals have six membered rings. The D_2O exchange technique on the n.m.r. spectrum indicated one primary and two secondary hydroxyl functions. Of the two acetals only the 1,3-structure has such a distribution of hydroxyl functions.

^{13}C n.m.r. spectroscopy showed C-1 and C-3 as having downfield shifts in the acetal relative to their chemical shifts in the deoxy polyol. These shifts were of the order expected if C-1 and C-3 were bonded to acetal ring oxygens.

IV Monobutylidene Acetals of Some Deoxy Fluoro Polyols

IV-A 3-Deoxy-3-fluoro-D-glucitol

1. Introduction

The acetalation studies discussed so far have been concerned with deoxy polyol systems. Such systems have a decrease in electronegativity at the deoxy position compared to the non deoxy polyol. In order to cover a wider spectrum of acetalation studies it was decided to take a look at some polyols where the hydroxyl function had been replaced by a more electronegative function. With this in mind a study of the acetalation of some deoxy fluoro polyols was attempted.

The synthesis of fluorinated carbohydrates has been the subject of considerable research during the last decade.[57] The attainability of such compounds no longer presents major difficulties hence all that was to be done was to choose some suitable compounds. The first of these compounds was 3-deoxy-3-fluoro-D-glucitol (Fig. IV-1). This was chosen because the acetalation of two other 3-substituted derivatives of D-glucitol had been studied. These were 3-deoxy-D-ribo-hexitol (section III) and 3-O-methyl-D-glucitol.[6] Acetalation data was therefore available with which comparisons could be made regarding the effect of the more electronegative fluorine atom.

3-Deoxy-3-fluoro-D-glucitol would experience a 1,3-interaction between the hydroxyl functions on C-2 and C-4 if the carbons were to adopt a planar zig-zag conformation. To relieve this interaction rotation occurs about a C-C bond. It is shown later in the ^{13}C

n.m.r. section (V-A) that for this deoxy fluoro polyol the rotation is about the C-2/C-3 bond giving the conformer illustrated below (Fig. IV-1).

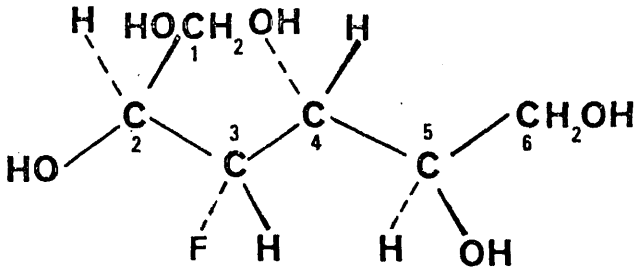


Fig. IV-1

The predicted most preferred acetal of 3-deoxy-3-fluoro-D-glucitol is a 2,4-acetal containing a six membered β-erythro ring. The next highest preferred ring is predicted to be the 4,6-ring, i.e. a β-ring. These possibilities being the same as the possibilities for 3-deoxy-D-ribo-hexitol (section III-A).
At present there are no reported acetals of 3-deoxy-3-fluoro-D-glucitol.

2. Results and Discussion

3-Deoxy-3-fluoro-D-glucitol was prepared in six stages (experiments 29 to 33) starting from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose by the scheme illustrated below (Fig. IV-2).
The reaction between 3-deoxy-3-fluoro-D-glucitol and n-butyraldehyde was monitored under identical conditions as previously (section II-A).

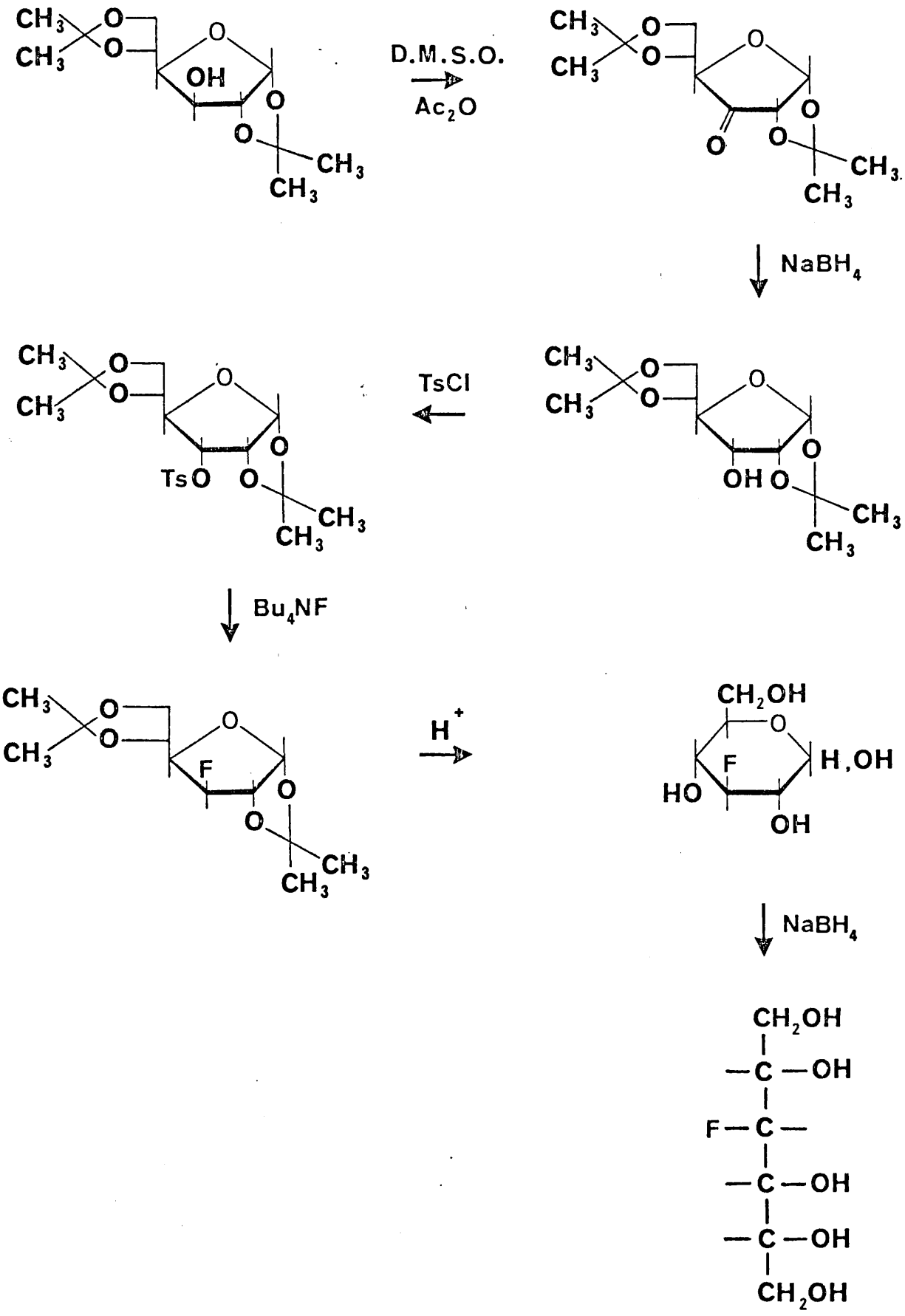


Fig. IV-2

The polarimetric study showed a steady decrease in optical rotation to a constant value. The gas liquid chromatography study showed the presence of two major monoacetals (Fig. IV-3) one of which was a kinetic phase, the other a thermodynamic phase. From the gas chromatograms taken at known time intervals the change in concentration of reactants and products with time was followed (Fig. IV-4). The initial rate coefficient of deoxy fluoro polyol measured from these studies was 1.33×10^{-4} litres $moles^{-1} sec^{-1}$.

Subsequent structural studies on the two monoacetals revealed 4,6-O-butylidene-3-deoxy-3-fluoro-D-glucitol (Fig. IV-5,I) to be the kinetic phase with 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol (Fig. IV-5,II) as the thermodynamic phase.

I II

Fig. IV-5

The time scale in the attainment of the reaction equilibrium was long compared to the other deoxy polyol systems studied. The 4,6-acetal took 30 hours to reach its equilibrium with the deoxy fluoro polyol, the 2,4 acetal taking between 60 and 75 hours.

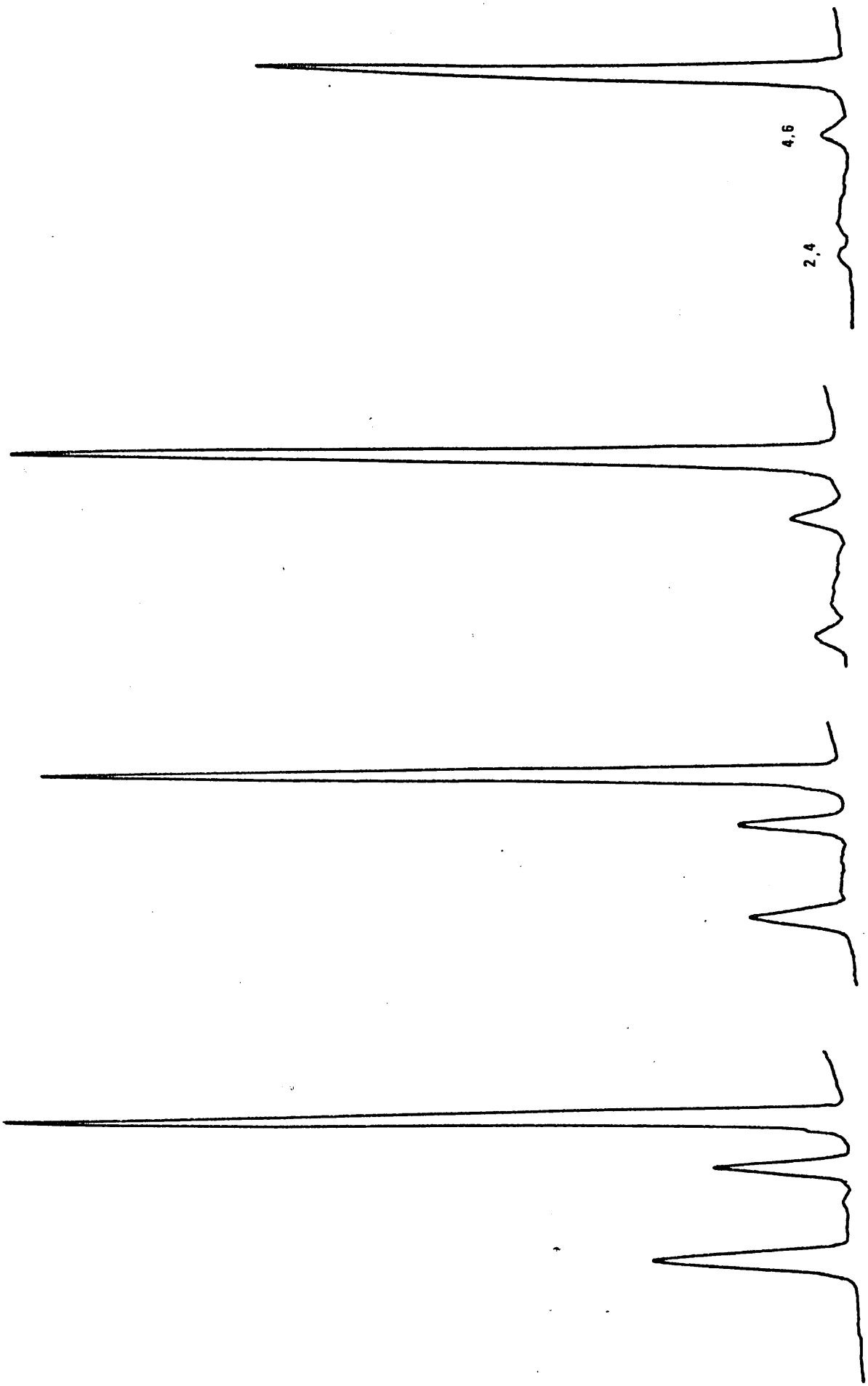


Fig. IV-3 Gas Liquid Chromatograms of the Reaction between n-Butyraldehyde and 3-Deoxy-3-fluoro-D-glucitol

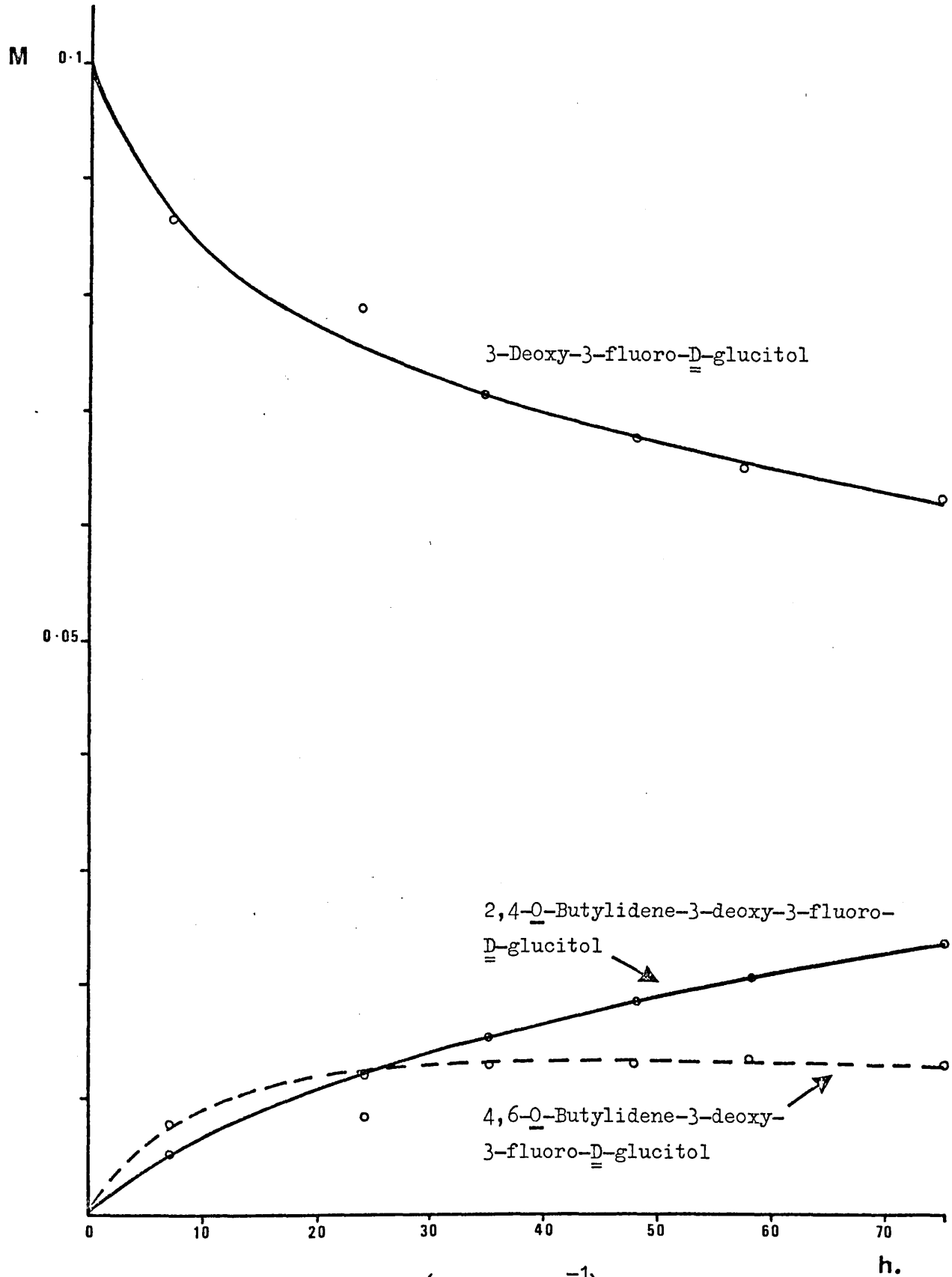
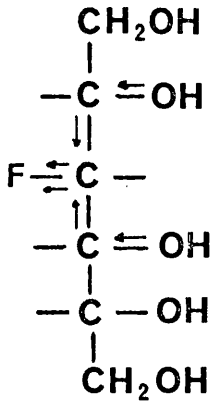


Fig. IV-4 Concentration (moles litre^{-1}) versus Time for 3-Deoxy-3-fluoro-D-glucitol and its Acetals in the Reaction with n-Butyraldehyde

The final concentrations of the monoacetals showed a 1.8:1 predominance of the 2,4-acetal. These results may be rationalized by consideration of the electron withdrawing inductive effect of the fluorine atom.

The withdrawal of electron density from neighbouring sites towards the fluorine atom could result in the oxygen atoms of C-2 and C-4 being electron deficient relative to the other oxygens in the molecule (Fig. IV-6).



← Indicates the direction of the inductive effect

Fig. IV-6

The mechanism for acetal formation is believed to involve formation of a protonated hemiacetal species with subsequent loss of water to form an oxocarbonium ion. Formation of the oxocarbonium ion is believed to be rate determining.[7] Attack at the C-2 and C-4 hydroxyl functions in the above molecule by the protonated hemiacetal species is rendered difficult because of the decreased nucleophilicity of these hydroxyls. Oxocarbonium ion formation at these sites will also be difficult. Therefore by rendering the rate determining step as more difficult to achieve a slower rate of acetalation will be observed for the deoxy fluoro polyols compared with the deoxy polyols.

The appearance of the 4,6-acetal as the kinetic phase may be due to the fact that oxocarbonium ion formation can occur more readily at the C-6 oxygen which is not so deficient in electron density. Then, cyclisation at C-4 results in the 4,6-acetal. This acetalation would be quicker than that giving the 2,4-acetal as both C-2 and C-4 are electron deficient. The situation is similar in principle to that prevailing in the 2-deoxy polyols when the kinetic phase was formed quickest due to enhanced nucleophilicity at appropriate oxygens.

The predominance of the 2,4-acetal at the final reaction equilibrium shows that although the fluorine atom is deactivating to acetalation it is not sufficiently deactivating to cause a reversal of ring preferences. The deactivation is sufficient however to permit the formation of a β-ring in the same equilibrium as a β-*erythro* ring.

A comparison between the acetalations of the deoxy fluoro polyol and 3-deoxy-D-*ribo*-hexitol shows the deoxy polyol to be faster in both initial rate coefficient of polyol and time taken to reach equilibrium. A comparison of the deoxy fluoro polyol with 3-O-methyl-D-glucitol shows the deoxy fluoro polyol as taking the shorter time to reach equilibrium, a situation at first sight anomalous to the deactivating effect of the fluorine. However, the deoxy fluoro polyol takes between sixty and seventy five hours to form 28% of the 2,4-acetal whereas the 3-O-methyl polyol forms 50% 2,4-acetal in ninety six hours. This shows the relative rate of formation of 2,4-acetal to be slower for the deoxy fluoro polyol agreeing with the above arguments.

3. Structural Analysis of 2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol (Fig. IV-5,II).

The monoacetal consumed 1.11 moles of periodate ion with liberation of 1.06 moles of formaldehyde. This indicated vicinal diol groups one of which was primary, the other secondary. Possible acetals consistent with this observation were the 1,4, 2,4, 4,5, 4,6 and 5,6-acetals.

^{1}H n.m.r. spectroscopy showed an acetal proton triplet centred at 4.61 δ with a ^{3}J value of 5.3 Hz, facts consistent with a six membered ring. This left only the 2,4 and 4,6-acetals as possibilities. The D_2O exchange technique indicated one secondary and two primary hydroxyl functions. Of the 2,4 and 4,6-acetals only the 2,4-acetal was consistent with this observation. Supporting evidence for the 2,4-ring came from ^{19}F and ^{13}C n.m.r. spectroscopy. The ^{19}F spectrum of the acetal showed coupling constant data (^{19}F-^{1}H) consistent with a 2,4-acetal (section V-C). ^{13}C n.m.r. spectroscopy showed C-2 and C-4 of the acetal deshielded relative to their chemical shifts in the deoxy fluoro polyol. The deshielding was of the order expected if C-2 and C-4 were bonded to acetal ring oxygens.

The mass spectrum of the acetylated methylated fluoro polyol derived from the acetal had a fragmentation pattern consistent with the original position of the acetal ring as being on C-2 and C-4.

4. Structural Analysis of 4,6-O-Butylidene-3-deoxy-3-fluoro-D-glucitol (Fig. IV-5,I).

Several attempts to isolate this monoacetal by the usual column chromatography techniques failed. The mixed monoacetals could be separated from unreacted polyol on an alumina column. When attempts were made to fractionate the monoacetals on a Dowex 1-X8(OH^-) resin column only the 2,4-acetal was eluted. Precisely what happened when the monoacetals were passed through the Dowex 1-X8(OH^-) column to cause the disappearance of the 4,6-acetal is uncertain. Similar complications arose when the monoacetals of 6-deoxy-6-fluoro-D-galactitol were passed down a Dowex 1-X8(OH^-) column and the matter is further discussed there.

Due to these difficulties it was decided to elucidate the structure of the acetal as part of a mixture with the 2,4-acetal. A solution of the two monoacetals free from polyol after passage down an alumina column was seeded with the 2,4-acetal. The deposited crystals were filtered off leaving a mother liquor enriched in the unisolatable acetal. The mixture of acetals were then methylated, the acetal rings hydrolysed and the free hydroxyls then acetylated. The acetylated methylated deoxy fluoro polyols derived from the two original acetals were then subjected to a gas liquid chromatography/mass spectrometry analysis (section VI). The mass spectral breakdown pattern of the acetylated methylated deoxy fluoro polyol derived from the unisolatable acetal showed the original acetal ring to be either 1,4 or 4,6-disposed.

The analysis was repeated starting with synthesis of the acetals from deoxy fluoro polyol labelled at C-1 with deuterium. The C-1 position of the deuterium label enabled a distinction to be made between the mass spectral breakdown patterns of the acetylated methylated deoxy fluoro polyols arising from 1,4 and 4,6-acetals (section VI). From this the unisolatable acetal was shown to have a 4,6-ring structure.

IV-B 6-Deoxy-6-fluoro-D-galactitol

1. Introduction

The conformation of the carbon chain in 6-deoxy-6-fluoro-D-galactitol in solution is predicted to be a planar zig-zag (Fig. IV-7).

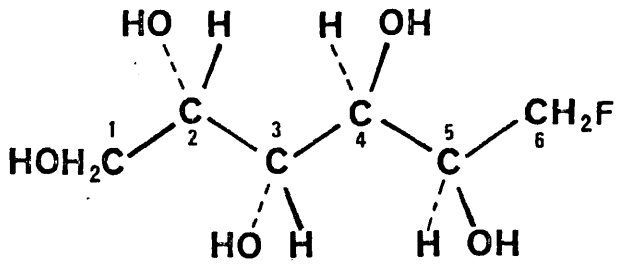


Fig. IV-7

The purpose of this particular acetalation study was to observe the effect of the fluorine atom on the kinetic control exhibited by 1-deoxy-D-galactitol (L-fucitol).[40] 1-Deoxy-D-galactitol is expected to have a planar zig-zag conformation of the carbon chain in solution hence the only difference between the two polyols is that one has a terminal deoxy function and the other a terminal deoxy fluoro function. Previous acetalation studies on 1-deoxy-D-galactitol have shown a 2,3-acetal to be a kinetic phase with a 4,6-acetal as a thermodynamic phase.[40] A 4,5-acetal was also detected. It is convenient for this discussion if 6-deoxy-D-galactitol were considered rather than the 1-deoxy isomer. There will be no difference in the acetalation pattern of the two deoxy polyols other than the numbering system. The position of the acetal

rings in 6-deoxy-D-galactitol becomes 4,5(kinetic phase) 1,3(thermodynamic phase) and 2,3. Thus when comparing acetalations of the deoxy and deoxy fluoro polyols it is easier to see relative ring positions. Prior to this study there were no reported acetals of 6-deoxy-6-fluoro-D-galactitol.

2. Results and Discussion

6-Deoxy-6-fluoro-D-galactitol was prepared from D-galactose in five stages (experiments 41 to 45) by the reaction scheme illustrated below (Fig. IV-8).

The reaction between 6-deoxy-6-fluoro-D-galactitol and n-butyraldehyde was monitored under the usual conditions. The polarimetric study showed a slight decrease in optical rotation of the reaction mixture followed by an increase back almost to the starting rotation. The gas chromatography analysis showed two main monoacetal peaks throughout the reaction both of which seemed to be formed under thermodynamic control. The initial rate coefficient of the deoxy fluoro polyol was measured as 3.23×10^{-4} litres moles^{-1} sec^{-1} by the usual method.

The reaction between D-fucitol (6-deoxy-D-galactitol) and n-butraldehyde was also monitored under identical conditions to the deoxy fluoro polyol reaction. From this the initial rate coefficient of D-fucitol was found to be 2.88×10^{-3} litres moles^{-1} sec^{-1}. The time taken for both reactions to reach equilibrium was the same, i.e. about 24 hours. This seems to indicate that the fluorine atom slows down the acetalation in the early stages of the reaction. This is presumably done by slowing down the rate of

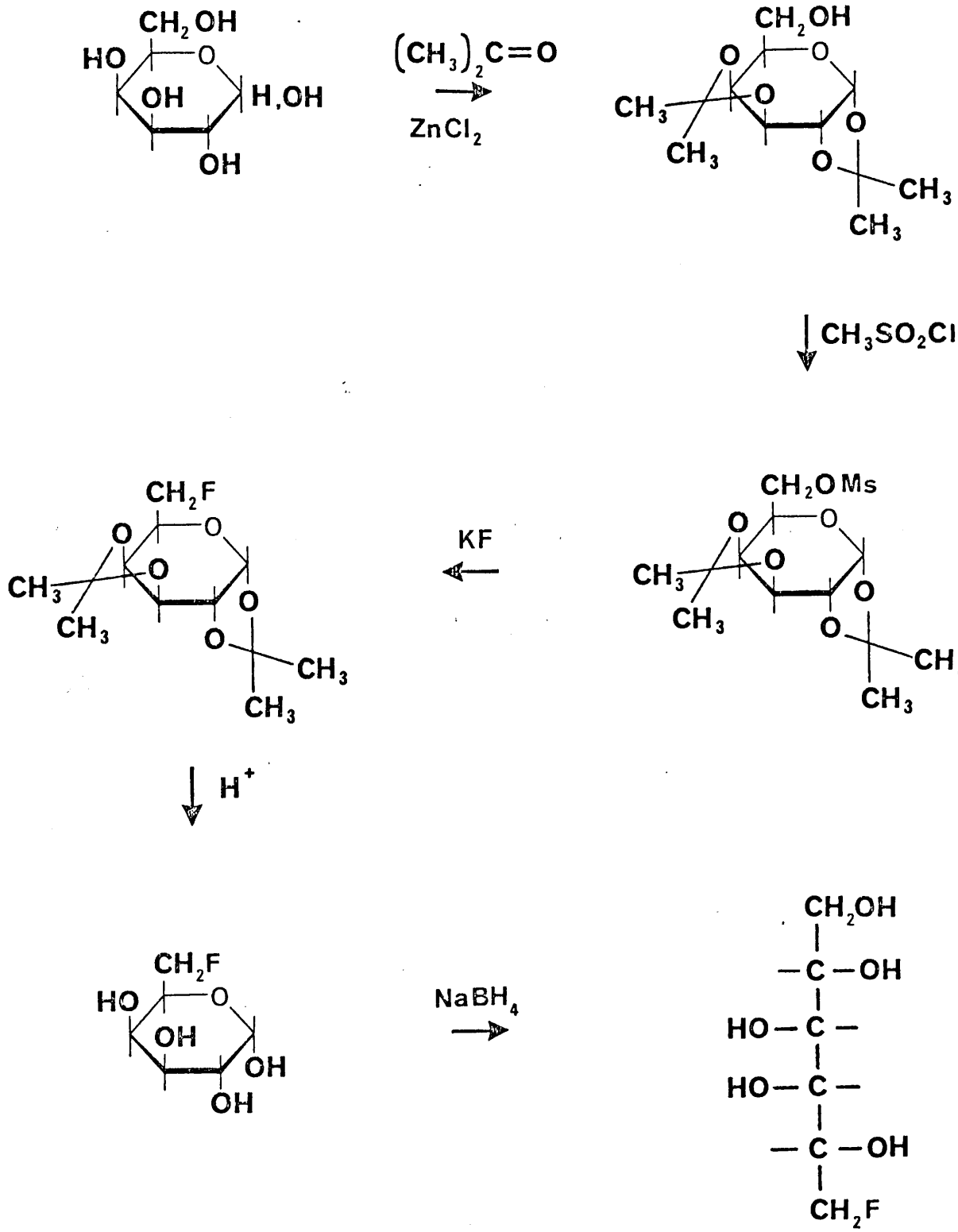
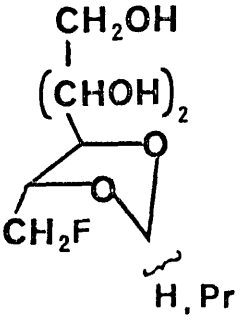

CH2OH
HO
OH
H,OH
OH
(CH3)2C=O
ZnCl2
CH2OH
CH3
CH3
CH3
CH3
CH3SO2Cl
CH2OMs
CH3
CH3
CH3
CH3
KF
CH2F
CH3
CH3
CH3
CH3
H+
CH2F
HO
OH
OH
OH
NaBH4
CH2OH
C
OH
HO
C
HO
C
C
OH
CH2F

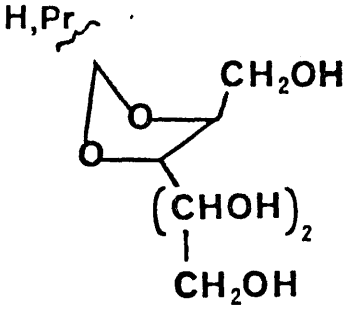
Fig. IV-8

formation of the kinetic phase. This could have two effects on the kinetic phase, it could be absent or its formation may be slow enough to make it appear as a thermodynamic phase along with other acetals of the reaction.

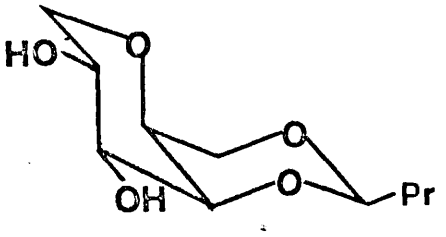
Attempts to isolate the acetals of the deoxy fluoro polyol resulted in a variety of acetal types being isolated. The only acetal isolated containing fluorine was 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol (Fig. IV-9,I). Other acetals isolated were 2,3-O-butylidene-D-galactitol (Fig. IV-9,II) and a compound believed to be 2,6-anhydro-1,3-O-butylidene-D-galactitol (Fig. IV-9,III). A further acetal was present as part of a mixture with the previously mentioned 2,6-anhydro acetal. The structure of this acetal is believed to be 2,5-anhydro-1,3-O-butylidene-L-altritol (Fig. IV-9,IV).



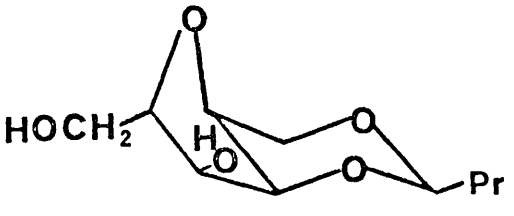
I



II



III



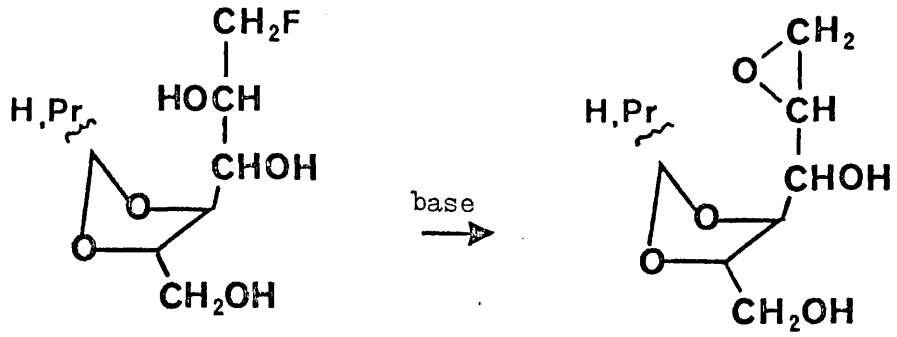
IV

Fig. IV-9

The turn of events which transformed the reaction mixture of fluoro acetals into the above mentioned products was the isolation procedure. The fluoro acetals were separated from unreacted polyol using an alumina column. Gas liquid chromatography before and after elution through this column indicated no change of structure of the fluoro acetals. When the fluoro monoacetals were passed down a Dowex 1-X8(OH^-) column for separation however, the acetals eluting from the column showed different gas liquid chromatography retention times to those applied to the column with one exception. This indicated that the Dowex 1-X8(OH^-) column was the cause of the changes in acetal structure.

The unchanged acetal recovered from the Dowex 1-X8(OH^-) column was 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol (Fig. IV-9,I). Of the other acetals obtained one had the fluorine replaced by hydroxyl, the others had fluorine replaced with formation of an anhydro ring system. If straightforward hydrolytic removal of fluorine was involved in the formation of 2,3-O-butylidene-D-galactitol on the column then it is perhaps surprising that any 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol was obtained. Rather, some other explanation seems needed to account for the 2,3-O-butylidene-D-galactitol which can also account for the preservation of 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol.

One such explanation involves 2,3-O-butylidene-6-deoxy-6-fluoro-D-galactitol (Fig. IV-10,I) as an original component of the acetalation mixture.



I II

Fig. IV-10

Micheel and co authors[58] have shown that anhydro sugars can be formed from fluoro sugars via an intramolecular displacement of the fluorine atom in the presence of base. The steric requirement for reaction is that the hydroxyl group and fluorine atom participating in the reaction should be trans disposed. For 2,3-O-butylidene-6-deoxy-6-fluoro-D-galactitol the C-5 hydroxyl function and the fluorine can easily attain such an orientation. Now, Dowex 1-X8(OH^-) resin could provide the base catalyst required for reaction as it is a strongly basic anion exchange resin. The anhydro derivative formed in the displacement would be 5,6-anhydro-2,3-O-butylidene-D-galactitol (Fig. IV-10,II). The oxirane ring could then be hydrolytically cleaved on the surface of the resin to give 2,3-O-butylidene-D-galactitol (Fig. IV-9,II).

There is also the possibility that anhydro rings could be formed from the other hydroxyl functions of the molecule i.e. C-1 or C-4 to give seven and four membered anhydro rings respectively.

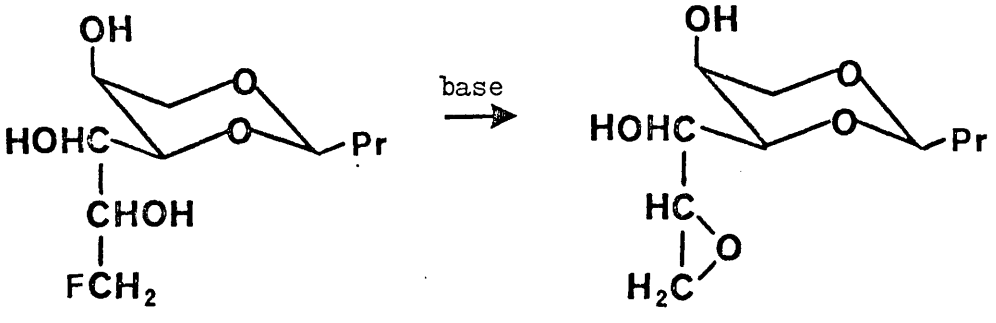
These rings are less probable however. The four membered anhydro ring (oxetane) has been found in carbohydrates but only occasionally. The seven membered anhydro ring (oxepane) is also known in carbohydrates but in the present case this oxepane ring may be difficult to form. This may be due to an unattainability of the trans disposition required between fluorine and hydroxyl for anhydro ring formation.

It may be for this reason that the 4,5-acetal of the fluoro polyol retains the fluorine atom. There are no readily accessible conformations of OH and F leading to anhydro ring formation for the 4,5-acetal. Because of this there is no loss of fluorine from this acetal. The overall conclusion therefore is that 2,3-O-butylidene-D-galactitol is formed only from 2,3-O-butylidene-6-deoxy-6-fluoro-D-galactitol.

Additional evidence for these conclusions may be obtained from the specific rotation of the isolated 2,3-O-butylidene-D-galactitol. The specific rotation $[\alpha]_D^{26}$ was found to be -30.2°. This large negative rotation is what is expected from an L-threo ring system[40,56] as present in the above acetal. If the 2,3-O-butylidene-galactitol had been formed only from 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol then it would possess a D-threo ring system. Such a system would have a large positive rotation as observed in 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol itself (see experiment 46). If the 2,3-O-butylidene——galactitol had been formed equally from both 2,3-O-butylidene-6-deoxy-6-fluoro-D-galactitol and 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol

then it would be a mixture of D and L isomers. As such, it would have no specific rotation as was the case for the previously obtained 2,3-O-butylidene-D L -galactitol.[40]

The formation of the 2,5 and 2,6-anhydro alditol acetals may be accounted for via the intermediates 1,3-O-butylidene-6-deoxy-6-fluoro-D-galactitol (Fig. IV-11,I) and 5,6-anhydro-1,3-O-butylidene-D-galactitol (Fig. IV-11,II). Just as the previously mentioned 2,3-acetal of the fluoro polyol could form an anhydro derivative in the presence of base then the 1,3-acetal may also (Fig. IV-11).



I II

Fig. IV-11

The 5,6-anhydro compound (II) may undergo intramolecular anhydro ring rearrangement to give 3,4,5 or 6 membered anhydro rings. The 2,5 and 2,6-anhydro derivatives may be formed by intramolecular attack by the C-2 oxygen at C-5 or C-6 respectively, i.e. those

carbons in the epoxide ring of II above. Attack at C-5 will result in an inversion of configuration at this carbon. Thus the D-galacto configuration is transformed into the L-altro configuration. Attack at C-6 results in no inversion of configuration hence the D-galacto configuration is retained in the 2,6-anhydro compound. Another possible route to the 2,6-anhydro compound is direct attack of the C-2 oxygen on C-6 of the deoxy fluoro acetal. This may be less likely however as it is difficult to see where the 2,5-anhydro derivative could arise from without the intermediate epoxide II above.

Considering the fact that the 5,6-anhydro-2,3-O-butylidene-D-galactitol underwent hydrolytic cleavage of its epoxide ring one may ask why the 2,5 and 2,6-anhydro rings of the 1,3-acetal do not follow suit. The retention of the anhydro ring in these compounds may be associated with a relief of bond angle strain in the five and six membered anhydro rings compared to a three membered epoxide ring.

There is a small conformational point as regards 2,6-anhydro-1,3-O-butylidene-D-galactitol. There are two possible conformations for the cis fused acetal and anhydro rings. These are the "O-inside" and "H-inside" conformations. The "O-inside" conformation is predicted to be the more stable for this derivative as it has the acetal propyl chain equatorially disposed. The "H-inside" conformation is unfavoured as it results in the propyl chain being axially disposed. The same points also arise regarding the conformation of 2,5-anhydro-1,3-O-butylidene-L-altritol.

Let us return now to the acetals of 3-deoxy-3-fluoro-D-glucitol. It may be recalled that the only isolatable acetal was the 2,4-acetal, the 4,6-acetal proving unisolatable. Inspection of models shows that for the 2,4-acetal none of the hydroxyl functions can be positioned favourably to allow anhydro ring formation via defluorination. In the 4,6-acetal however the correct positioning of hydroxyl and fluorine is possible. If anhydro formation occurred for the 4,6-acetal the question as to what happened to the product arises. No other acetal apart from the 2,4-acetal was observed to be eluted from the Dowex 1-X8(OH^-) column. One possibility is that the anhydro compound or some derivative thereof may have had similar chromatographic behaviour to the 2,4-acetal. This could conceivably have led to it being undetected. The 2,4-acetal was purified by crystallisation so any derivative of the 4,6-acetal may have been present in the mother liquor of this crystallisation. Unfortunately this possibility was not investigated.

Returning to the acetalation of 6-deoxy-6-fluoro-D-galactitol it seems that the original acetalation reaction produced the predicted acetals. This may be inferred from the isolation of compounds containing the three expected acetal rings (1,3, 2,3 and 4,5).

3. Structural Analysis of 4,5-O-Butylidene-6-deoxy-6-fluoro-D-galactitol (Fig. IV-9,I).

Micro elemental analysis on the acetal was in agreement with the proposed structure. The acetal consumed 2.12 moles of periodate ion with liberation of 0.82 moles of formic acid and 1.04 moles of

formaldehyde. This suggested the presence of three consecutive hydroxyl functions, one of which was primary the other two secondary. The only possible monoacetal of 6-deoxy-6-fluoro-D-galactitol in agreement with these observations was 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol.

The ^{1}H n.m.r. spectrum of the acetal showed an acetal proton triplet at 4.98 δ with a ^{3}J value of 4.5 Hz, both facts providing additional evidence for the ring size. ^{13}C n.m.r. spectroscopy also indicated a five membered acetal ring from the presence of diastereoisomeric acetal carbon resonances with the expected chemical shift values for five membered rings.

A gas liquid chromatography/mass spectrometry analysis on the acetylated methylated fluoro polyol derived from the acetal had a fragmentation pattern which was consistent with the original position of the ring as being on C-4 and C-5 (section VI-2-iii).

4. Structural Analysis of 2,3-O-Butylidene-D-galactitol (Fig. IV-9,II).

The acetal had micro elemental analysis figures which were in agreement with a monobutylidene acetal of a hexitol. Elemental analysis also showed no significant traces of fluorine. The acetal consumed 1.99 moles of periodate ion with liberation of 1.02 moles of formaldehyde and 0.94 moles of formic acid. The only acetals of galactitol consistent with these observations were the 1,3 and 2,3-acetals.

Finally, the acetal had an identical ^{13}C n.m.r. spectrum and mass spectrum (acetylated, methylated derivative for mass spectrum) to an authentic specimen of 2,3-O-butylidene-D,L-galactitol.[45,89] On the basis of these observations it was accorded the 2,3-ring structure.

The structural analyses of 2,5-anhydro-1,3-O-butylidene-L-altritol and 2,6-anhydro-1,3-O-butylidene-D-galactitol place heavy emphasis on ^{13}C n.m.r. spectroscopy. These analyses are discussed at length in the ^{13}C n.m.r. section (V-A-3-iii) rather than here.

V-A Carbon-13 (^{13}C) n.m.r. Spectroscopy of Deoxy Polyols, Deoxy Fluoro Polyols and their Mono-O-Butylidene Acetals

1. Introduction

Although the earliest reported data on ^{13}C n.m.r. spectroscopy date back to 1957[59] the utilisation of the technique as a regular feature of structure elucidation did not occur until the early seventies. This delay to fruition of such a promising and valuable technique was caused by the problems associated with obtaining good quality reproducible ^{13}C spectra.

The natural abundance of the ^{13}C isotope is only 1.1% compared to 99.98% for the proton. Also, at the same field strength the ^{13}C isotope is much less sensitive to resonance (1.59%) compared to the proton due to its low gyromagnetic ratio. This low abundance and sensitivity of the ^{13}C isotope have been contributory to the difficulties associated with obtaining ^{13}C spectra.

These difficulties have been overcome however by pulse Fourier transform (PFT) n.m.r. spectroscopy. The PFT method allows natural abundance ^{13}C spectra to be recorded on a reasonably small amount of sample(100 mg) in a relatively short time (1 hour). The principles and applications of PFT ^{13}C spectroscopy have been most adequately reviewed[60] and a wholesale rediscussion of this will not be presented here. Instead, a synopsis of some salient points which will be useful later in this section will be attempted.

In the absence of ^{13}C-^{1}H spin-spin coupling each magnetically unique carbon atom in an organic molecule will give rise to a single line in the ^{13}C spectrum of that molecule. Splittings of the lines

due to $^{13}C-^{13}C$ spin-spin couplings are not observed in the natural abundance spectra due to the low abundance of the ^{13}C isotope. If the molecule under observation is enriched in ^{13}C then such couplings are observed. Thus the natural abundance ^{13}C spectrum of D-glucitol (Fig. V-1) is expected to consist of six lines and this has proved so. [61,62]

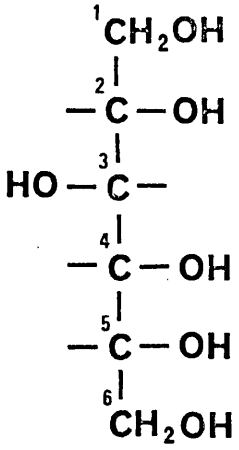


Fig. V-1

The $^{13}C-^{1}H$ couplings are washed out by irradiating the sample under observation with a second radio frequency whose width covers the entire range of the Larmor frequencies of the protons. The spectra obtained without $^{13}C-^{1}H$ couplings are known as "broad band decoupled" or "decoupled" ^{13}C spectra and are the type most commonly encountered in the literature. ^{13}C spectra obtained when $^{13}C-^{1}H$ couplings are observed are known as "undecoupled" spectra.

They are more complex than the decoupled spectra due to second order effects arising from $^{13}C-^{1}H$ splitting patterns of similarly shielded ^{13}C nuclei. A third type of ^{13}C spectrum is the "off resonance decoupled" spectrum. In this method the decoupling frequency is a few hundred hertz outside the range of the Larmor frequencies of the protons. This causes geminal and longer range couplings to collapse. One bond $^{13}C-^{1}H$ couplings decrease to 10-50 Hz depending upon the frequency range of the decoupling frequency. This results in methyl, methylene and methine carbon atoms appearing as intense first order quartets, triplets and doublets respectively. Examples of each type of spectra are Figs. V-2 to V-5 for the case of 2-deoxy-D-lyxo-hexitol.

Originally the shifts of ^{13}C lines were relative to standards such as CS_2 or benzene. Nowadays they are most likely to be relative to T.M.S. as are protons. A similar scale applies, ie T.M.S. is at 0 δ and deshielding of nuclei is accompanied by an increasing positive number on the δ scale. The range of chemical shifts of ^{13}C nuclei is from 0 δ to 200 δ for most organic molecules. The $^{13}C-^{1}H$ coupling constants are much larger than $^{1}H-^{1}H$ coupling constants. For one bond $^{13}C-^{1}H$ couplings a range of 100-250 Hz is observed, for vicinal and longer range couplings smaller values are observed. For the vicinal couplings the magnitude of the coupling is dependent on the dihedral angles between the coupled nuclei.[63] The relationship is of the Karplus type found for protons. Further relevant points of interest to this section are those works dealing with ^{13}C spectroscopy of the polyols and of acetals.

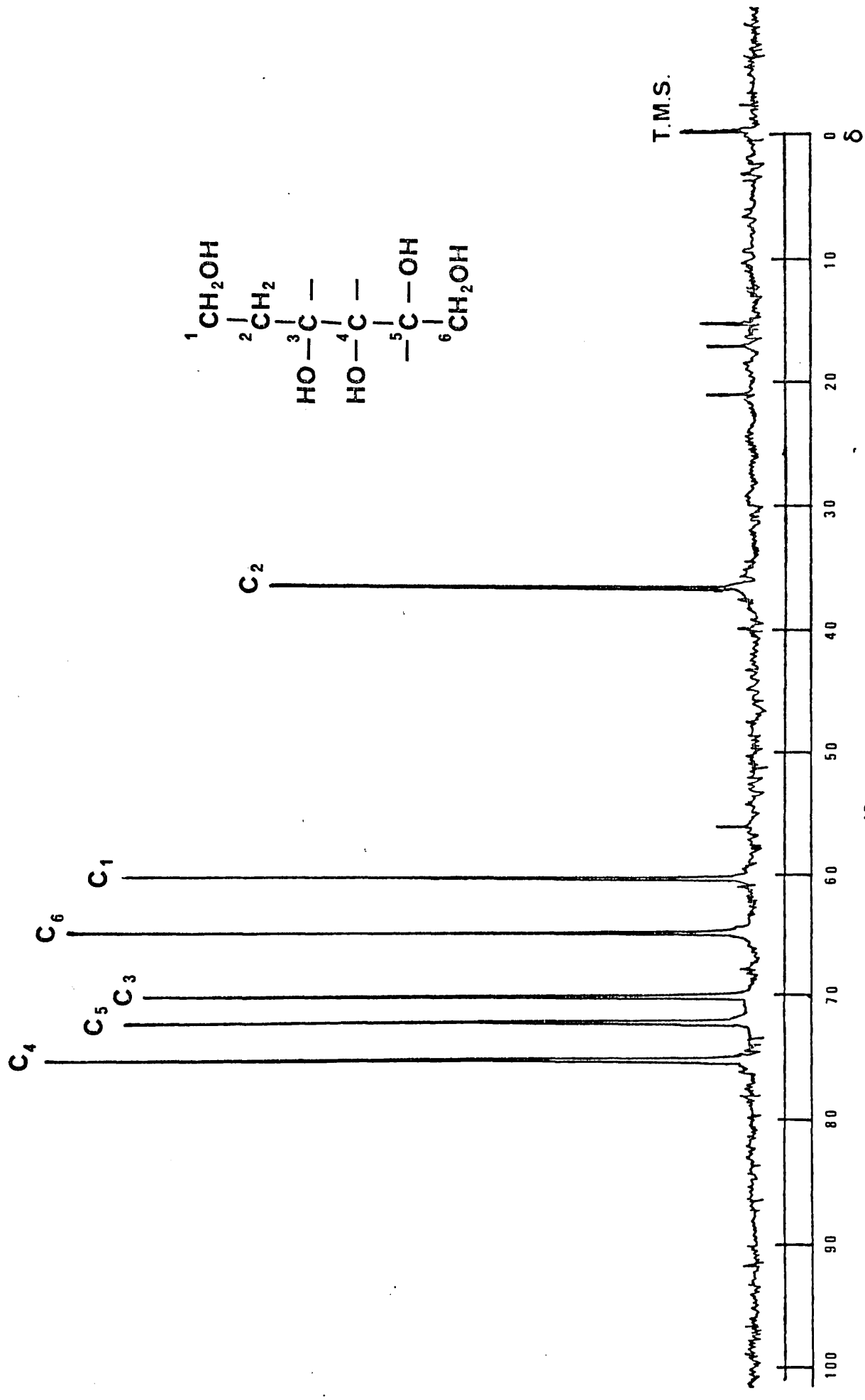


Fig. V-2 Proton Decoupled ^{13}C n.m.r. Spectrum of 2-Deoxy-D-lyxo-hexitol

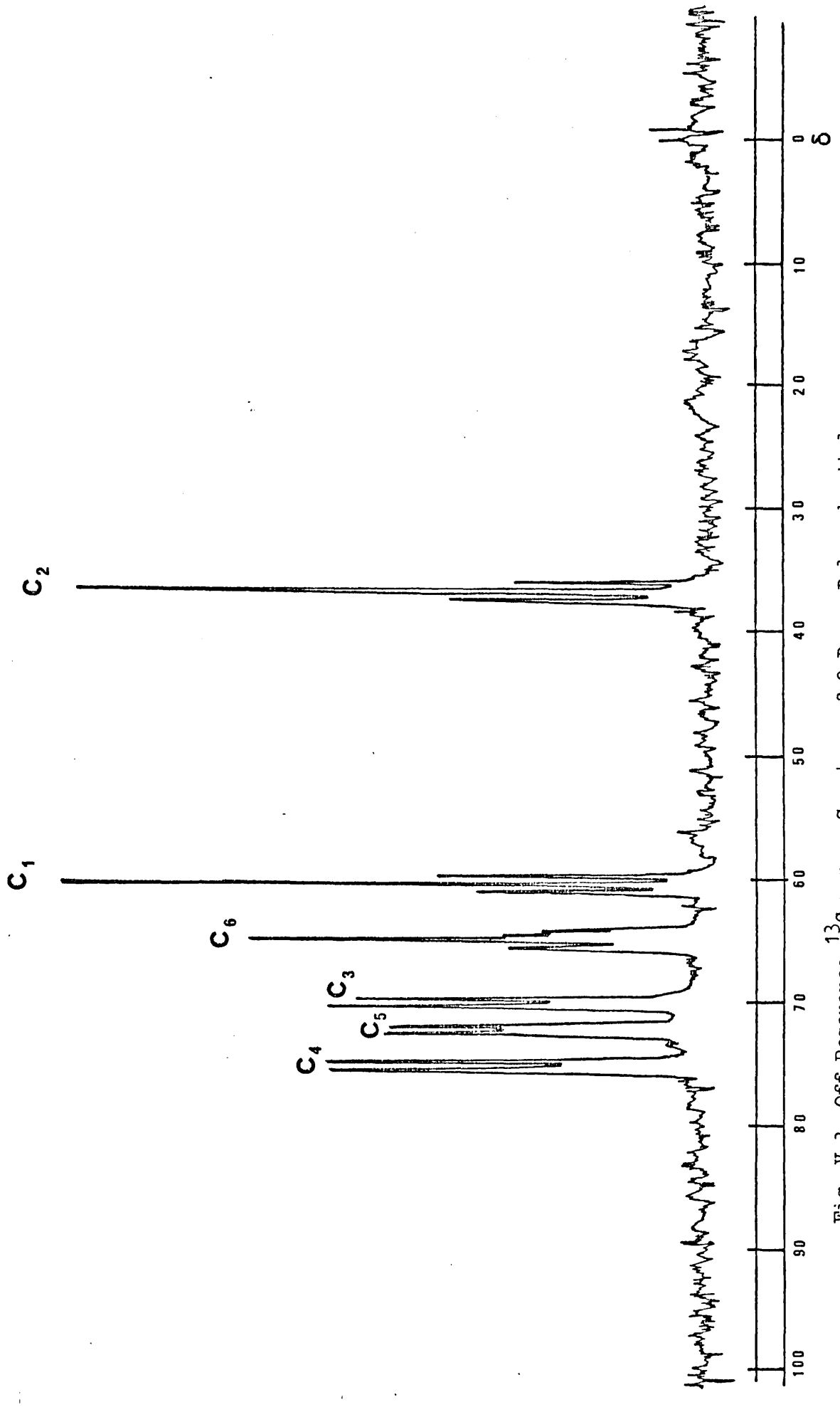


Fig. V-3 Off Resonance ^{13}C n.m.r. Spectrum of 2-Deoxy-D-lyxo-hexitol

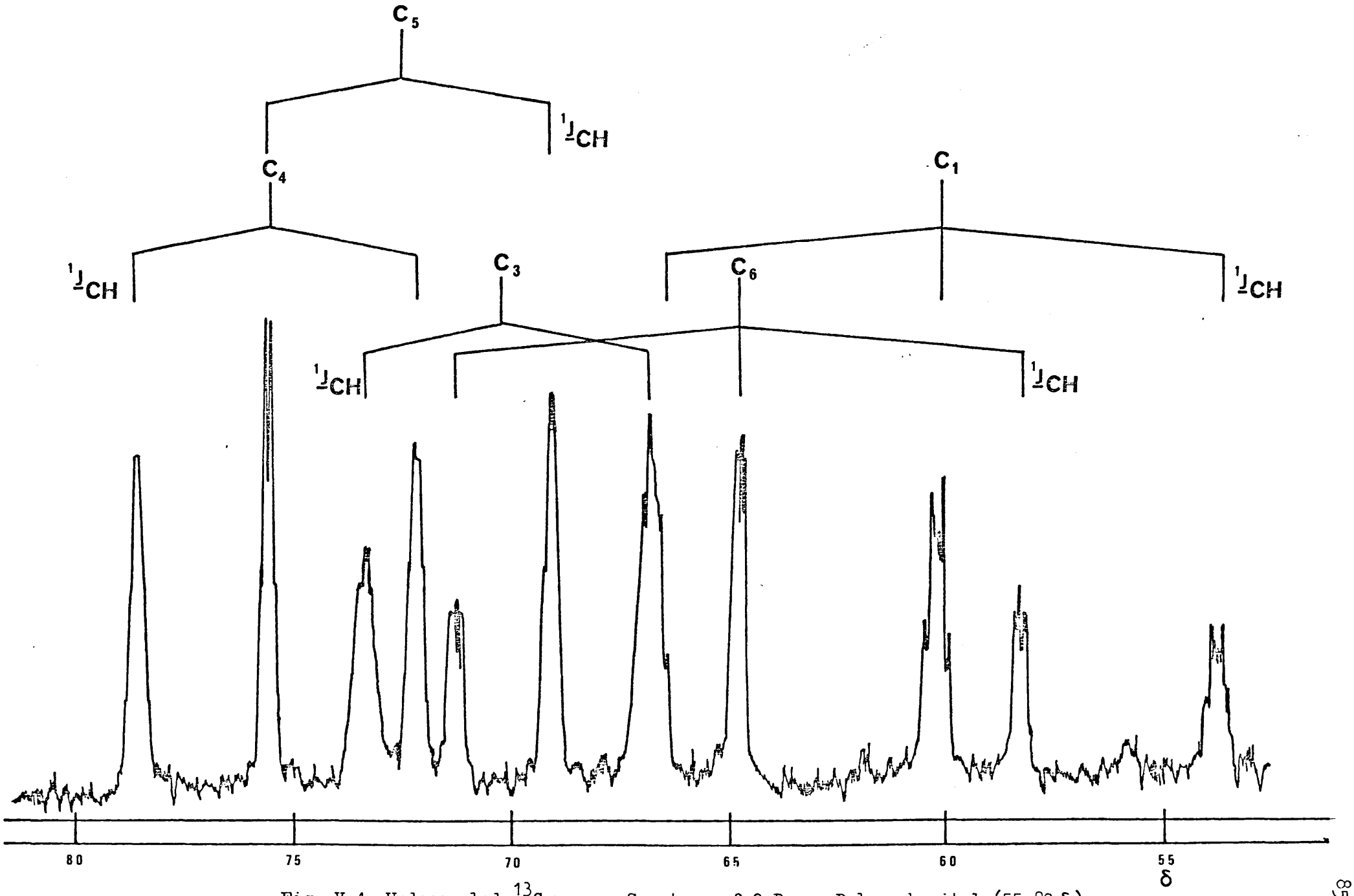


Fig. V-4 Undecoupled ^{13}C n.m.r. Spectrum of 2-Deoxy-D-lyxo-hexitol (55-80 δ)

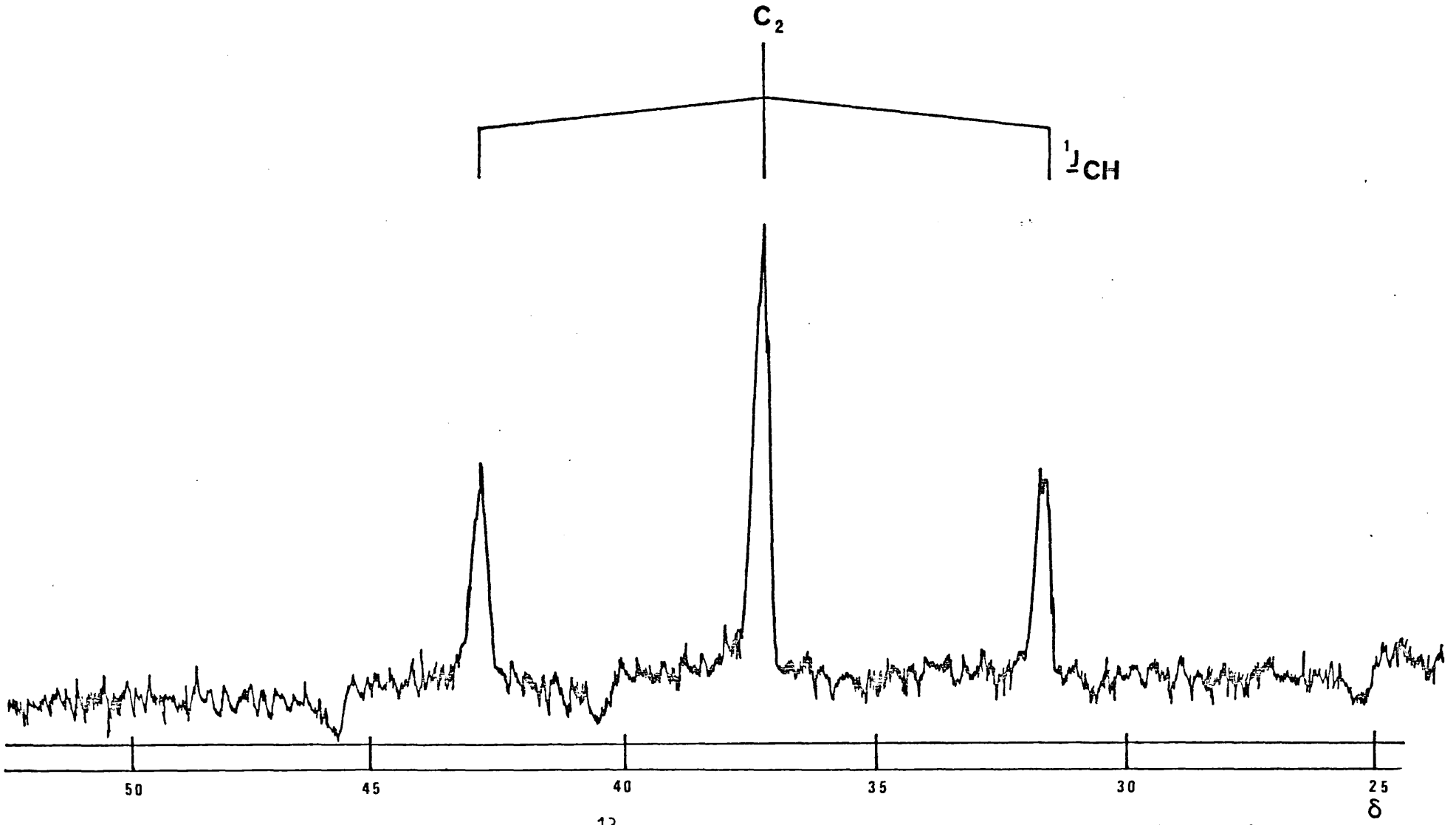


Fig. V-5 Undecoupled ^{13}C n.m.r. Spectrum of 2-Deoxy-D-lyxo-hexitol (25-50 δ)

The first publication concerning ^{13}C n.m.r. spectroscopy of polyols was by Voelter et al.[61] They presented chemical shift data for various polyols and a few deoxy polyols. This initial study was confined to recognisance of different shift ranges for primary and secondary hydroxylated carbons. Later work by the same authors dealt with the full interpretation of the ^{13}C spectra of galactitol and its mono- and di-O-methyl ethers.[64]

More recent work on polyols has concerned the assignment of the ^{13}C resonances of ribitol, D-glucitol and 4-O-methyl-D-glucitol.[62] The utilisation of methyl derivatives as an aid to spectral interpretation lies in the fact that O-methylation causes an 8–10 p.p.m. deshielding of the α carbon[65,66] (the directly attached carbon). The β carbons (adjacent carbons) experience a smaller shift whilst carbons further away are virtually unaffected.

Other ^{13}C work dealing with polyhydroxy compounds mainly concerns cyclic derivatives such as the monosaccharides[65,67] and the inositols.[66] It was from these early papers that much of the data relating ^{13}C chemical shifts to configuration was obtained. An example of this is the change in chemical shifts accompanied by change in configuration of one carbon atom when looking at scyllo- and myo-inositols[66] (Fig. V-6).

scyllo-inositol myo-inositol

Fig. V-6

The chemical shifts of all the carbons in scyllo-inositol are 118.8 relative to CS_2. The change of configuration of one carbon as in myo-inositol causes shieldings of C-2, C-1 and C-3, C-4 and C-6, whilst C-5 is practically unaffected.

Looking now at the acetals, there have been several publications regarding ^{13}C of acetals of carbohydrates. [68,69] Two useful features emerge from these early studies, on the one hand those carbon atoms of the sugar ring whose oxygen atoms become acetal ring oxygens are deshielded by about 8–10 p.p.m. (Fig. V-7).

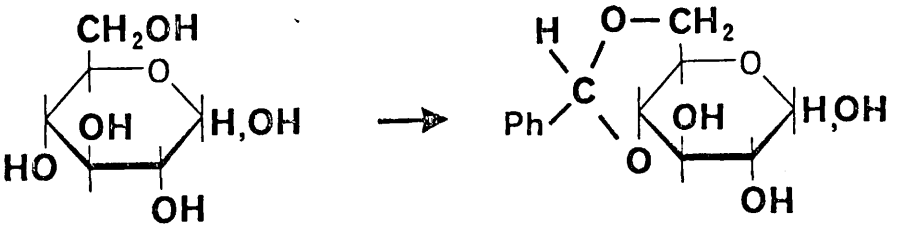


Fig. V-7

On the other hand the carbon atom adjacent to both those deshielded acetal ring carbons is shielded by about 8–10 p.p.m.

Other types of acetals studied have included 1,3-dioxane and its derivatives. The earliest report[70] gives the ^{13}C shifts of the parent molecule, later work those of its derivatives.[71-74] This later work by Riddell[72] then Eliel[73] dealt with substituent effects on ^{13}C chemical shifts when various alkyl functions were introduced into 1,3-dioxane. The results were similar to those obtained from the alkyl cyclohexanes,[75] in that alkylation deshielded the α carbon as well as producing other shift differences related to conformation. Further information on the use of ^{13}C n.m.r. is available in the review by Wilson and Stothers[76] (stereochemical approach), the review by Rosenthal and Fendler[77] (carbohydrates) and the monograph by Stothers[78] (theory and background).

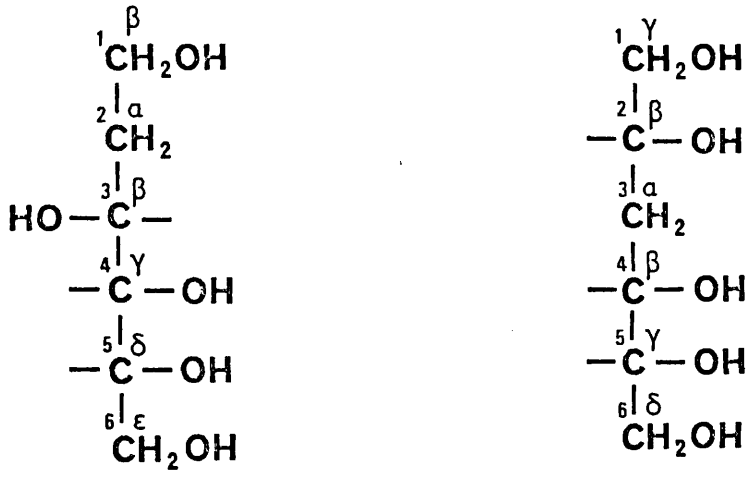
2. Assignment of the ^{13}C n.m.r. Signals of the Deoxy and Deoxy Fluoro Polyols

The ^{13}C chemical shifts and one bond $^{13}C-^{1}H$ coupling constants of the deoxy polyols and two fluoro analogues are listed in tables V-1 and V-2. Table V-3 lists the ^{13}C chemical shifts of some ordinary polyols, the values of which are used for comparative purposes with the deoxy compounds. The values for the normal polyols are not those currently appearing in the literature. Rather, they were taken from related studies[79] to the work presented here, and obtained from the same spectrometer under similar conditions. The comparisons made should be more valid than would be if other data were used. I am indebted to Dr D. Lewis for allowing me to

reproduce his data on the normal polyols. For each secondary deoxy polyol there is a pair of epimeric parent non deoxy polyols. At the time of writing however some data on the ordinary polyols was incomplete hence some omissions. The deoxy polyols are discussed apart from the fluoro analogues as different shielding characteristics apply to each group.

(i) Deoxy Polyols

The numbering and lettering system used for the deoxy polyols is illustrated for two examples in Fig. V-8 below.



2-deoxy-D-arabino-hexitol 3-deoxy-D-ribo-hexitol

Fig. V-8

The ^{13}C chemical shifts of the deoxy polyols were assigned mainly by α,β and γ substituent effects arising from the deoxy function. The substituent chemical shifts for the deoxy polyols when compared to the parent non deoxy polyols are tabulated for easy access in Table V-4. A positive sign indicates deshielding, i.e. movement to lower field with a higher δ shift value. These effects are discussed in detail below. Certain distinctions can be made without

Deoxy Polyol	C-1	C-2	C-3	C-4	C-5	C-6
2-Deoxy-D-arabino-hexitol	61.4	38.0	69.7	75.8	73.9	65.8
2-Deoxy-D-lyxo-hexitol	61.1	37.2	70.8	75.9	72.9	65.6
2-Deoxy-D-erythro-pentitol	61.4	37.0	71.8	77.5	65.3	-
3-Deoxy-D-ribo-hexitol	67.5	72.3 or 72.5	37.6	72.3 or 72.5	77.1	64.9
4-Deoxy-D-xylo-hexitol	65.3	77.2	70.3 or 71.0	38.5	70.3 or 71.0	68.6
1-Deoxy-D-arabinitol	21.1	68.9	77.0	74.0	65.5	-
3-Deoxy-3-fluoro-D-glucitol	64.2	73.7	94.8	72.4	73.0	65.1
6-Deoxy-6-fluoro-D-galactitol	66.0	72.9	72.1	? Between	? 71.3 and 71.9	88.2

Table V-1 ^{13}C chemical shifts (δ p.p.m.) of some deoxy polyols

Deoxy Polyol	$\underline{J}^1_{C-H}$	$\underline{J}^2_{C-H}$	$\underline{J}^3_{C-H}$	$\underline{J}^4_{C-H}$	$\underline{J}^5_{C-H}$	$\underline{J}^6_{C-H}$
2-Deoxy-D-arabino-hexitol	143	125	143	140	143	143
2-Deoxy-D-lyxo-hexitol	144	125	143	142	143	144
2-Deoxy-D-erythro-pentitol	144	125	130	143	143	-
3-Deoxy-D-ribo-hexitol	145	144	126	144	144	143
4-Deoxy-D-xylo-hexitol	143	143	143	124	143	143
1-Deoxy-D-arabinitol	126	141	141	141	147	-
3-Deoxy-3-Fluoro-D-glucitol	143	?	153	?	?	145
6-Deoxy-6-Fluoro-D-galactitol	146	146	?	?	146	153

Table V-2 Directly bonded $^{13}C-^{1}H$ spin-spin coupling constants (Hz) of some deoxy polyols

Polyol	C-1	C-2	C-3	C-4	C-5	C-6
D-Arabinitol	65.8 or 66.0	73.2	73.5	73.9	65.8 or 66.0	-
Ribitol	65.4	75.0	75.0	75.0	65.4	-
Allitol	65.0	74.7	74.9	74.9	74.7	65.0
Galactitol	66.1	73.0	72.3	72.3	73.0	66.1
D-Glucitol	65.3	75.6	72.4	73.9	73.7	65.6
D-Mannitol	66.0	73.8	72.1	72.1	73.8	66.0

uncertain values

Table V-3 ^{13}C Chemical shifts (δ p.p.m.) of some polyols

Deoxy Polyol	C-1	C-2	C-3	C-4	C-5	C-6
2-Deoxy-D-arabino-hexitol (D-glucitol)	-3.9	-37.6	-2.7	+1.9	+0.2	+0.2
" (D-mannitol)	-4.6	-35.8	-2.4	+3.7	+0.1	-0.2
2-Deoxy-D-lyxo-hexitol (galactitol)	-5.0	-35.8	-1.5	+3.6	-0.1	-0.5
2-Deoxy-D-erythro-pentitol (ribitol)	-4.0	-38.0	-3.2	+2.5	-0.2	-
3-Deoxy-D-ribo-hexitol (allitol)	+2.5	-2.2 or -2.4	-37.3	-2.4 or -2.6	+2.4	-0.1
" (D-glucitol)	+2.2	-3.1 or -3.3	-34.8	-1.4 or -1.6	+3.4	-0.7
4-Deoxy-D-xylo-hexitol (galactitol)	-0.8	+4.2	-1.3 or -2.0	-33.8	-2.0 or -2.7	+2.5
" (D-glucitol)	0.0	+1.6	-1.4 or -2.1	-35.4	-2.7 or -3.4	+3.0
3-Deoxy-3-fluoro-D-glucitol (D-glucitol)	-1.1	-1.9	+22.4	-1.5	-0.7	-0.5
6-Deoxy-6-fluoro-D-galactitol (galactitol)	-0.1	-0.1	-0.2	?	?	+22.1

Table V-4 ^{13}C Substituent chemical shifts (p.p.m.) of the deoxy and deoxy fluoro polyols.
The polyol in parentheses is that one used for comparison to get the substituent shift.

substituent effects however. Carbons bearing primary hydroxyls are distinguished from those with secondary hydroxyls using the off resonance spectra. The former appear as first order triplets, the latter as first order doublets. The complete collection of ^{13}C spectra have not been illustrated, rather some typical examples were chosen to represent each category.

The most readily recognisable ^{13}C resonance of the deoxy polyols is that from the deoxy function. Under off resonance conditions the secondary deoxy carbons appear as first order triplets in the range 37.0 δ to 38.5 δ. The only primary deoxy carbon studied appeared as a first order quartet under similar conditions with chemical shift 21.1 δ. The high field chemical shift relative to the remaining resonances is brought about by lack of an oxygen substituent, other carbons being hydroxylated. Oxygen substitution causes a deshielding of the α carbon of 35 p.p.m. upwards.[76,80] A comparison between the chemical shifts of the deoxy carbons and their corresponding non deoxy carbons in the non deoxy polyols shows the deoxy carbons to be shielded by 33.8 δ to 44.9 δ.

Carbon shieldings accompanying loss of oxygen are useful for the identification of the carbons β to the deoxy carbon. For the 2-deoxy polyols C-1 is always at higher field than the other primary hydroxyl carbon of the molecule. This is due to C-1 experiencing a β shielding whereas the other primary hydroxyl carbon does not. A comparison of chemical shifts for the 2-deoxy and appropriate non deoxy polyols shows C-1 to be shielded by 3.9 to 5.0 p.p.m. whereas the other primary hydroxyl carbon has a very similar chemical shift to its parent polyol. The 3.9 to 5.0 p.p.m.

shielding is of the same magnitude found by Roberts et al [80] for a series of acyclic and alicyclic alcohols.

The positions of the C-1 resonances were confirmed by preparation of the C-1/^{2}H deoxy polyols then analysis of their spectra. The preparation of deuterated derivatives as an aid to ^{13}C spectral assignments is well established. [81,82] The modification caused by introduction of deuterium is either to make the α carbon resonance disappear[83] or appear as a triplet[84] in the decoupled spectrum. Certain marginal ^{13}C shift changes are also observed due to deuterium substitution. The ^{13}C decoupled spectra of 2-deoxy-D-arabino-hexitol before and after deuterium labelling are illustrated (Figs. V-9 and V-10). In this case the C-1 signal appears as a triplet in the decoupled spectrum centred at 61.0 δ. The 0.4 p.p.m. shift to higher field agrees with Gorin's[82] findings on deuterium induced ^{13}C shifts.

Let us now return to the other carbons which are β to the deoxy functions. They are all methine carbons, giving first order doublets in the off resonance ^{13}C spectra. They can be distinguished from the other methine carbons by their higher field chemical shift. The shift range of methine carbons β to a deoxy function is 68.9 δ to 72.5 δ. All other methine carbons have shifts to lower field. For the 2-deoxy polyols and 1-deoxy-D-arabinitol there is only one methine carbon β to the deoxy function and hence it is easy to identify. For the 3- and 4-deoxy polyols however there are two such carbons. For these polyols the shifts of these carbons are too similar to permit assignation to a particular carbon atom. Whereas methylene carbons β to a deoxy function were

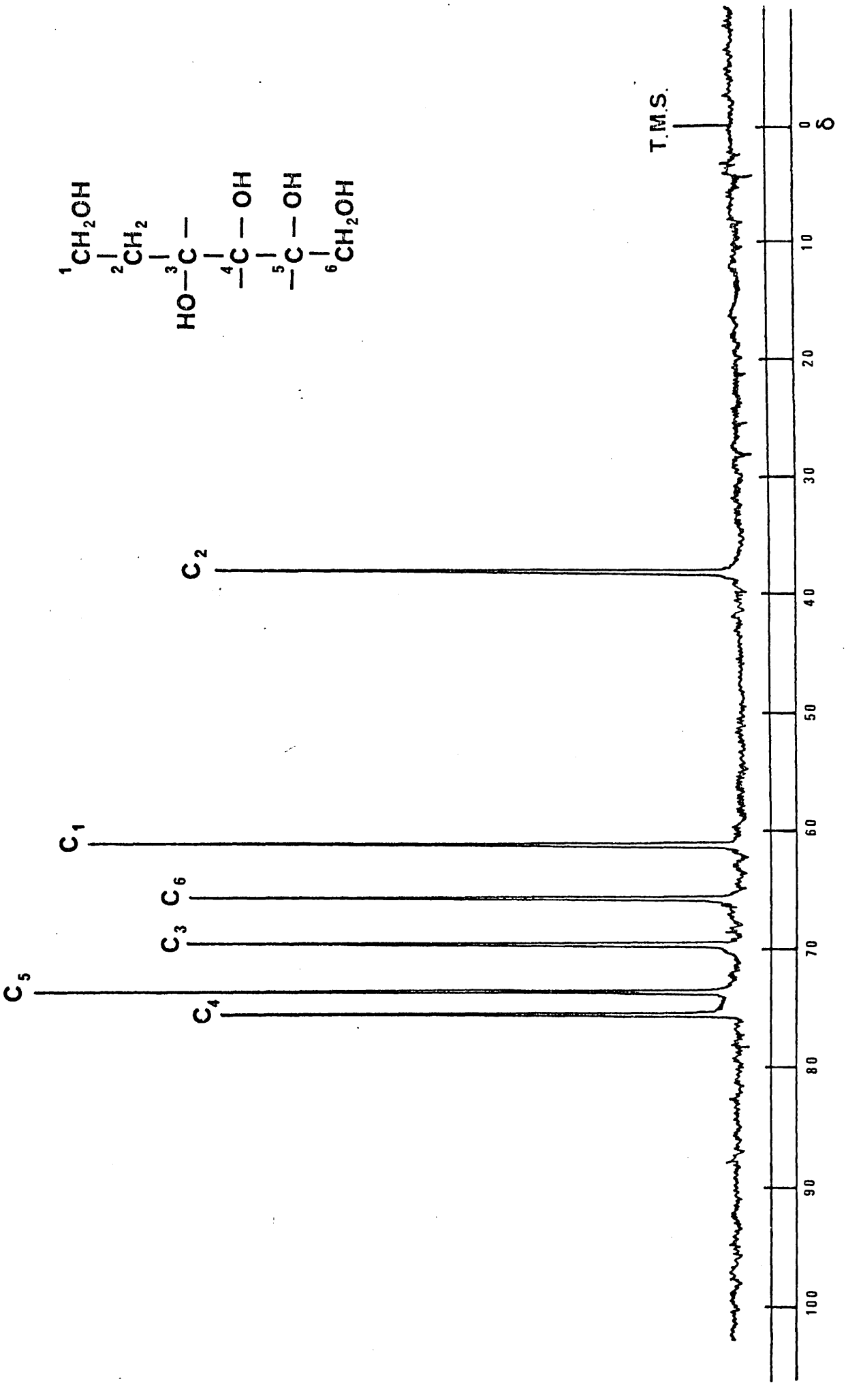


Fig. V-9 Decoupled ^{13}C n.m.r. Spectrum of 2-Deoxy-D-arabino-hexitol

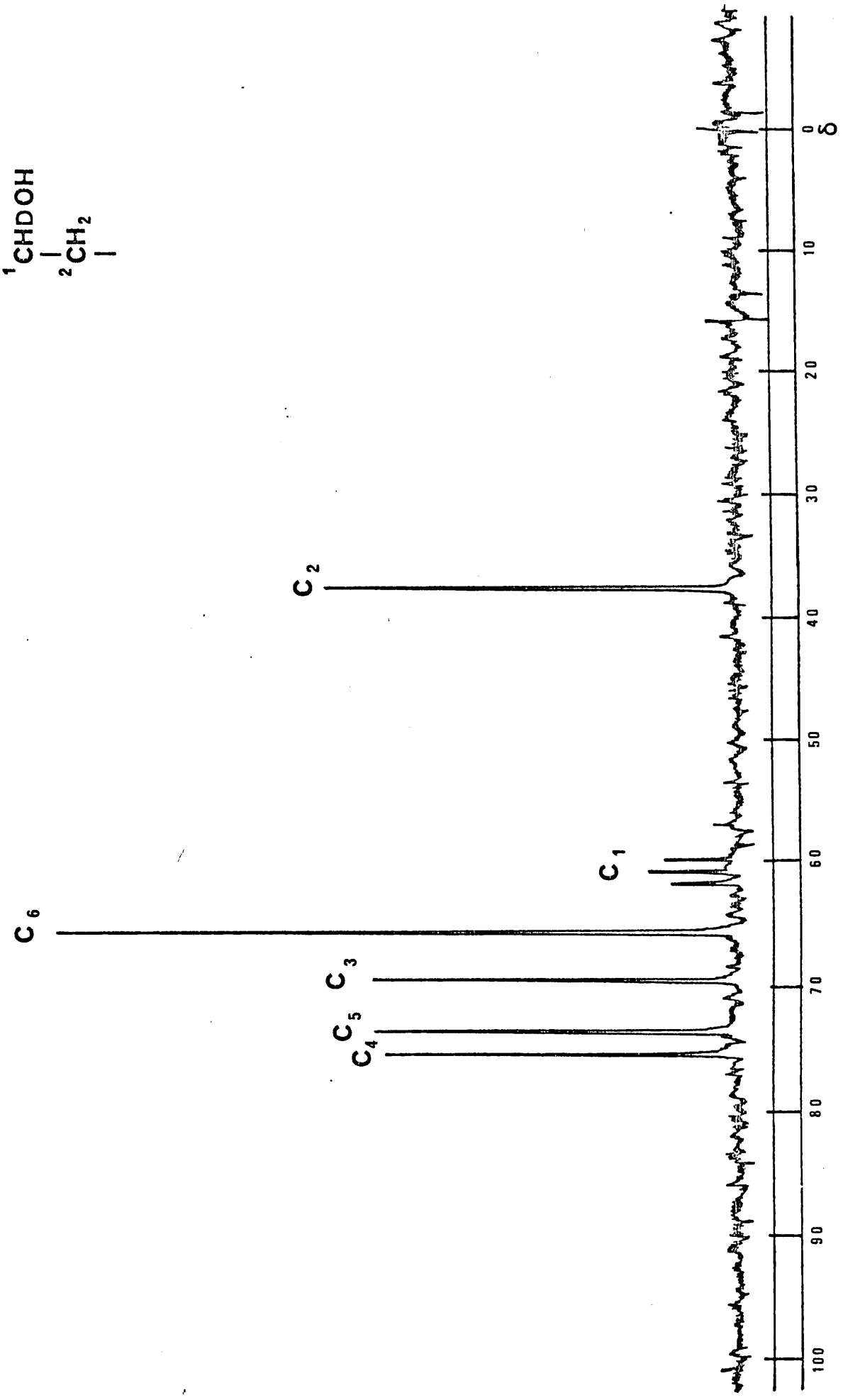


Fig. V-10 Decoupled ^{13}C n.m.r. Spectrum of C-1/ ^{2}H-2-Deoxy-D-arabino-hexitol

shielded by 3.9 to 5.0 p.p.m., similar methine carbons were only shielded by 1.3 to 3.4 p.p.m.

Having discussed the ^{13}C resonance positions of carbons α and β with respect to the deoxy function attention can be focussed towards those more distant. Of these, the γ carbons show the greater deshielding compared with the parent non deoxy polyols. The γ effect [76] is a well known feature in ^{13}C n.m.r. spectroscopy. Briefly, substitution of hydrogen with alkyl, halo, hydroxy or amino functions causes a shielding of the γ carbons. This shielding varies between 1 and 6 p.p.m. depending on the nature of the substituent and the conformation of the molecule under investigation. For the polyols the substituent is hydroxyl. Hence, when removed as in the deoxy polyols the γ shielding will also be removed. This results in a deshielding of the carbons γ to the deoxy function. Wilson and Stothers [76] give the γ effect of a secondary hydroxyl as shielding by 3.7 p.p.m.

The carbons γ to the deoxy function are invariably the lowest field carbons of their type. γ Methylene carbons are the lowest field methylene carbons, and γ methine carbons are the lowest field methine carbons. Comparisons with the parent non deoxy polyols show γ deshieldings of between 1.6 and 4.2 p.p.m. for the deoxy polyols. This variance is probably due to the different conformations available to the parent epimers. D-Mannitol exists with the carbons in a planar zig-zag conformation in solution whereas its C-2 epimer D-glucitol has a sickle conformation. 2-Deoxy-D-arabino-hexitol is expected to have a planar zig-zag carbon chain, thus comparison with another planar zig-zag should probably show different deshieldings than those found by comparison with a sickle conformer.

Carbons further away than γ to the deoxy function do not exhibit shieldings or deshieldings of any consistency. Grover and Stothers[85] have studied the long range hydroxyl substituent effects for a series of decalols. They concluded that the δ effect is markedly dependent upon configuration. The conformations of the non deoxy polyols with regard to the hydroxy-carbon δ interactions are illustrated below (Fig. V-11).

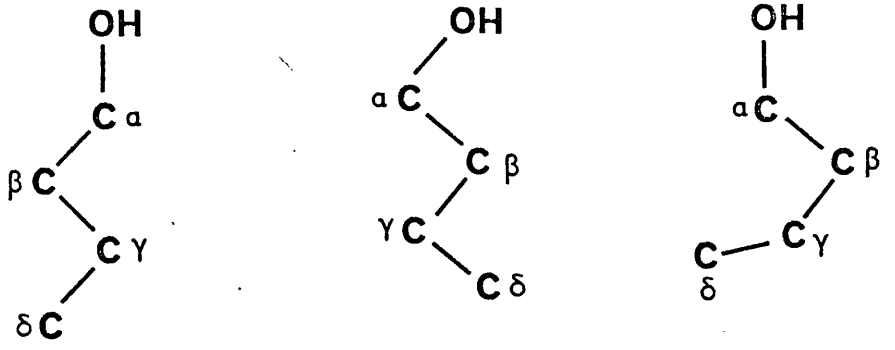


Fig. V-11

Grover and Stothers, for a series of decalols found these conformations to be associated with shieldings of 0.1 and 1.4 p.p.m. on the δ carbon.[85] When the δ interaction is removed as in the deoxy polyols the appropriate deshieldings are to be expected. Looking at the shift data in tables V-1 and V-3 only 2-deoxy-D-arabino-hexitol has δ carbon deshieldings relative to its parent non deoxy polyols (0.2 and 0.1 p.p.m.). The other deoxy polyols have δ carbon shieldings of a similarly small magnitude. The problem associated with the δ effect is that the effect is of the margin of error associated with the ^{13}C chemical shifts hence any conclusions should be drawn with caution.

The carbons ε to the deoxy function are present only in 2-deoxy-D-arabino- and lyxo-hexitols. Shift data are available only for three comparisons, which are not enough to draw any conclusions from. Two cases are shielding (0.2, 0.5 p.p.m.) the other deshielding (0.2 p.p.m.).

In summary, the ^{13}C chemical shifts were obtained for the deoxy polyols by considering α, β and γ effects from the deoxy function in conjunction with chemical shift data from appropriate non deoxy polyols. Once the chemical shifts were ascertained the following trends emerged.

1. The deoxy carbon is at highest field, the range being 37.0 δ to 38.5 δ for methylene deoxy carbons, 21.1 δ for methyl carbons.

2. Carbons with primary hydroxyls have chemical shifts between 61.1 δ and 68.6 δ.

3. Carbons with secondary hydroxyls have chemical shifts between 68.9 δ and 77.5 δ.

4. Carbons β to the deoxy function are the highest field of their type, i.e. methine or methylene.

5. Carbons γ to the deoxy function are the lowest field of their type.

The $^{13}C-^{1}H$ one bond coupling constants (table V-2) are rather featureless, oxygenated carbons showing couplings between 140 to 147 Hz, deoxy carbons having couplings around 125 Hz. Two and three bond $^{13}C-^{1}H$ couplings were not measured. The couplings for the fluoro polyols are discussed in the following section.

(ii) Deoxy Fluoro Polyols

The same system of numbering and lettering used for the deoxy polyols applies to the deoxy fluoro polyols. The ^{13}C chemical shift, coupling constant and substituent shift data are listed in the same tables (V-1, V-2 and V-4) as the deoxy polyols. The ^{13}C shift assignments were not based so strongly on substituent effects as previously. Rather, they were based more on the $^{13}C-^{19}F$ spin-spin coupling constants. Total interpretation of the deoxy fluoro polyol spectra proved impossible due to complexities in the spectra arising from $^{13}C-^{19}F$ splittings of very similarly shielded nuclei. Heteronuclear $^{13}C-^{19}F$ decoupling which may have aided the interpretation was unavailable from the machine used to obtain the ^{13}C spectra. The ^{13}C spectra of both deoxy fluoro polyols are discussed below.

(a) 3-Deoxy-3-fluoro-D-glucitol

The proton decoupled ^{13}C spectrum (Fig. V-13) of 3-deoxy-3-fluoro-D-glucitol consists of ten lines. These lines arise through spin-spin coupling of carbons one to five with the fluorine nucleus on C-3. There is overlapping of two lines and C-6 is not coupled to fluorine thus the ten lines are explained.

The introduction of the fluorine atom allows the C-3 signal to be easily identified. The C-3 signal is at the lowest field of all the ^{13}C lines due to it being deshielded by the directly attached electronegative fluorine atom. It also has a very large one bond $^{13}C-^{19}F$ coupling ($^{1}J_{CF}$). For the present case the chemical shift of C-3 is centred at 94.8 δ as a doublet in the proton decoupled spectrum, with a $^{1}J_{CF}$ coupling of 173.6 Hz. Wray [86]

has found that for certain fluoropyranose derivatives the average $^{1}J_{CF}$ coupling is 179.5 ± 3.6 Hz for the function illustrated below (Fig. V-12).

J_{CF} = 179.5 ± 3.6 Hz

Fig. V-12

The variance in coupling is due to the different possible configurations the hydroxyls and fluorine can have. The average chemical shift for the fluorinated carbon in the above function was found by Wray[86] to be 92.7 δ. The C-3 atom of 3-deoxy-3-fluoro-D-glucitol can be compared with the above examples as it fits in with the substitution pattern of the above structure. This comparison of $^{1}J_{CF}$ value and chemical shift shows enough compatibility to be confident about the assignment.

Apart from C-3 the chemical shifts of the other carbon atoms are close enough together to cause minor assignment difficulties particularly because of the splittings caused by ^{13}C-^{19}F couplings. To overcome this the C-1/^{2}H derivative of the polyol was prepared and its ^{13}C spectrum examined This immediately showed the position of C-1 as this is the only signal modified when compared to the ^{13}C spectrum of the non deutero polyol. C-1 was found to have a chemical shift of 64.2 δ and a $^{3}J_{CF}$ coupling of 7.4 Hz. The chemical shift of C-1 is in the expected range for a primary hydroxyl, it is also shielded by 1.1 p.p.m. relative to D-glucitol. The magnitude of the

$^{3}J_{CF}$ with respect to the conformation of the polyol will be discussed shortly. In the meanwhile the simplification of the ^{13}C spectrum caused by C-1 deuteration enables the C-6 signal to be identified. The off resonance decoupled ^{13}C spectrum (Fig. V-14) of the deutero polyol shows the C-6 signal appears as a first order triplet centred at 65.1 δ with no $^{13}C-^{19}F$ coupling. Again the chemical shift is in the range expected for a primary hydroxyl and there is also a slight shielding of 0.5 p.p.m. compared to D-glucitol. Wray [86] found that $^{4}J_{CF}$ couplings were extremely small and sometimes non existent for the series of carbohydrates he studied. The lack of $^{4}J_{CF}$ coupling for C-6 is consistent with his findings.

Let us now return to the conformational consequences of the other $^{13}C-^{19}F$ couplings. The conformation of 3-deoxy-3-fluoro-D-glucitol is not expected to be planar zig-zag in solution due to the 1,3-interaction between the hydroxyl functions on C-2 and C-4. There are two ways to relieve this interaction, one is by a 120° rotation about the C-2/C-3 bond, the other by a 120° rotation about the C-3/C-4 bond. Each way can be further divided into two by the possibility of a clockwise rotation or anti-clockwise rotation about the respective bonds. The clockwise/anti-clockwise choice is restricted however by the fact that a 1,3-interaction between hydroxyl and carbon arises in one of the choices for each bond and this is unfavourable. The conformations resulting from favoured rotations of the C-2/C-3 and C-3/C-4 bonds are illustrated below (Fig. V-15).

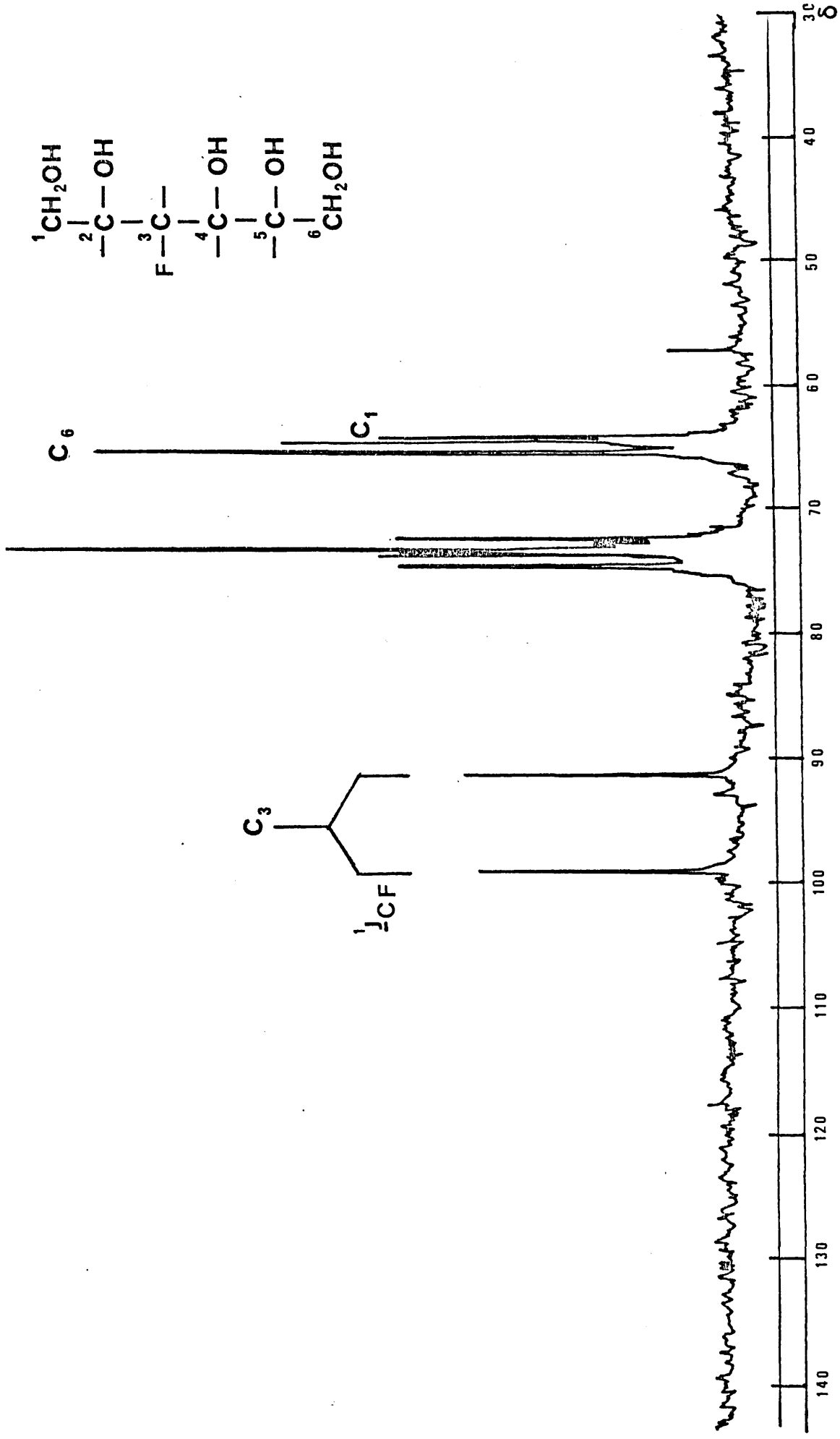


Fig. V-13 Proton Decoupled ^{13}C n.m.r. Spectrum of 3-Deoxy-3-fluoro-D-glucitol

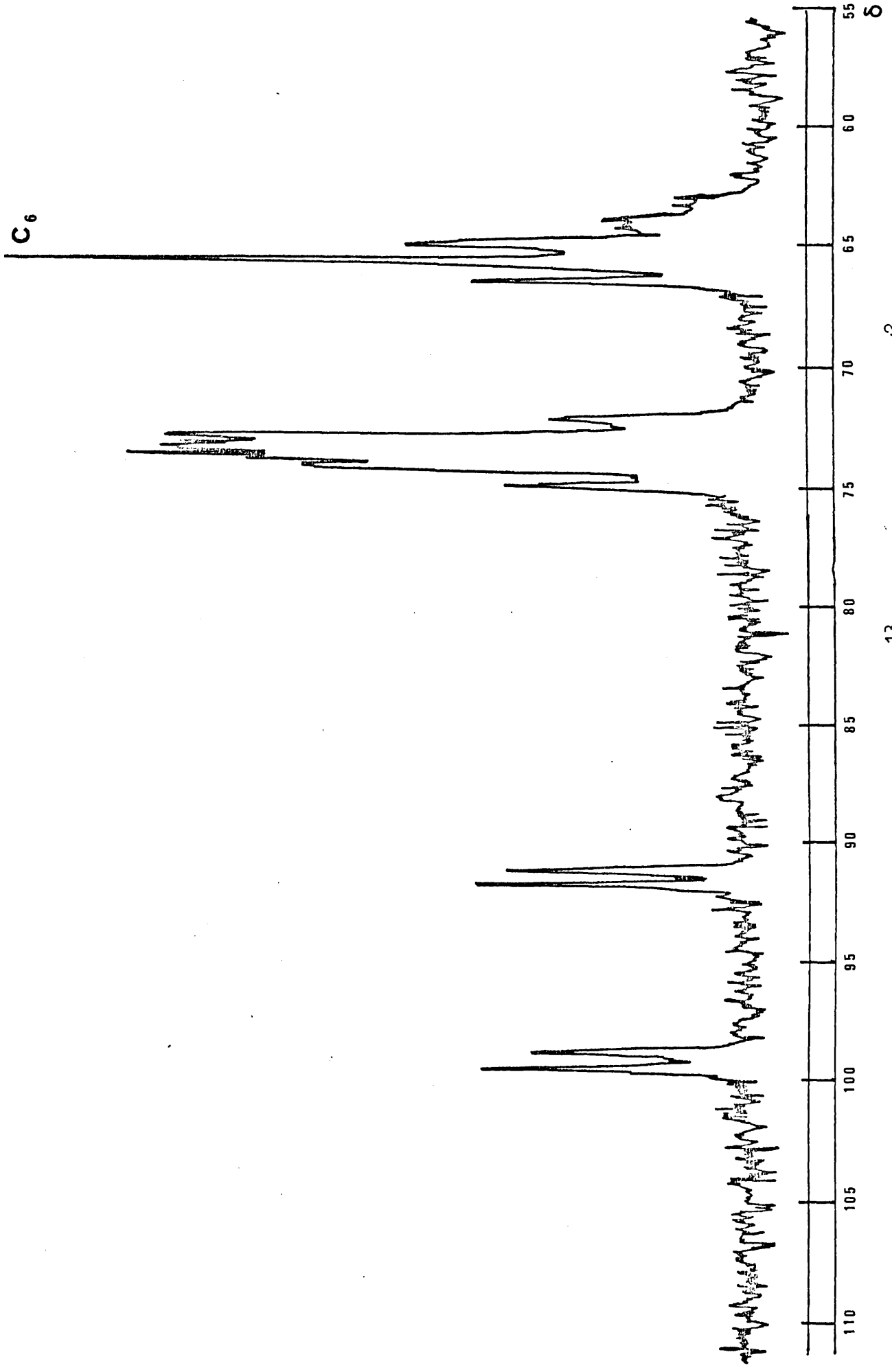
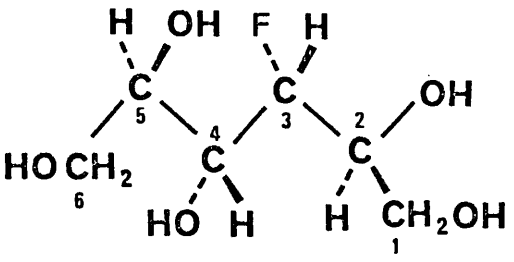
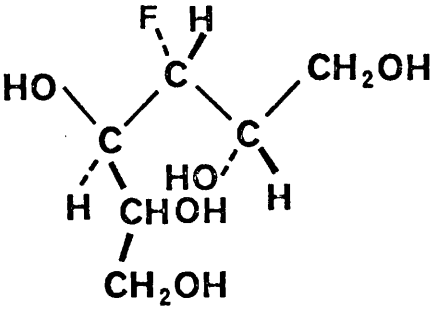


Fig. V-14 Off Resonance Proton Decoupled ^{13}C n.m.r. Spectrum of C-1/^{2}H-3-Deoxy-3-fluoro-D-glucitol



I



II

Fig. V-15

Conformation I above arises from a 120° rotation of the C-2/C-3 bond whilst conformation II arises from a 120° rotation of the C-3/C-4 bond. The $^{3}J_{CF}$ couplings in the above conformations are to C-1 and C-5. For conformation I the $^{13}C\text{-}1/^{19}F$ coupling is a trans coupling and the $^{13}C\text{-}5/^{19}F$ coupling is a gauche coupling. This situation is reversed for conformation II. Wray[86] found that for very similarly substituted conformations to those above that the trans coupling was about 8 Hz and the gauche coupling about 5.5 Hz. Having previously found $^{3}J_{CF}$ for C-1 to be 7.4 Hz it seems reasonable to assume that C-1 is trans to the fluorine on C-3 and therefore the conformation of the polyol in solution is that shown by I above.

The check on the above statement is to look at the $^{3}J_{CF}$ for C-5 to see whether it is of the magnitude expected for a gauche coupling. The ^{13}C signals for C-2, C-4 and C-5 were tightly bunched together in the original proton decoupled ^{13}C spectra of the fluoro and deutero fluoro polyol. An expansion of the proton decoupled ^{13}C spectrum (Fig. V-16) showed C-2, C-4 and C-5 as being responsible for five lines, one of which was twice the intensity of

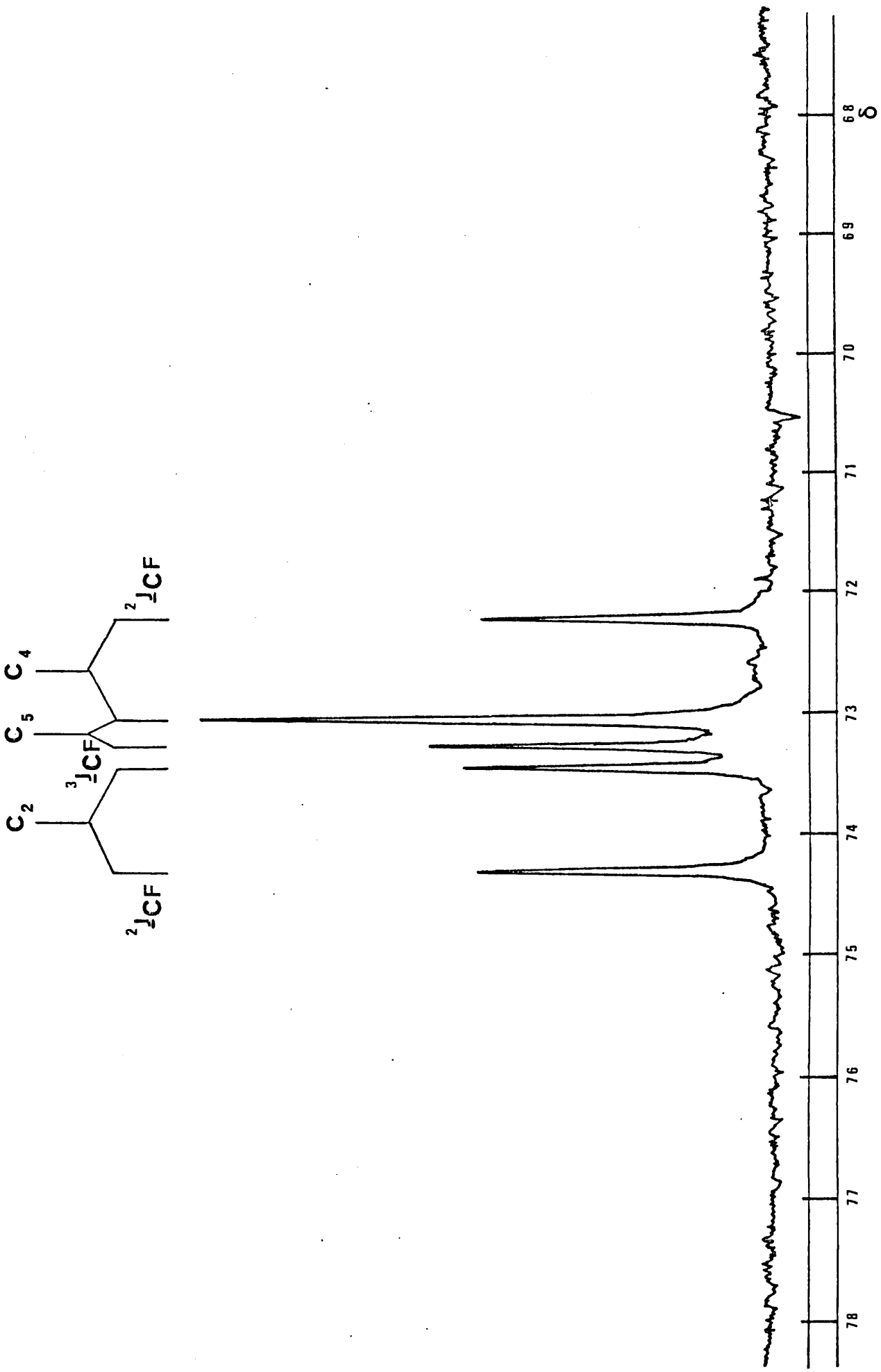


Fig. V-16 Proton Decoupled ^{13}C n.m.r. Spectrum of 3-Deoxy-3-fluoro-D-glucitol (68-78 δ)

the remaining four. As $^{13}C-^{19}F$ couplings are expected for all three carbon atoms the probability is that there are six lines, two of which are coincident. The $^{2}J_{CF}$ couplings of C-2 and C-4 are expected to be very similar as both carbon atoms are similarly substituted and similarly orientated with respect to the fluorine on C-3. Wray[86] found that for the C-CHF-CHOH-C fragment, a $^{2}J_{CF}$ value of 17.5 $\pm$ 0.3 Hz was present when the oxygen on the carbon coupled to fluorine was gauche to the fluorine. Looking back at conformation I in Fig. V-15 both the oxygen atoms on C-2 and C-4 are gauche with respect to the fluorine on C-3, hence couplings of approximately 17.5 Hz are expected as $^{2}J_{CF}$values for C-2 and C-4.

The only possible interpretation of the lines in Fig. V-16 yielding this is that with the lowest field signal of the five and its adjacent signal comprising a doublet with $^{2}J_{CF}$ of 19.1 Hz. The highest field signal of the five and half of its adjacent doubly intense signal comprise the other $^{2}J_{CF}$ doublet with coupling 19.1 Hz. This gives chemical shifts of 72.4 and 73.7 δ for these two carbon atoms. It is shown later by β substituent effects that the C-2 signals are centred at 73.7 δ and the C-4 signals are centred at 72.4 δ. The relevant splitting patterns are illustrated on the spectrum (Fig. V-16). This leaves the middle line of the five shown in Fig. V-16 and half of its adjacent doubly intense signal as arising from C-5. The chemical shift of C-5 is found to be 73.0 δ and its $^{3}J_{CF}$ value is 4.4 Hz. The $^{3}J_{CF}$ value is in agreement with a gauche coupling which was predicted earlier when the $^{3}J_{CF}$ value for C-1 was found thus giving further support for conformation I (Fig. V-15).

Having found the chemical shifts for C-1, C-3, C-5 and C-6 and also obtained a set of values for C-2 and C-4, one can compare this chemical shift data with the appropriate ^{13}C shifts of D-glucitol. The most apparent substituent effect is on C-3 where the directly attached fluorine atom deshields C-3 by 22.4 p.p.m. relative to D-glucitol. Wray[86] found a similar substituent effect (21.02 ± 0.88 p.p.m.) for carbon atoms directly bonded to fluorine where the oxygen substituents on adjacent carbons were gauche to the fluorine. This particular stereochemistry is found in 3-deoxy-3-fluoro-D-glucitol and is illustrated in Fig. V-15I hence the comparison is valid and a reasonable fit.

All the remaining carbon atoms of the fluoro polyol are shielded by small amounts relative to D-glucitol. It is possible however to assign the chemical shifts of C-2 and C-4 from the expected magnitude of their β substituent effects caused by fluorine. The β substituent effect is dependent upon the orientation to the fluorine of the oxygen on the β carbon. For the present case both oxygens on C-2 and C-4 are gauche to the fluorine on C-3 (Fig. V-15). Wray[86] found the β gauche substituent effect to be shielding by 1.43 ± 0.43 p.p.m. C-2 and C-4 were previously assigned to the signals at either 72.4 or 73.7 δ, this gives shieldings of C-2 of 1.9 or 3.2 p.p.m. and shieldings of C-4 of 0.2 or 1.5 p.p.m. The 3.2 and 0.2 p.p.m. shieldings for those carbons are too high and too low respectively for a gauche β substituent effect but the 1.5 and 1.9 p.p.m. shieldings are much better. In order that C-2 can be shielded by 1.9 p.p.m. and C-4 be shielded by 1.5 p.p.m. C-2 must be assigned to the signal centred at 73.7 δ and C-4 that signal at 72.4 δ.

Although the C-1, C-5 and C-6 carbons also show a shielding substituent effect the cause of this is unknown and all that can be said is that it is similar to that found by Wray[86] for the series of carbohydrates he studied.

(b) 6-Deoxy-6-fluoro-D-galactitol

The ^{13}C spectra of 6-deoxy-6-fluoro-D-galactitol are complicated by $^{13}C-^{19}F$ couplings, there are however two readily identifiable signals. The first of these is C-6 which shows up as a doublet in the proton decoupled spectrum centred at 88.2 δ with a $^{1}J_{CF}$ value of 164.7 Hz. The low field position and large $^{1}J_{CF}$ value for C-6 are in agreement with Wray's[86] work on the $-CH_2F$ function where he found a $^{1}J_{CF}^{av}$ value of 167.4 Hz and chemical shift of 83.56 δ^{av}. Under off resonance conditions each component of the doublet appears as a first order triplet confirming the $-CH_2-$ part of the CH_2F function.

The other readily identifiable signal is that of C-1 which appears as a first order triplet under off resonance conditions with zero $^{13}C-^{19}F$ coupling. The triplet appearance confirms a $-CH_2-$ function and the chemical shift of 66.0 δ is what is expected of a primary hydroxyl. The remaining four carbon atoms of the fluoro polyol are tightly bunched together, an expansion of the proton decoupled ^{13}C spectrum is illustrated in Fig. V-17. The most intense signal is that at lowest field and is probably due to C-2. C-2 is five bonds removed from the fluorine atom and is not expected to show any $^{5}J_{CF}$ coupling. For the compounds studied by Wray[86] there were no cases where a $^{5}J_{CF}$ coupling was found. As the signal at 72.9 δ is of approximately twice the intensity of the remaining six signals (Fig. V-17) it seems reasonable to assume it is not

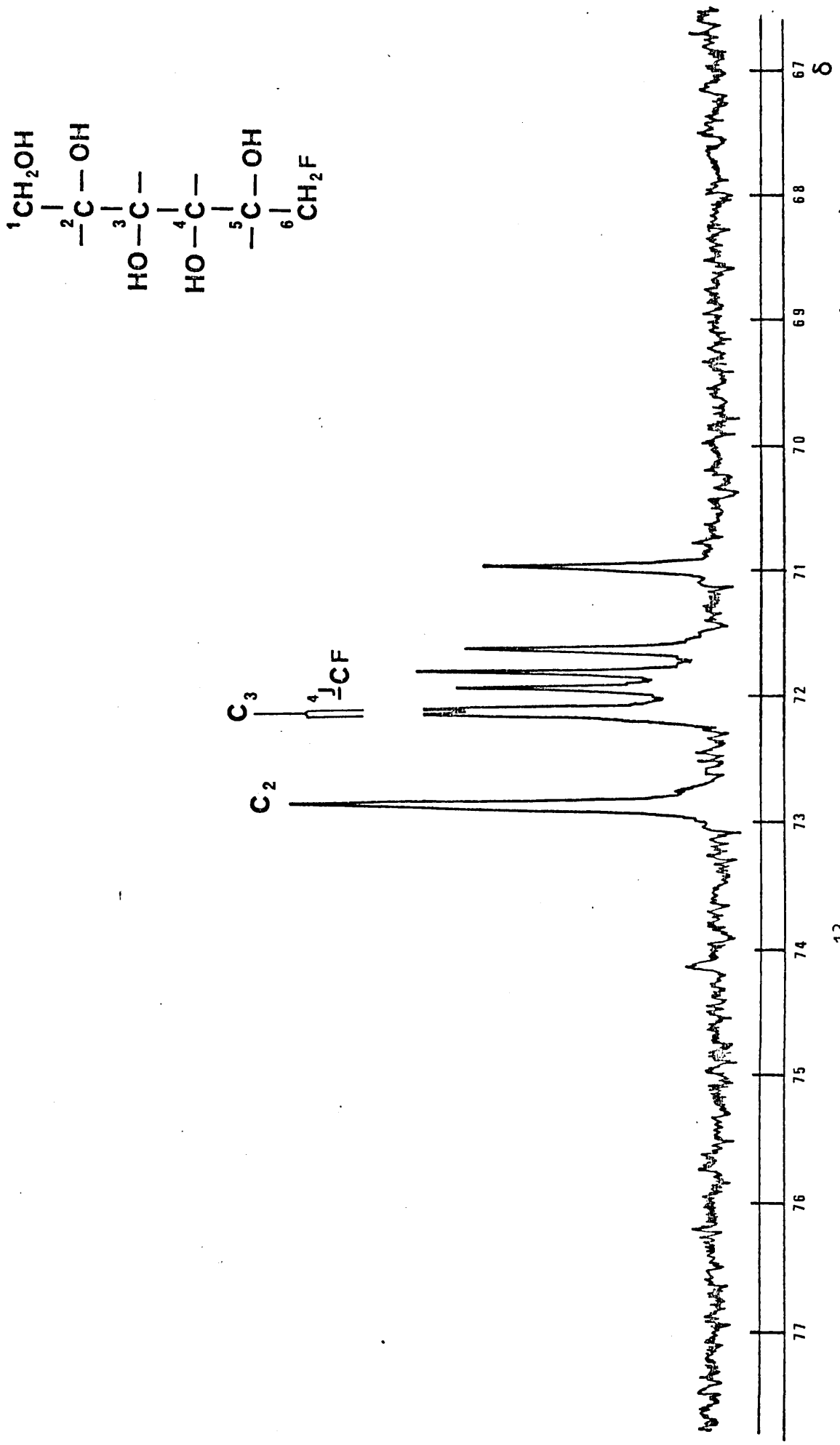


Fig. V-17 Proton Decoupled ^{13}C n.m.r. Spectrum of 6-Deoxy-6-fluoro-D-galactitol (67-77 δ)

coupled to fluorine and is due to C-2.

Utilisation of the magnitude of $^{4}J_{CF}$ values enables C-3 to be identified. Wray[86] found that $^{4}J_{CF}$ was dependent on the orientation of the coupled nuclei and varied between 0 and 1.9 Hz. Of the six lines resulting from C-3, C-4 and C-5 the only combination giving a $^{4}J_{CF}$ value in the required range is that of the very narrow doublet adjacent to the doubly intense line (Fig. V-17) previously assigned to C-2. This gives C-3 a chemical shift of 72.1 δ and a $^{4}J_{CF}$ value of 1.0 Hz. Of the remaining four lines from C-4 and C-5 no assignments can be made with any confidence as there are several possibilities for the coupling values which all fall into the expected values for the $^{2}J_{CF}$ and $^{3}J_{CF}$ couplings. All that can be said is that C-4 and C-5 have their chemical shifts between 71.3 δ and 71.9 δ which is the range covered by the four lines.

Looking at the substituent effects of the fluorine atom one again sees deshielding of the α carbon. The deshielding is by 22.1 p.p.m. This is in good agreement with that found by Wray[86] for the $-CH_2F$ function in 6-deoxy-6-fluoro-D-glucose. The substituent effects on the other carbons are all shielding except for C-1 which experiences no effect. The cause of this again is unknown but is similar to work by Wray.[86]

3. ^{13}C n.m.r. Spectroscopy of the Mono-O-Butylidene Acetals of the Deoxy and Deoxy Fluoro Polyols

The ^{13}C chemical shifts of the mono-O-butylidene acetals of the 2-deoxy polyols are listed in table V-5. Table V-6 lists the ^{13}C chemical shifts of the remaining mono-O-butylidene acetals from various other deoxy polyols and deoxy fluoro polyols. The numbering system

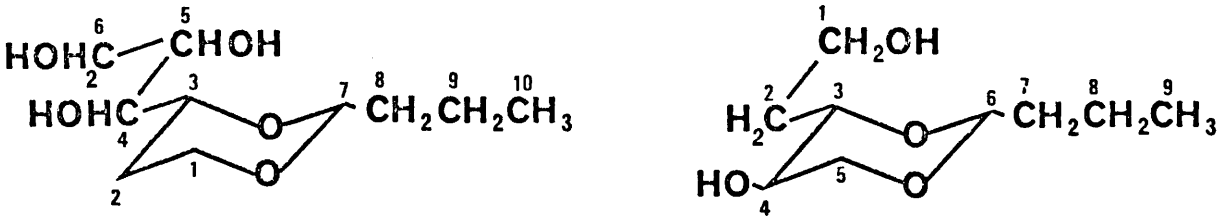
Acetal	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1,3-O-Butylidene-2-deoxy-D-arabino-hexitol	69.0	29.4	78.4	75.6	73.3	65.5	105.0	38.9	19.6	15.9
4,6-O-Butylidene-2-deoxy-D-arabino-hexitol	61.2	37.4	67.8	85.2	63.2	72.5	104.7	38.0	19.8	15.8
1,3-O-Butylidene-2-deoxy-D-lyxo-hexitol	68.8	29.8	78.4	74.7	72.3	65.3	104.4	38.5	19.2	15.6
4,5-O-Butylidene-2-deoxy-D-lyxo-hexitol	60.6	37.6	70.8	81.9	81.5	64.7	107.0	37.6	19.2	15.7
	60.6	37.6	70.8	82.7	80.7	64.3	106.3	37.6	19.2	15.7
4,6-O-Butylidene-2-deoxy-D-lyxo-hexitol	61.0	37.6	68.8	83.5	64.9	74.2	104.8	38.3	19.4	15.7
1,3-O-Butylidene-2-deoxy-D-erythro-pentitol	68.6	28.9	79.0	75.7	64.4	104.3	38.5	19.1	15.5	-
3,5-O-Butylidene-2-deoxy-D-erythro-pentitol	60.3	36.4	81.2	67.7	72.7	104.8	38.1	19.8	15.8	-

Table V-5 ^{13}C Chemical shifts for the mono-O-butylidene acetals of the 2-deoxy polyols relative to T.M.S. (0 δ).

Acetal	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
2,4-O-Butylidene-3-deoxy-D-ribo-hexitol	66.6	78.4 or 79.2	30.5	78.4 or 79.2	75.7	64.5	104.2	38.3	19.4	15.6
1,3-O-Butylidene-4-deoxy-D-xylo-hexitol	74.1	68.1	78.1	37.0	70.5	68.4	104.8	38.5	19.4	15.7
2,3-O-Butylidene-4-deoxy-D-xylo-hexitol	64.1	84.7	78.0	?	71.6	68.6	106.7	?	19.6	16.1
	63.5	83.9	77.1				106.1			
2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol	62.7	79.2 or 80.4	85.5	79.2 or 80.4	70.8	64.7	104.4	38.0	19.3	15.6
4,5-O-Butylidene-6-deoxy-6-fluoro-D-galactitol	65.2	?	?	?	?	86.0	107.0	37.6	19.3	15.9
							107.2	37.4		

Table V-6 ^{13}C Chemical shifts for the mono-O-butylidene acetals of some deoxy and deoxy fluoro polyols relative to T.M.S. (0 δ).

used for the carbon atoms is illustrated for two examples in Fig. V-18 below.



1 3-O-butylidene-2-deoxy -D-arabino-hexitol

3,5-O-butylidene-2-deoxy -D-erythro-pentitol

Fig. V-18

One small point to note is that the acetals of 2-deoxy-D-erythro-pentitol contain nine carbon atoms whereas all other acetals contain ten carbon atoms. This results in a difference of one as to which carbon atom is the acetal carbon, it also affects the numbering of the propyl side chain. The structures of the majority of the acetals had been elucidated before their ^{13}C spectra were obtained hence the work presented here is mainly an explanation of the ^{13}C spectra of the acetals in terms of shielding trends etc.

Once the trends were apparent then the spectra of unknown monoacetals could be interpreted. This was done for two or three cases where sufficient structural evidence was not forthcoming from other techniques. A representative problem of this type is discussed later in this section. One of the more

important trends used is the shielding and deshielding of carbon atoms in the acetal relative to their analogous carbons in the polyol. Hence, table V-7 has been included giving easy reference to the so called substituent chemical shifts caused by acetalation. A positive sign indicates an increase in δ value relative to T.M.S. hence a shift to lower field, i.e. a deshielding. The signals in the ^{13}C spectra of the acetals can be conveniently put into two categories, firstly the signals due to the propyl side chain and the acetal carbon, secondly those due to the polyol backbone.

(i) ^{13}C Signals from the Propyl Side Chain and the Acetal Carbon

The signals from the propyl side chain are invariably those at highest field although in some acetals the deoxy carbon atom has its resonance in the same region. The high field position is due to lack of an oxygen substituent hence more shielding than the remaining carbons which bear an oxygen substituent. Under off resonance conditions the $-CH_2-CH_2-CH_3$ carbon atoms appear as a first order triplet, triplet and quartet respectively. This is illustrated in Fig. V-19 which is the off resonance ^{13}C spectrum of 4,6-O-butylidene-2-deoxy-D-arabino-hexitol. The signal of C-8 is overlapping slightly with the deoxy carbon signal C-2, but the triplet structure is still discernible.

Acetal	C-1	C-2	C-3	C-4	C-5	C-6
1,3-O-Butylidene-2-deoxy-D-arabino-hexitol	+7.6	-8.6	+8.7	-0.2	-0.6	-0.3
4,6-O-Butylidene-2-deoxy-D-arabino-hexitol	-0.2	-0.6	-1.9	+9.4	-10.7	+6.7
1,3-O-Butylidene-2-deoxy-D-lyxo-hexitol	+7.7	-7.4	+7.6	-1.2	-0.6	-0.3
4,5-O-Butylidene-2-deoxy-D-lyxo-hexitol (I)	-0.5	+0.4	0.0	+6.0	+8.6	-0.9
" " " Other diastereoisomer " (II)	-0.5	+0.4	0.0	+6.8	+7.8	-1.3
4,6-O-Butylidene-2-deoxy-D-lyxo-hexitol	-0.1	+0.4	-2.0	+7.6	-8.0	+8.6
1,3-O-Butylidene-2-deoxy-D-erythro-pentitol	+7.2	-8.1	+7.2	-1.8	-0.8	-
3,5-O-Butylidene-2-deoxy-D-erythro-pentitol	-1.1	-0.6	+9.4	-9.8	+7.5	-
2,4-O-Butylidene-3-deoxy-D-ribo-hexitol	-0.9	?	-7.1	?	-1.4	-0.4
2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol	-1.5	+5.5 or +6.7	-9.3	+6.8 or +8.0	-2.2	-0.4
1,3-O-Butylidene-4-deoxy-D-xylo-hexitol	+8.8	-9.1	+7.1 or +7.8	-1.5	+0.2 or -0.5	-0.2
2,3-O-Butylidene-4-deoxy-D-xylo-hexitol (For the above acetal it was not possible to distinguish between the two diastereoisomers)	-1.2 or -1.8	+6.7 or+7.5	?	?	?	0.0

Table V-7 ^{13}C Substituent chemical shifts (p.p.m.) of the deoxy polyol carbon atoms caused by acetalation.

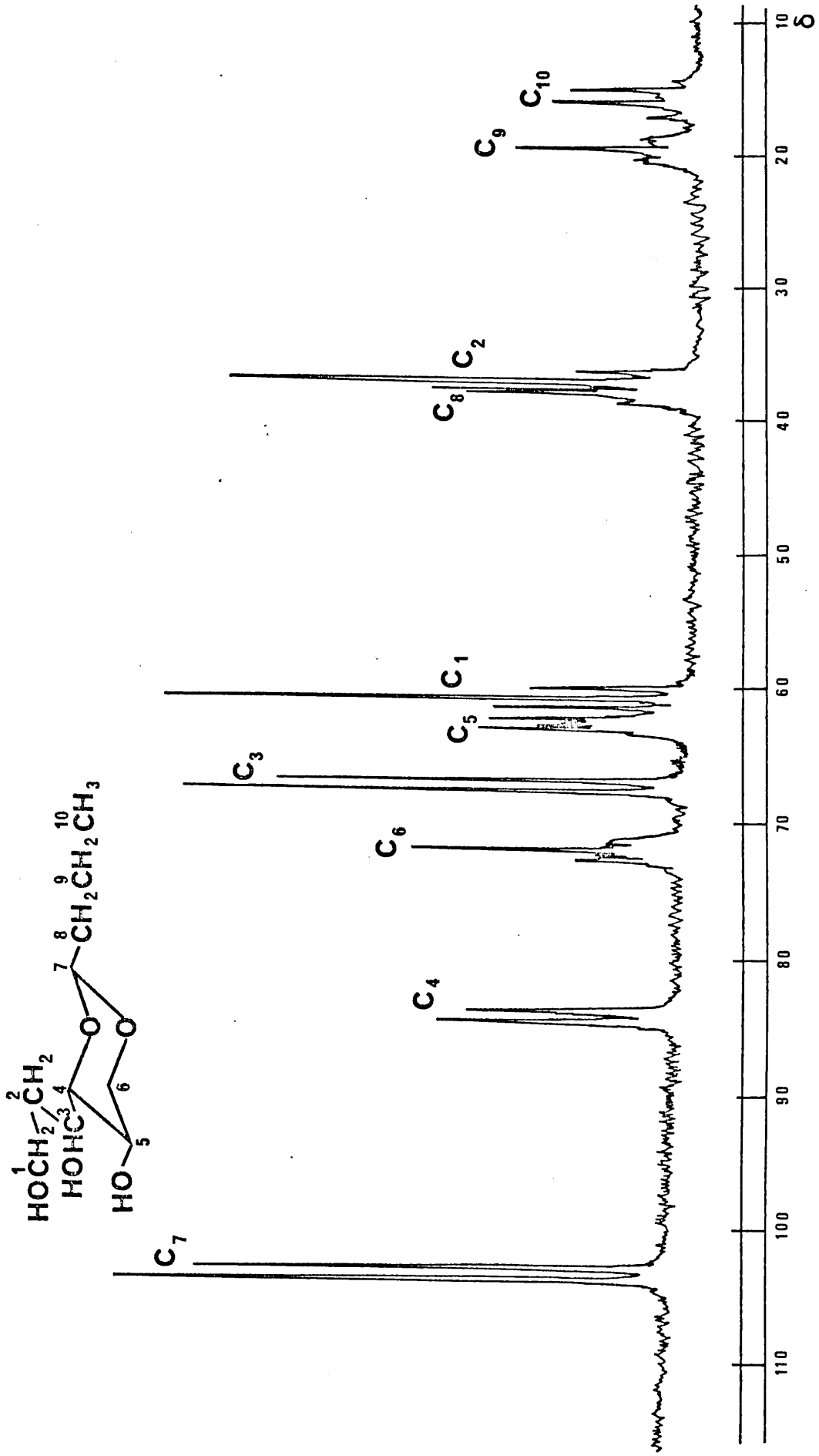


Fig. V-19 Off Resonance ^{13}C n.m.r. Spectrum of 4,6-O-Butylidene-2-deoxy-D-arabino-hexitol

The highest field signal of the propyl chain is always that from the methyl group. For the acetals listed in tables V-5 and V-6, its ^{13}C chemical shift is 15.8 $\delta \pm$ 0.3 p.p.m. The next highest field signal is from the methylene carbon adjacent to the methyl group, its ^{13}C chemical shift being 19.4 $\delta \pm$ 0.4 p.p.m. The deshielding of this methylene carbon relative to the methyl carbon is characteristic of alkyl chains and was noted by Grant and Paul [87] in their study of such systems. The deshielding is caused by substitution of a proton by a methyl group, i.e. $-\overset{*}{C}H_3 \longrightarrow -\overset{*}{C}H_2CH_3$ deshields the asterisked carbon. The remaining methylene carbon of the propyl chain is next to the acetal carbon which bears two oxygen atoms. This results in this methylene carbon being deshielded by a β oxygen substituent effect. This is reflected in its ^{13}C chemical shift of 38.2 $\delta \pm$ 0.8 p.p.m. which is to much lower field than the other two propyl chain carbons. There are no strong features in the ^{13}C chemical shifts of the propyl chain carbons which follow structural trends. This is in marked contrast to that of the acetal carbons.

The acetal carbons have the most easily recognised signal in the ^{13}C spectra of the cyclic acetals. They are the lowest field signals as they have the greatest deshielding through having two oxygen substituents. This has been observed by various groups of workers [70-74] who have studied the ^{13}C spectra of 1,3-dioxane and its derivatives. The ^{13}C chemical shift of the acetal carbon in 1,3-dioxane itself is 94 $\longrightarrow$ 95 δ [71,73] relative to T.M.S. When the acetal carbon is substituted by an alkyl group however it is deshielded in the same manner as that found by Grant and Paul [87] for alkyl chains. This is illustrated in Fig. V-20.

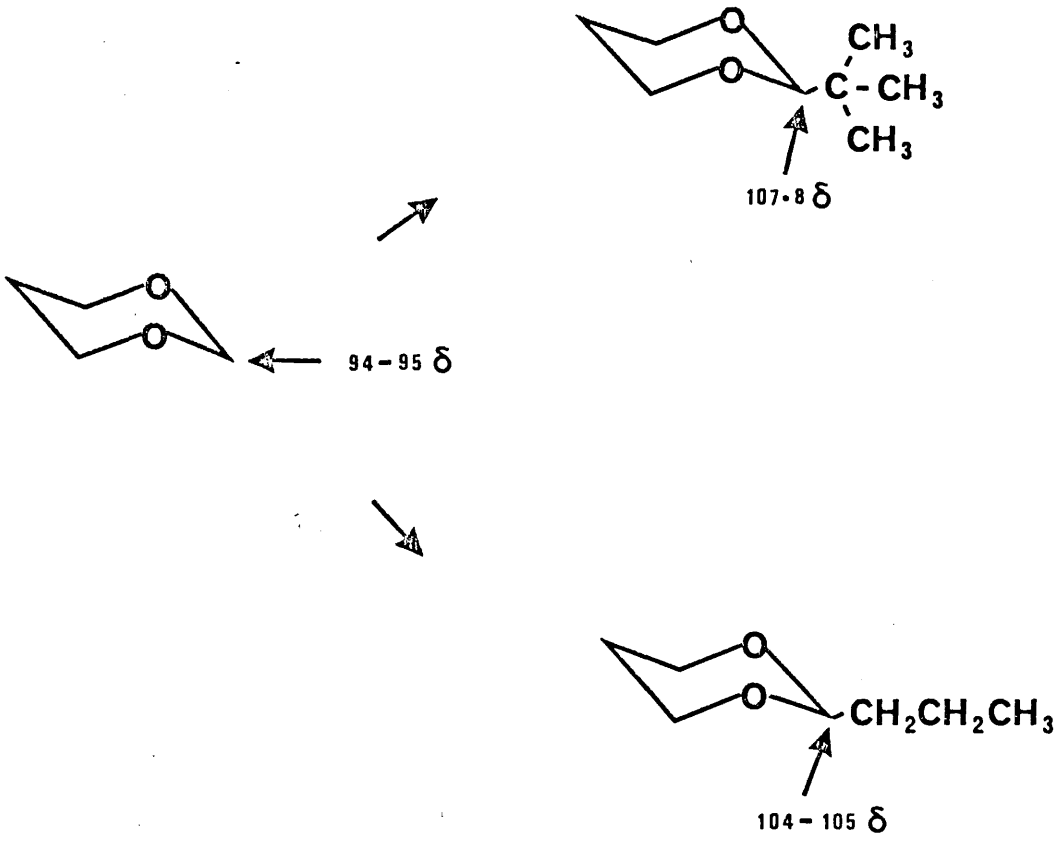


Fig. V-20

For the butylidene acetals in tables V-5 and V-6 the acetal carbons appear under off resonance conditions as doublets (characteristic of methine groups) between 104.2 δ and 107.2 δ. As the alkyl chain is kept constant for all the acetals in the two tables it is possible to distinguish the acetal ring size. For the six membered rings the acetal carbon resonance is between 104.2 δ and 105δ. For the five membered rings the resonance is between 106.1 δ and 107.2 δ. The 1.1 p.p.m. difference in chemical shift is sufficiently large to give confidence when assigning ring sizes.

For the six membered acetals there is only one acetal carbon signal present in the ^{13}C spectra. For the five membered rings however there are usually two acetal carbon signals. These arise from diastereoisomerism about the acetal carbon, which can occur much more readily for the five membered ring than the six membered. This can be verified by looking at the appropriate data in tables V-5 and V-6. It is also illustrated in Fig. V-21 which is the

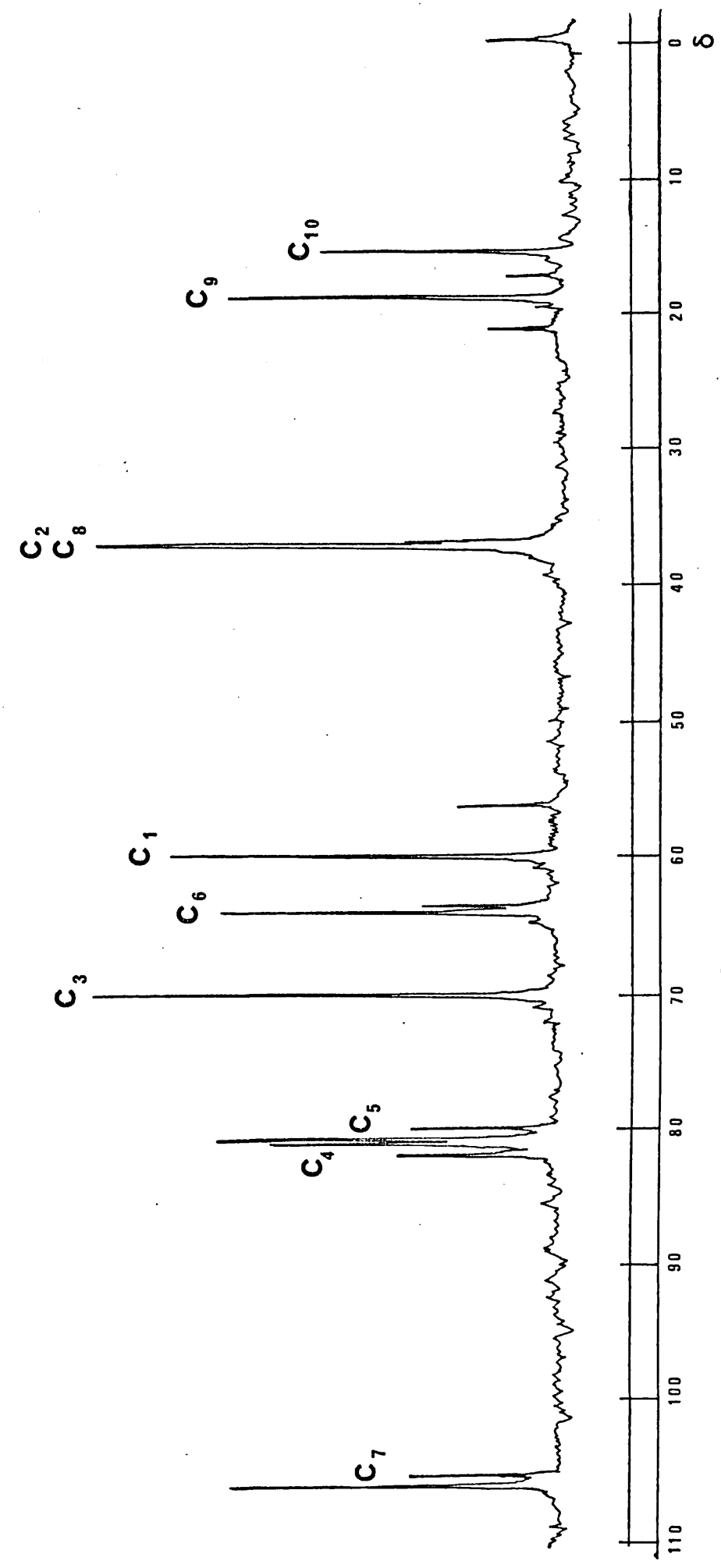


Fig. V-21 Decoupled ^{13}C n.m.r. Spectrum of 4,5-O-Butylidene-2-deoxy-D-lyxo-hexitol

proton decoupled ^{13}C spectrum of 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol showing two acetal carbon signals. Diastereoisomers can thus be detected by their ^{13}C n.m.r. spectra and again this helps in the assignation of ring sizes as the diastereoisomerism usually occurs only for five membered rings.

(ii) ^{13}C Signals from the Polyol Backbone in the Acetals

The ^{13}C chemical shifts of the carbon atoms constituting the polyol chain part of the acetal were assigned by a variety of means. Perhaps the most accurate method was specific frequency off resonance decoupling (S.F.O.R.D.). Here, the off resonance ^{13}C spectrum of the acetal was recorded whilst the sample was also irradiated with another frequency known to be associated with a particular proton in the acetal. This results in the normal off resonance ^{13}C spectrum being obtained, except that the carbon atom coupled to the proton associated with the specifically applied frequency is fully decoupled and appears as a singlet. In order to use this technique the ^{1}H n.m.r. spectrum of the sample must be sufficiently analysed so that the environment of the proton is accurately known.

The best results of S.F.O.R.D. were obtained from 4,6-O-butylidene-2-deoxy-D-arabino-hexitol for which the ^{1}H n.m.r. spectrum had been fully analysed and computer simulated. Fig. V-22 shows the effect of recording the ^{13}C off resonance spectrum whilst irradiating with the frequency associated with the proton that resonates at 3.05 δ in the 220 MHz ^{1}H n.m.r. spectrum. When compared with the normal off resonance spectrum of the sample (Fig. V-19) the second lowest field doublet has collapsed to a singlet. Now, the proton resonating at 3.05 δ is known to be on C-4 (see later section on ^{1}H n.m.r. of the acetals) hence that doublet which collapsed to a singlet must be C-4.

There is a slight modification in the appearance of the adjacent higher field carbon signal because the protons attached to this

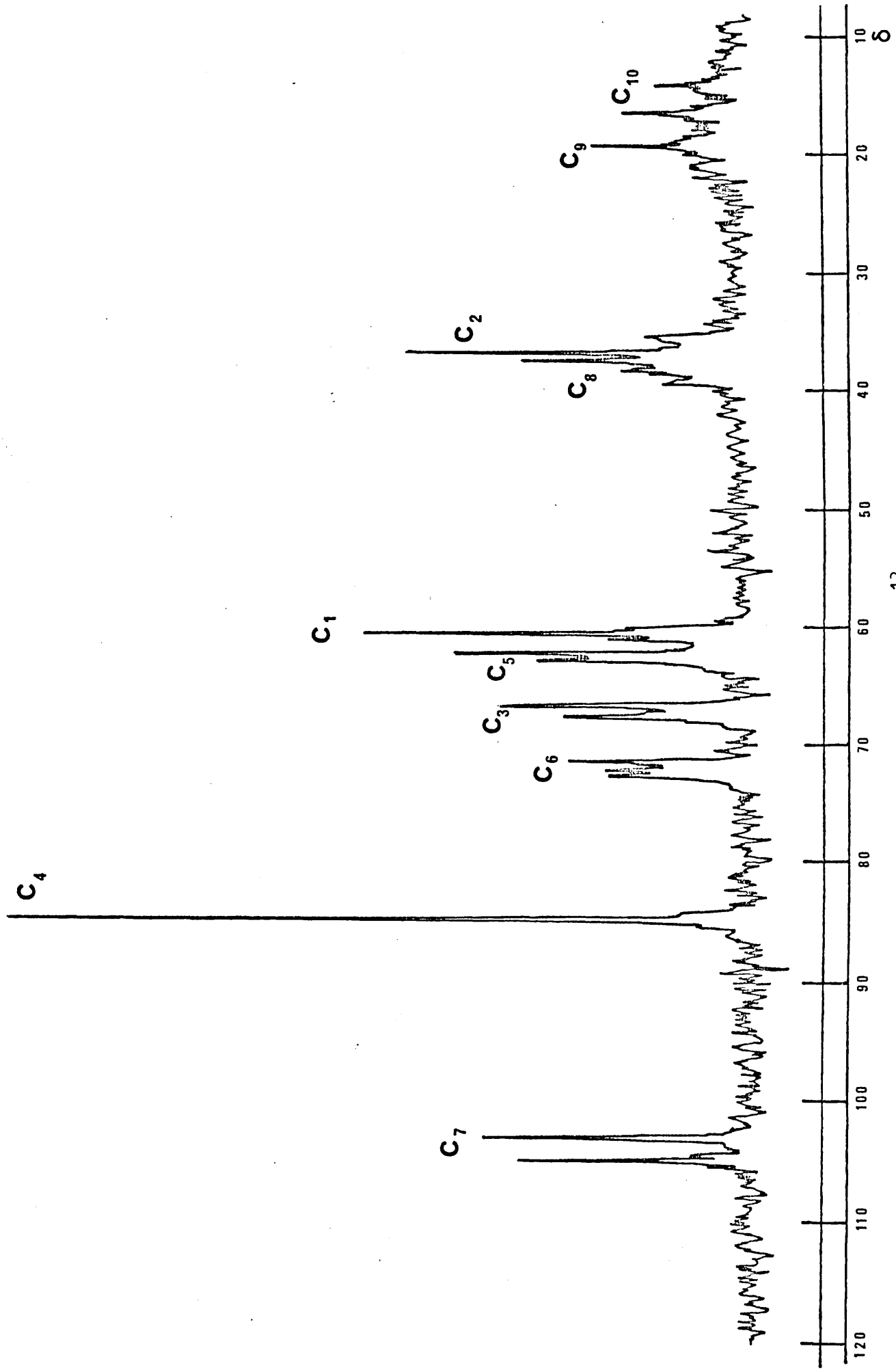


Fig. V-22 C-4 Specifically Decoupled Off Resonance ^{13}C n.m.r. Spectrum of 4,6-O-Butylidene-2-deoxy-D-arabino-hexitol

signal are also near to 3.05δand partial collapse occurs. The overall modification caused by S.F.O.R.D. however leaves no ambiguities as to which signal is due to C-4. A series of off resonance ^{13}C spectra were taken for this acetal, each one being irradiated with a different specific decoupling frequency associated with known protons. When the decoupling frequency is far away from the proton resonance no decoupling is observed in the ^{13}C spectrum. As the decoupling frequency nears the proton resonance the ^{13}C resonance becomes more and more collapsed to a singlet, until total collapse is achieved. Then the splitting of the ^{13}C resonance slowly returns as the decoupling frequency passes by.

By taking such a series of spectra it was possible to make the assignments shown for 4,6-O-butylidene-2-deoxy-D-arabino-hexitol in table V-5. The same technique was used on 3,5-O-butylidene-2-deoxy-D-erythro-pentitol in order to distinguish between the C-2 deoxy carbon and the methylene carbon of the propyl chain adjacent to the acetal carbon. The chemical shifts of the protons on C-2 are at lower field than those on C-7 (see ^{1}H n.m.r. section later). The irradiation at 2.4 δ is removed from the resonance positions of the C-2 and C-7 protons hence no decoupling is observed (Fig. V-23). As the decoupling frequency is changed from 2.4 δ to 2.0δit approaches the resonance frequency of the C-2 protons, hence the ^{13}C spectrum recorded with irradiation at 2.0 δ has C-2 preferentially decoupled (Fig. V-23). No effect is observed on the C-7 signal as the resonance positionsof its appended protons are to even higher field.

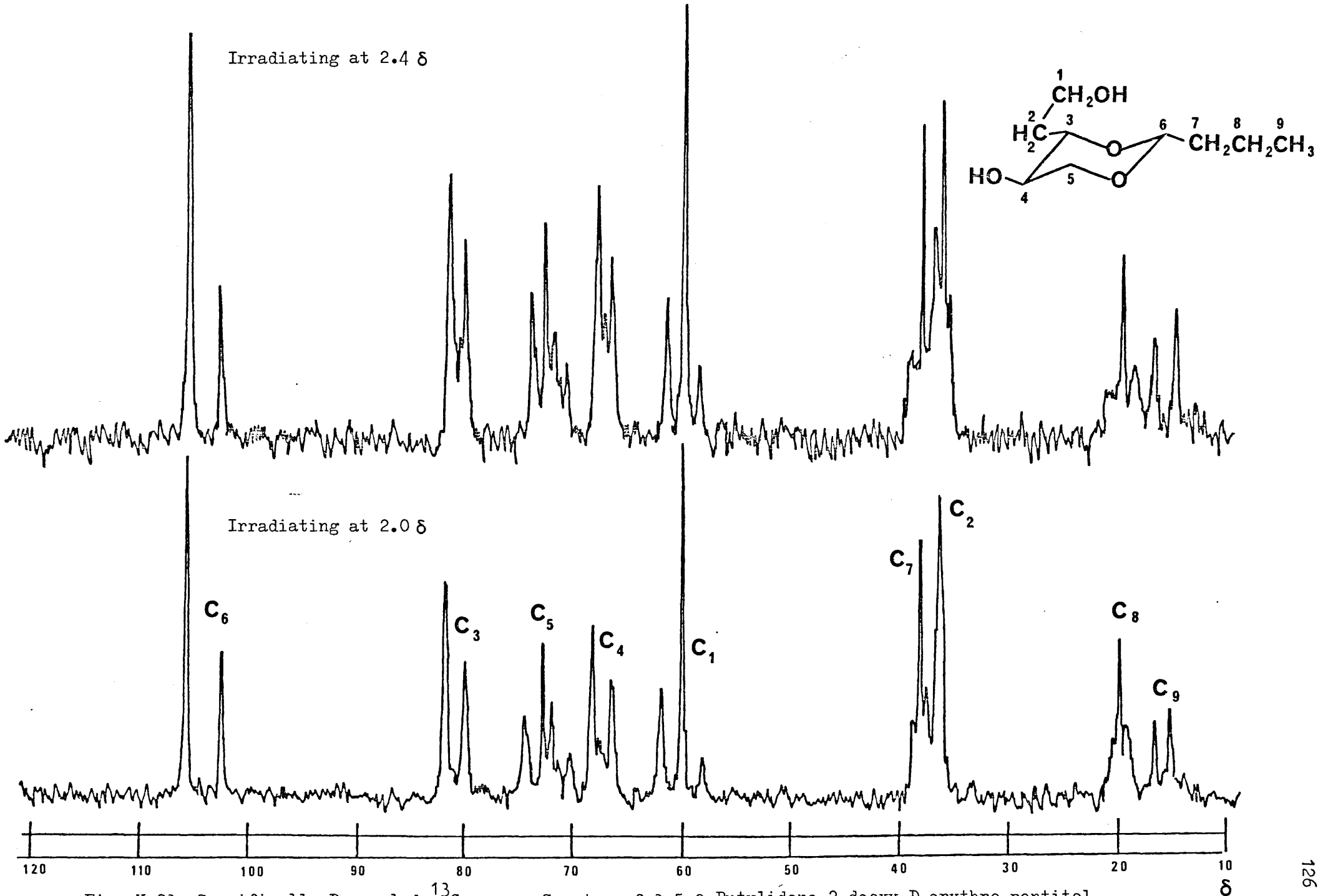


Fig. V-23 Specifically Decoupled ^{13}C n.m.r. Spectra of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol

With the trends and assignments in hand for 4,6-O-butylidene-2-deoxy-D-arabino-hexitol it was possible to make the assignments listed in tables V-5 and V-6 for the other acetals. Distinctions between methylene and methine carbons were made using the off resonance spectra. Differentiation was then made between members of each category using those shielding and deshielding trends found in the fully assigned ^{13}C spectrum of the above mentioned 4,6-acetal. In most cases the ^{13}C shifts of the acetals were separated enough to render the assignments as being unambiguous. When the ^{13}C shifts were close together then more subtle methods were used, one such example is the distinction between C-4 and C-5 in 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol.

Fig. V-24 shows the relative positions of the C-2 and C-3 ^{13}C chemical shifts for 2,3-O-butylidene-D-arabinitol,[88] 2,3-O-butylidene-D L-galactitol[89] and 2,3-O-butylidene-6-deoxy-D-galactitol.[89] Two signals for each carbon atom arise through diastereoisomerism about the acetal carbon. The assignments for the above three acetals are possible only when the data for 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol is considered. The assignments of the resonances of that acetal are only possible by considering the shift data for the previous three acetals, i.e. the four acetals in all lend themselves towards a mutual assignment method which is discussed below. The ^{13}C chemical shift data for the C-2/C-3 carbons of the three first mentioned acetals was illustrated on a scale represented as in Fig. V-24. This showed what seemed to be two distinct pairs of resonances for each acetal, the problem being which pair was due to C-2 and which pair was due to C-3. Now, 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol can be renamed as 2,3-O-butylidene-5-deoxy-D-arabino-

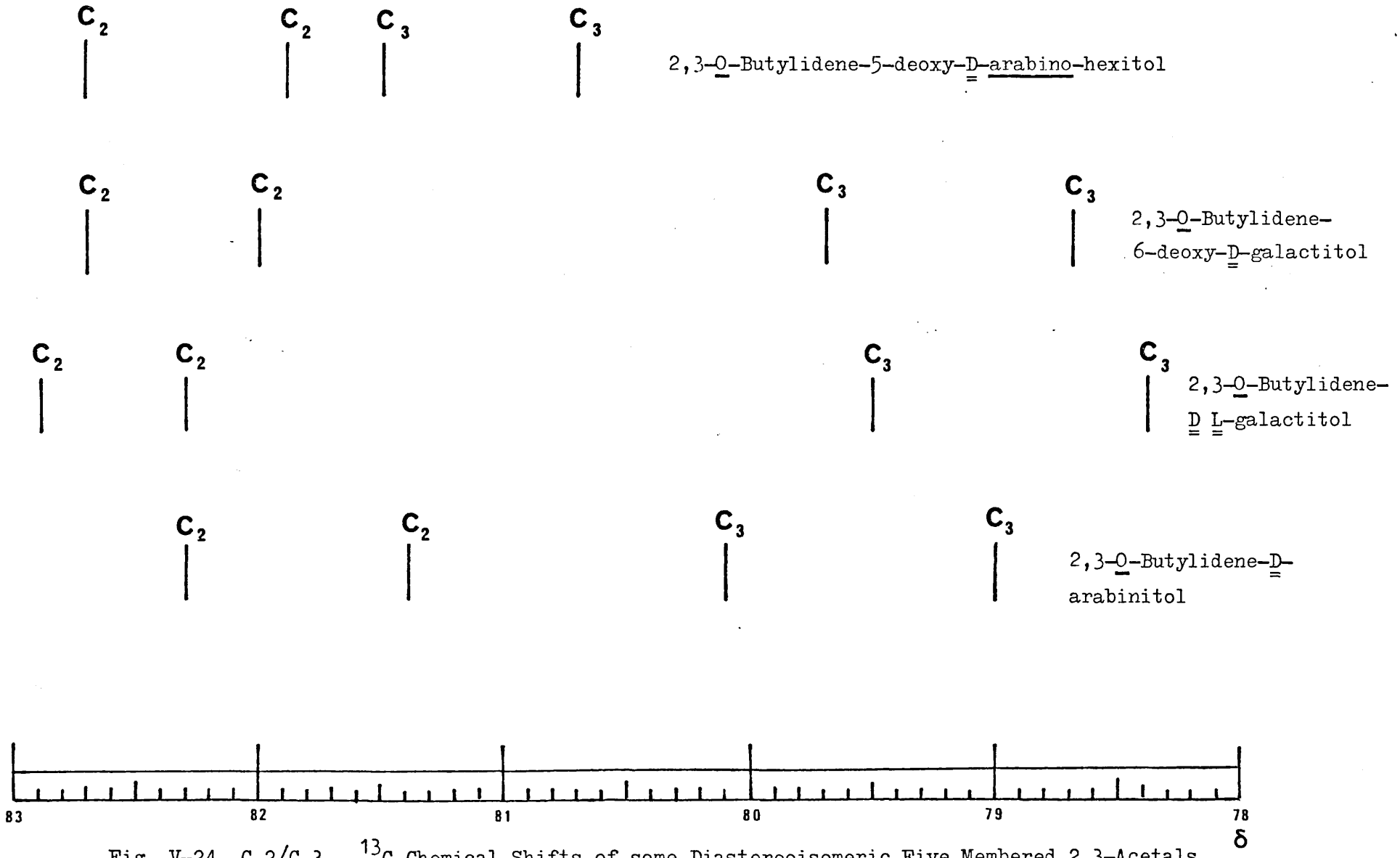


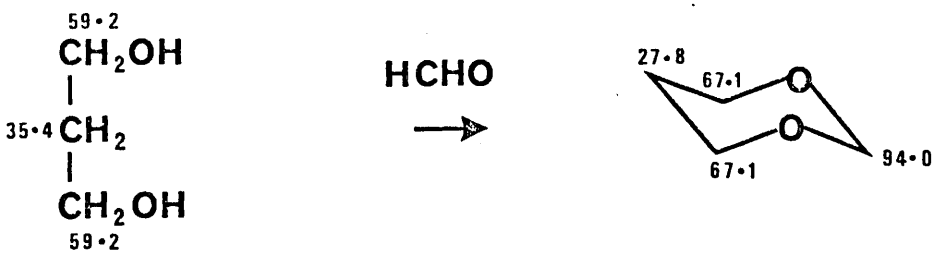
Fig. V-24 C-2/C-3 ^{13}C Chemical Shifts of some Diastereoisomeric Five Membered 2,3-Acetals

hexitol, this gives it a 2,3-acetal ring which is easier to discuss when comparing it with the other three acetals. The 5-deoxy function will have a deshielding γ effect on C-3 but C-2 should behave as normal. Therefore the C-3 ^{13}C resonances of the acetal of the 5-deoxy polyol should appear at lower field than the C-3 resonances of the other three acetals, whilst the C-2 resonances should all be very similar. When the ^{13}C shift values for C-2 and C-3 of the acetal of the 5-deoxy polyol were put onto Fig. V-24 one pair lined up with the three pairs at low field. The other pair was at a lower field than the three other pairs of resonances. By virtue of the fact that the C-2 resonances are expected to be unchanged but the C-3 resonances should be deshielded by the 5-deoxy function the four pairs of resonances at lowest field are assigned to the C-2 carbons. This leaves the higher field pairs of resonances as belonging to the C-3 carbons. Having found the C-2 and C-3 chemical shifts reconversion back to the original name for the appropriate acetal gives the assignments listed in table V-5.

It proved impossible however to assign all the ^{13}C signals for all the acetals. Difficulties usually arose when signals were very close together or diastereoisomers were present and the position could not be resolved as above. Having made a list of the ^{13}C chemical shifts attention can be directed more towards the substituent chemical shifts caused by acetalation of the polyols. The consistency of these substituent effects adds weight to the accuracy of the ^{13}C shift assignments for the acetals.

Inspection of the substituent chemical shifts in table V-7 shows that the ^{13}C chemical shifts of the carbon atoms constituting the polyol backbone part of the acetal differ from their corresponding

shifts in the original polyols. Those carbons of the polyol which become carbons bearing ring oxygen atoms are substantially deshielded (5.5 — 9.4 p.p.m.) upon acetalation. The carbons adjacent to both carbons with ring oxygens are substantially shielded (7.1 — 10.7 p.p.m.) compared to their shifts in the polyols. These trends are to be expected because if one looks at the simplest case of 1,3-dioxane and propane-1,3-diol (Fig. V-25) where no ambiguities are possible for the ^{13}C chemical shifts the same trends occur.



propane-1,3-diol 1,3-dioxane

Fig. V-25

The ^{13}C chemical shifts of propane-1,3-diol[78] and 1,3-dioxane[72] relative to T.M.S. are shown next to the appropriate carbon atom above. The direction and magnitude of the substituent shifts caused by acetalation are similar to those found for the deoxy polyols and their acetals.

The deshielding of those carbons bearing oxygen ring atoms is also predicted from the early work of Hall and Johnson[65] who noted

deshieldings of carbons when O-alkylation was performed. The acetalation of the deoxy polyols is very similar to O-alkylation in that the hydroxyl protons are replaced by a carbon atom (Fig. V-26).

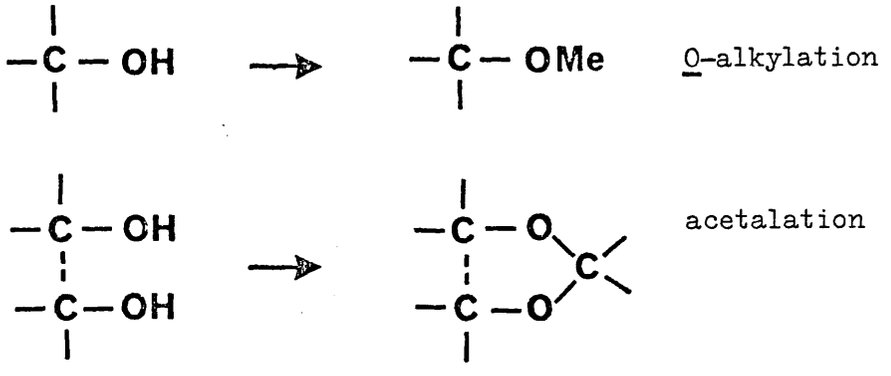
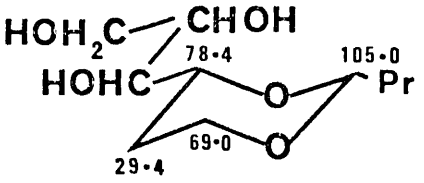


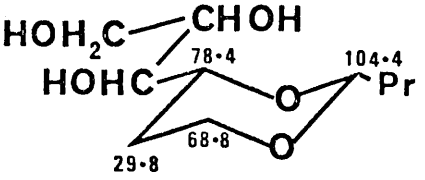
Fig. V-26

Again the magnitude of the alkylation substituent shift is similar to that found for the appropriate carbons in the acetals.

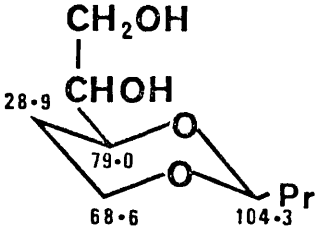
The remaining carbons of the deoxy polyols show small variable substituent effects upon acetalation. The only apparent trend is that the carbons that are not ring carbons but are adjacent to ring carbons are always shielded by a small amount (maximum of 2.2 p.p.m.). Having looked at substituent chemical shifts between the polyols and the butylidene acetals derived therefrom we can now look at substituent effects between the butylidene acetals and 1,3-dioxane. For example, 1,3-acetals of the 2-deoxy polyols have ring carbon ^{13}C chemical shifts that can be directly related to the ring carbon ^{13}C chemical shifts of 1,3-dioxane[72] by using substituent effects. Fig. V-27 shows the appropriate acetals with chemical shifts relative to T.M.S.



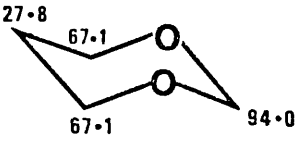
1,3-O-butylidene-?-deoxy-D-arabino-hexitol



1,3-O-butylidene-?-deoxy-D-lyxo-hexitol



1,3-O-butylidene-?-deoxy-D-erythro-pentitol



1,3-dioxane

Fig. V-27

The substituent effect of the propyl chain on the acetal carbon has been discussed previously in the section concerned with the propyl chain and the acetal carbon. If one looks at the three butylidene acetals in the above diagram all are substituted at C-4 with an equatorial group of the type $-(CHOH)_nCH_2OH$ (n = 1 or 2) relative to 1,3-dioxane. The numbering system is that illustrated for 1,3-dioxane and not that previously illustrated for the acetals themselves. Kellie and Riddell[72] found that equatorial methyl substitution at C-4 of 1,3-dioxane deshields C-4 by 5·7 p.p.m. Hence deshielding of C-4 in the three butylidene acetals in Fig. V-27 is to be expected. The deshielding occurs in each case

but is either by 11.3 p.p.m. or 11.9 p.p.m. The larger deshielding is because the substituent group is hydroxylated, hence a β hydroxyl substituent effect will also operate on C-4 of the acetal ring. The magnitude of a β hydroxyl substituent effect varies from 4 p.p.m. upwards and is deshielding.[80] Hence when both deshielding substituent effects are added together the resultant deshielding of C-4 is comparable to that found for the three acetals above.

Equatorial methyl substitution at C-4 of 1,3-dioxane also deshields C-5 by about 7 p.p.m. [72] If one looks at the ^{13}C chemical shifts of the C-5 atoms in the three butylidene acetals above and compare the values with C-5 of 1,3-dioxane, deshieldings of 1.1 — 2.0 p.p.m. are apparent. This lower deshielding compared to a methyl group is again due to the present C-4 substituent being hydroxylated. The C-5 atoms are γ to the hydroxylated substituent carbon and the γ substituent effect of hydroxyl is shielding by about 4 p.p.m. Thus the composite of the two substituent effects on C-5 is only slightly deshielding.

The substituent effect of a C-4 equatorial methyl group on C-2 and C-6 of 1,3-dioxane is very small hence the C-2 and C-6 ^{13}C shifts of the three butylidene acetals in Fig. V-27 are expected to be similar to their ^{13}C shifts in 1,3-dioxane. The C-2 shifts although somewhat deshielded have been discussed previously. The C-6 shifts are approximately the same as those in 1,3-dioxane. By similar application of substituent effects from hydroxyl, methylene and hydroxymethyl groups the ^{13}C chemical shifts of the ring carbons in all the other six membered butylidene acetals listed in tables V-5 and V-6 can be correlated with the analogous ring carbons of 1,3-dioxane.

(iii) ^{13}C n.m.r. Spectroscopy as an Aid to Structure Determination

It may be recalled that in section IV-B the acetalation of 6-deoxy-6-fluoro-D-galactitol was studied. Products arising from the acetalation and work up procedure were postulated as consisting of acetals of the deoxy fluoro polyol, galactitol and certain anhydro polyols. This small section deals with the structure elucidation of the anhydro polyol acetals, namely 2,6-anhydro-1,3-O-butylidene-D-galactitol and 2,5-anhydro-1,3-O-butylidene-L-altritol.

The anhydro compounds were obtained as a two component mixture, the ^{13}C n.m.r. spectrum of which showed fifteen lines (decoupled). Fractional crystallisation resulted in partial removal of one component, the ^{13}C n.m.r. spectrum of which showed nine lines. The chemical shifts and types of carbons present in this pure component are shown below.

15.7 δ (CH_3)	68.8 (CH)	75.4 (CH)
19.1 (CH_2)	71.3 (CH_2)	78.3 (CH)
38.3 (CH_2)	72.9 (CH)	104.7 (CH)

The line at 71.3 δ is double the intensity of the other signals and hence due to two CH_2 functions with coincident chemical shifts. The three highest field signals indicate the presence of an acetal propyl side chain. The lowest field signal at 104.7 δ indicates the presence of a six membered acetal ring. A lack of diastereoisomeric acetal carbon resonances also supports this conclusion. The remaining six carbons are made up of two methylene and four methine carbons.

The first indication that the acetal is not a deoxy fluoro polyol derivative is the absence of any ^{13}C-^{19}F couplings in the ^{13}C n.m.r. spectrum. Micro elemental analysis of the acetal and on the two component mixture showed no traces of fluorine hence it is concluded that defluorination has occurred for both components. The defluorination of the CH_2F function of the original deoxy fluoro polyol had been found for another acetal isolated from the same reaction, namely 2,3-O-butylidene-D-galactitol. There, defluorination occurred with replacement of fluorine by hydroxyl. If this type of defluorination were happening for the present acetal then it should be an acetal of galactitol with a six membered ring.

Previous studies[45] have indicated the most stable acetal of galactitol with a six membered ring to be the 1,3-acetal. The 1,3-ring system is also expected to be formed in the acetalation of 6-deoxy-6-fluoro-D-galactitol. The ^{13}C n.m.r. spectrum of 1,3-O-butylidene-DL-galactitol has been analysed;[89] the chemical shifts are shown below next to the appropriate carbon atoms (Fig. V-28).

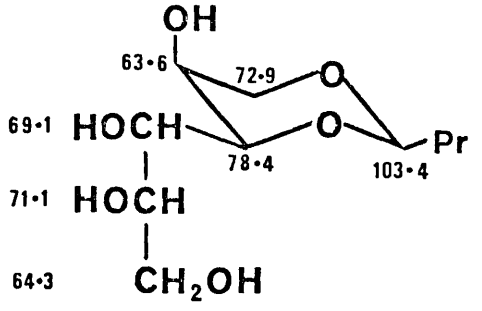


Fig. V-28

There are several marked differences in the ^{13}C spectrum of the acetal above and that of the isolated component from the mixture. The CH_2 carbons in the polyol backbone of the unknown acetal have chemical shifts of 71.3 δ whereas the same carbons in 1,3-O-butylidene-DL-galactitol have shifts of 64.3 and 72.9 δ. This would seem to indicate that if a 1,3-ring is present in the unknown acetal then C-6 also appears to be involved in some sort of ring or has been etherified. Both possibilities would lead to a deshielding of C-6 and could cause its resonance position to be in the 71.3 δ region. The highest field methine carbon resonance in 1,3-O-butylidene-DL-galactitol is at 63.6 δ (C-2), whereas in the unknown monoacetal the highest field methine signal is at 68.8 δ, others being at 72.9, 75.4 and 78.3 δ. Again, if a 1,3-ring is present in the unknown acetal this suggests that C-2 has been etherified or involved in a ring system.

The ^{13}C shift data indicate that defluorination has not occurred with simple replacement of fluorine by hydroxyl. Another possible type of replacement is intramolecular displacement of fluorine to yield an anhydro ring. It is known that anhydro compounds can be formed from fluorinated sugars.[58] The conformational requirements for formation of such compounds were previously discussed in section IV-B and will not be further discussed here.

The size of the anhydro ring can vary from three membered to six membered for a 1,3-acetal of galactitol. The three

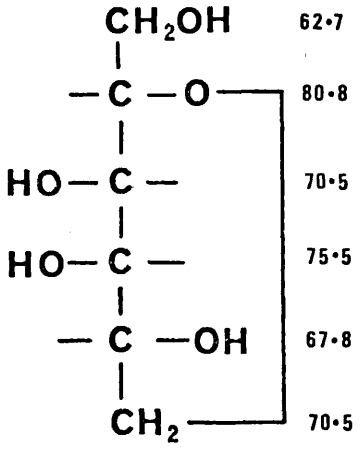
membered anhydro ring (epoxide) can be eliminated as certain substituent effects caused by epoxide formation from the alcohol are absent in the ^{13}C n.m.r. spectra of the mixture and the component isolated from it. For example, if one looks at the ^{13}C chemical shift of the carbons in ethylene glycol[61] and ethylene oxide[70] a shielding of approximately 27 p.p.m. is caused by epoxide formation. The chemical shifts in the above two papers were converted to a T.M.S. reference using shifts of 129 and 194 δ for benzene and carbon disulphide respectively.

If a 27 p.p.m. shielding was added to any of the ^{13}C chemical shifts of 1,3-O-butylidene-DL-galactitol resonances should be observed in the 40-50 δ region. The absence of such resonances in the ^{13}C n.m.r. spectrum of the mixture eliminates the possibility of an epoxide ring. Similar substituent effects for oxetane formation can be obtained by looking at the ^{13}C chemical shifts of oxetane[61] and propane-1,3-diol.[78] This shows that the carbons bearing the oxetane ring oxygen are deshielded by approximately 13 p.p.m. upon oxetane formation. That carbon flanked by these two carbons becomes shielded by approximately 12 p.p.m.

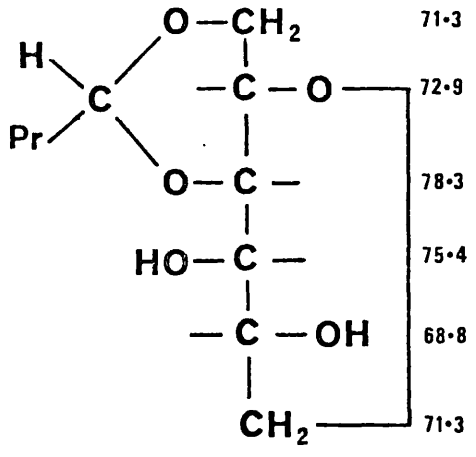
The substituent effects caused by oxetane formation do not provide such a clear elimination of the four membered anhydro ring that was possible previously for the epoxide ring. If the oxetane substituent effects are kept in mind during the following discussions then it is possible with the use of ^{13}C shift data and other structural evidence presented to exclude the presence of an oxetane ring. This leaves only five and six membered anhydro

rings as possibilities.

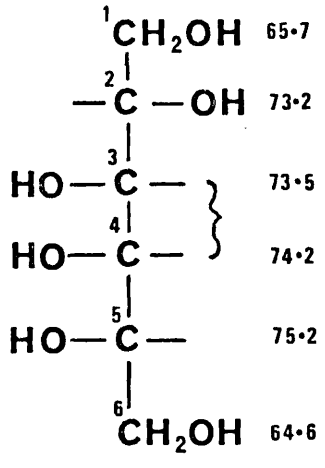
Now, the deshieldings experienced by C-2 and C-6 in the isolated component seem to suggest that if an anhydro ring is present then they may be involved in it. Que and Gray[159] have reported the ^{13}C chemical shifts of 2,6-anhydro-D-galactitol. The shifts are shown next to the carbons in the diagram below (Fig. V-29,I).



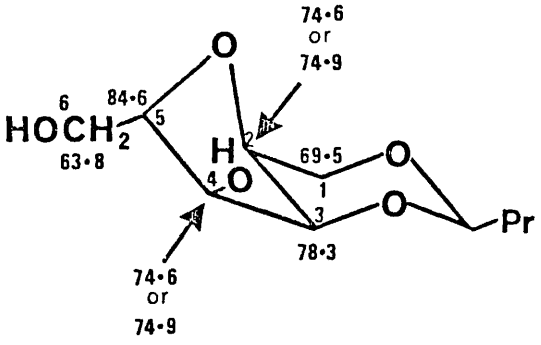
I



II



III



IV

Fig. V-29

The values reported by Que and Gray[159] were relative to a CS_2 reference. They have been converted to the T.M.S. scale using a chemical shift of 194 δ for CS_2 relative to T.M.S.

Let us now consider the effect on the ^{13}C chemical shifts of I above if a 1,3-acetal ring were formed. The previous discussion in this section shows that those polyol carbons becoming carbons bearing acetal ring oxygens are deshielded by 8-10 p.p.m. If such deshieldings are added to the C-1 and C-3 chemical shifts of I above the resultant shifts are predicted to be in the region of 70.7 - 72.7 δ (C-1) and 78.5 - 80.5 δ (C-3). The data listed previously for the unknown acetal shows CH_2 signals at 71.3 δ and a CH signal at 78.3 δ. Both are close to the predicted values for C-1 and C-3 respectively in a 1,3-acetal of 2,6-anhydro-D-galactitol. The other major substituent effect caused by acetalation is the 8 - 10 p.p.m. shielding on that carbon flanked by the two carbons bearing acetal ring oxygens. In the present case this is C-2. If this shielding is added to the chemical shift of C-2 in I above a predicted shift of 70.8 - 72.8 δ emerges. The ^{13}C spectrum of the unknown acetal shows a resonance at 72.9 δ which is very close to that predicted for a 1,3-acetal derivative.

The previous studies on the deoxy polyols showed that carbons other than those becoming directly involved in the acetal ring experienced relatively little change in chemical shift upon acetalation. If this observation is applied here then the remaining carbons (C-4, C-5 and C-6) are expected to have similar chemical shifts in the anhydro polyol and the 1,3-acetal derived therefrom. A glance at the chemical shifts of I and

II above (Fig. V-29) reveals how the resonances of the unknown acetal may be assigned to fit in with this prediction.

Further evidence in favour of the type and structure of the acetal was obtained from other techniques. The chemical ionisation mass spectrum indicated a molecular weight of 218, consistent with the type of anhydro acetal shown in Fig. V-29,II. Also, the acetal consumed 1.10 moles of periodate ion without liberation of formaldehyde thereby indicating vicinal diol groups both of which must be secondary. The ^{1}H n.m.r. spectrum of the acetal showed certain coupling constants which were consistent with the proton environments of the anhydro ring (section V-B).

Finally, a comparison of the molecular rotations of the acetal (-147°) and the 4,6-O-benzeneboronate of 1,5-anhydro-D-galactitol ($+172^{\circ}$)[160] showed a reasonable similarity between the two. The opposite signs of molecular rotation for the compounds are discussed below. The proposed 2,6-anhydro-1,3-acetal structure and the above mentioned benzene boronate both contain cis fused ring systems with the same configurations at the asymmetric centres with the exception of the boron and acetal carbon atoms. The difference in molecular rotation caused by this slight structural difference was measured by comparing the molecular rotations of methyl 4,6-O-benzylidene-α-D-galactopyranoside ($+406^{\circ}$) [161] and the 4,6-O-benzeneboronate of methyl α-D-galactopyranoside ($+411^{\circ}$).[160] These compounds have the same slight structural difference as the above mentioned anhydro derivatives. The marginal difference in molecular rotation

between the galactopyranoside derivatives suggests that a valid comparison may be made between the anhydro derivatives. The observed similarity in molecular rotation supports the proposed structure. Although the two anhydro derivatives are not mirror images by virtue of the boron and acetal carbon atoms they are expected to have opposite signs of molecular rotation arising from their substitution pattern on galactitol. When all the above evidence is considered it seems reasonable to assume the acetal to be 2,6-anhydro-1,3-O-butylidene-D-galactitol.

By subtracting the ^{13}C resonances of the isolated component from the ^{13}C n.m.r. spectrum of the mixture from which it originated it was possible to obtain the ^{13}C chemical shifts of the unisolated acetal. These are listed below.

15.7 δ (CH_3)	63.8 (CH_2)	74.9 (CH)	102.2 (CH)
19.1 (CH_2)	69.5 (CH_2)	78.3 (CH)	
38.3 (CH_2)	74.6 (CH)	84.6 (CH)	

The multiplicity and chemical shift values reveal an acetal propyl chain and a six membered acetal ring. The remaining resonances are attributed to the carbons of the polyol backbone. As was mentioned previously micro elemental analysis on the mixture revealed no traces of fluorine and this is confirmed by a lack of any $^{13}C - {}^{19}F$ couplings. Again straightforward replacement of fluorine by hydroxyl cannot have occurred as the chemical shifts of the unknown compound are significantly different from 1,3-O-butylidene-DL-galactitol. This is assuming the six membered acetal ring is a 1,3-ring.

In section IV-B the structure of this unisolatable component was proposed as being 2,5-anhydro-1,3-O-butylidene-L-altritol (Fig. V-29, IV). The ^{13}C chemical shifts of L-altritol[79] are shown next to the appropriate carbons in Fig. V-29,III. The following discussion attempts to show how the ^{13}C chemical shifts of L-altritol will be modified via anhydro ring formation and acetalation substituent effects to fit with the above listed values for the unknown acetal on the basis of the proposed structure.

First of all let us consider the methylene carbons, the chemical shifts of which are 63.8 and 69.5 δ. Both are attached exo to the anhydro ring. The ^{13}C chemical shifts of the anhydro polyols studied by Que and Gray[159] show such carbons to be slightly shielded (up to 4.0 p.p.m.) compared to the free polyol. The comparisons are made using the ^{13}C chemical shift data listed in table V-3 (section V-A). Of the two methylene carbons only C-1 is involved in the acetal ring, C-6 being removed from the site of the acetal ring. By virtue of its position in the acetal ring, C-1 is expected to experience an 8-10 p.p.m. deshielding relative to the free polyol whereas C-6 should not experience any substituent shift effect from the acetal ring. The composite substituent effects of anhydro and acetal ring formation should place C-1 at lower field than C-6, the resonances at 63.8 and 69.5 δ are therefore assigned to C-6 and C-1 respectively.

Let us now consider the methine carbons C-2, C-3, C-4 and C-5, i.e. those carbons in the anhydro ring system. C-2 bears the anhydro ring oxygen but is also flanked by the carbons bearing the acetal ring oxygens. Inspection of the data given by Que and Gray[159] for the anhydro polyols and that listed in table V-3 for ordinary polyols shows that anhydro ring formation causes a 5-10 p.p.m. deshielding of those carbons which end up as bearing the anhydro ring oxygen. It is also known that the acetal ring carbon flanked by carbons bearing acetal ring oxygens is shielded by 8-10 p.p.m. Thus little net change in chemical shift is expected for C-2 in going from L-altritol to the anhydro acetal as the two substituent effects oppose each other. Either of the resonances at 74.6 and 74.9 δ in the anhydro acetal could be assigned to C-2 as they both show only a small deviation from the chemical shift in the free polyol (73.2 δ).

The other carbon bearing the anhydro ring oxygen in the anhydro acetal is C-5. It is not expected to experience any substituent effect from the 1,3-acetal ring. Addition of the 5-10 p.p.m. deshielding caused by anhydro ring formation to the chemical shift of C-5 in the free polyol (75.2 δ) gives a predicted shift of 80.2 - 85.2 δ. There are two resonances in the spectrum of the anhydro acetal which may be considered as possibilities, i.e. at 78.3 and 84.6 δ. The proposed structure of the anhydro acetal has cis vicinal C-O bonds in the anhydro ring with C-5 bearing a hydroxymethyl group trans to the hydroxyl group on the adjacent carbon (C-4). The chemical shifts listed by Que and Gray[159] for carbons such as C-5 are in the 83 δ region.

For this reason C-5 in the anhydro acetal is assigned to the resonance at 84.6 δ .

The remaining carbons of the polyol backbone to discuss are C-3 and C-4. They are both in the anhydro ring system and both adjacent to a carbon bearing the anhydro ring oxygen. The C-O bonds are cis orientated with respect to one another. Que and Gray[159] list the chemical shifts of very similar carbons in five membered anhydro rings. A comparison of the Que and Gray data and that listed for the polyols in table V-3 shows such carbons to experience a variable substituent effect upon anhydro ring formation (+0.2 to -2.8 p.p.m.). The data for erythritol is not listed in table V-3 but is also taken from reference 79.

Let us consider C-3 first of all. It is involved in the acetal ring as it bears an acetal ring oxygen. This will deshield it by 8-10 p.p.m. relative to the free polyol. This deshielding should ensure that C-3 is at lower field than C-4 as they both have similar chemical shifts in the polyol but C-4 experiences no deshielding of any magnitude. The chemical shift possibilities for C-3 and C-4 in the anhydro acetal are 78.3 δ and one of the resonances at 74.6 or 74.9 δ. The resonance at 78.3 δ is assigned to C-3 on the basis of its lower field resonance position. This assignation invokes an anhydro formation substituent effect of between -2.8 and -5.9 p.p.m., the lower value of which is compatible with that discussed previously. Assignment of C-4 to one of the resonances at 74.6 or 74.9 δ results in a deshielding substituent effect of between +0.4 and +1.4 p.p.m. compared to its resonance position

in the free polyol. Although this is slightly larger than that discussed previously it is still feasible as the deviation at best is only 0.2 p.p.m. outside the limits.

Supporting evidence for the proposed structure was obtained from periodate oxidation and gas liquid chromatography. The integrated peak areas of the gas chromatogram of the two component mixture showed the ratio of the two components as 1.03:1 i.e. practically equal. Now, the isolated 2,6-anhydro-1,3-O-butylidene-D-galactitol was shown to consume 1.10 moles of periodate ion. Periodate oxidation on the two component mixture resulted in uptake of 0.61 moles of periodate ion. However, 0.55 moles of this uptake must be attributed to the 2,6-anhydro acetal leaving the other component as consuming 0.05 moles of periodate. This can be considered as practically no uptake of periodate which is what is expected from 2,5-anhydro-1,3-O-butylidene-L-altritol (Fig. V-29, IV).

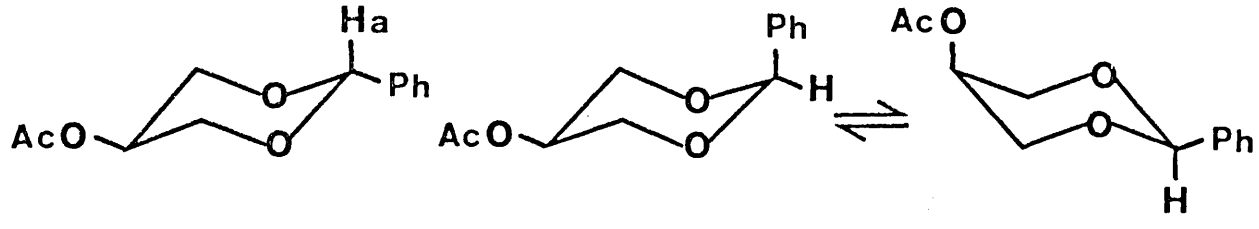
To summarise the ^{13}C n.m.r. section the chemical shifts of the deoxy and deoxy fluoro polyols have been assigned by consideration of substituent effects with respect to their non deoxy derivatives. The structures of the butylidene acetals of these deoxy, deoxy fluoro and other polyol derivatives have then been elucidated by considering further substituent effects caused by acetalation. The chemical shifts of those acetals with six membered rings can also be related to the parent 1,3-dioxane ring by use of ^{13}C substituent effects.

V-B Proton (^{1}H) n.m.r. Spectroscopy of the Mono-O-Butylidene Acetals of the Deoxy Polyols

1. Introduction

As far as organic chemistry in general or carbohydrate chemistry in particular is concerned the most important development regarding structure elucidation of molecules in modern times must be ^{1}H n.m.r. spectroscopy. The development of this field is such that most university undergraduate chemistry courses are designed to familiarise the student with this technique. For this reason further reappraisal of the theory and background of ^{1}H n.m.r. spectroscopy seems unwarranted, instead any readers are referred to the classical monographs[90,91] along with specialist reviews,[92] hopefully rendering further rediscussion unnecessary. Instead, the following introduction is centred around the ^{1}H n.m.r. spectroscopy of compounds having similar structures to the acetals discussed later in this section.

The earliest reported work on ^{1}H n.m.r. spectroscopy of acetals of polyhydric alcohols was by Baggett et al.[93] They reported two different types of spectra for the cis and trans isomers of derivatives of 5-hydroxy-1,3-dioxane (Fig. V-30).



I trans Fig. V-30 II cis

The acetal proton for conformation I above was shown to have a chemical shift of 5.42 δ , whilst that of conformations II had a chemical shift of 5.49 δ . The differences in chemical shift of these acetal protons were ascribed to the axial/equatorial environment they occupied. The acetal proton in conformation I had a strictly axial environment, whilst there was a supposed average chemical shift for the acetal proton in conformations II through ring inversion. The authors then used this data regarding acetal proton chemical shifts to obtain the configuration of the phenyl group for the above isomers and for a series of other benzylidene acetals having six membered rings.[94]

Later ^{1}H n.m.r. studies[95,96] from the same research school showed that it was possible to distinguish between five and six membered acetal rings from the position of the acetal proton resonance. The shift range for this particular proton was 4.98 - 5.18 δ for 4-substituted 2-phenyl-1,3-dioxanes and 5.33 - 5.54 δ for 4-substituted 2-phenyl-1,3-dioxolanes. Further intricacies associated with the chemical shift of the acetal protons enabled the authors to assign absolute configurations at the acetal carbons for a series of five and six membered benzylidene acetals.[95,96] There have been several other publications relating acetal ring size to the chemical shift of the acetal proton.[31,44,97] The general conclusion is that the shift of an acetal proton in a five membered ring is at lower field than the corresponding proton in a six membered ring. It is also reported that the coupling constant for the acetal proton gives insight into acetal ring size,[31] The $^{3}J_{HH}$ for a five membered ring being 0.2 to 0.3 Hz smaller than the analogous acetal proton coupling for a six membered ring.

The studies introduced so far have not gone into great detail about the chemical shifts and coupling constants of the remaining protons of the 1,3-dioxane ring or any of its derivatives. There has however been an abundance of work regarding the chemical shifts and spin systems of these ring protons. The earliest of these works dealt with the ^1H chemical shifts and geminal and vicinal proton coupling constants of 1,3-dioxane itself,[98,99] (Fig. V-31) and a few alkylated derivatives.

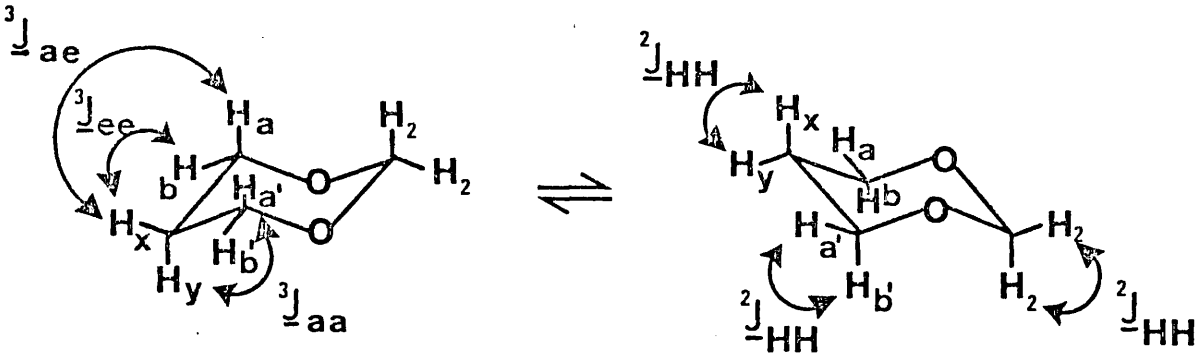


Fig. V-31

The proton chemical shifts of 1,3-dioxane[98] were found to fall into three ranges, the lowest field signals belonging to the H_2 protons, the highest field signals belonging to the H_x and H_y protons and the intermediate range arising from the $H_{aa'}$ and $H_{bb'}$ protons. When the ring inversion process was stopped by alkyl substitution the geminal and vicinal proton coupling constants were extracted from the spectra of various 1,3-dioxane derivatives.[99] The geminal ($^2J_{HH}$) coupling

constants were found to be in the range 10.9 ⟶ 11.5 Hz for protons on C-4/C-6 of a 1,3-dioxane derivative, and approximately 6 Hz for geminal protons on C-2. The sign of the geminal coupling constants is negative. Vicinal couplings ($^3J_{HH}$) between diaxially disposed protons ($^3J_{aa}$) were found to be between 9.3 and 11.0 Hz, vicinal couplings between axial equatorial protons ($^3J_{ae}$) were found to be 3.2 - 4.5 Hz.

Further studies[100,101] on the magnitude of geminal coupling constants in 1,3-dioxane derivatives showed the geminal protons on C-5 to have a larger negative value than geminal protons on C-4(6). This is brought about by the fact that the protons on C-4(6) experience inductive removal of electrons from the symmetric CH_2 orbitals by the adjacent oxygen atom. The lone pairs of electrons on the oxygen can also back donate electron density into the antisymmetric CH_2 orbitals. Both of these mechanisms lead to a positive increase in the coupling constant.[102]

More detailed analysis[100] into the chemical shifts of the ring protons of 1,3-dioxane derivatives revealed that of the protons on C-5, that which is axial is to lower field. This is presumably due to deshielding by the two ring oxygen atoms, the electron lone pairs of which have a 1,3-interaction with the C-5 axial proton (Fig. V-32). The C-5 equatorial proton is placed so as not to experience this deshielding effect.

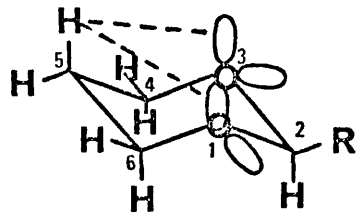


Fig. V-32

The protons on C-4(6) are also influenced by the electron lone pairs of the adjacent oxygen atom. The equatorial C-4(6) proton is at lower field than the axial proton,[100] presumably because it is gauche to two electron lone pairs whereas the axial proton is gauche to only one (Fig. V-32) resulting in greater deshielding for the equatorial proton.

The above shielding trends may be modified however by substitution on the 1,3-dioxane ring. As the acetals discussed later are substituted derivatives of 1,3-dioxane it may be profitable to look at these substituent effects. For example, the presence of an equatorial alkyl function at C-4 causes the axial proton at C-4 to be shielded, the magnitude of the shielding depending upon the alkyl function.[103] An equatorial 4-methyl group has a strong shielding effect on the C-5 axial proton (0.4 - 0.5 p.p.m.). In certain cases this shielding of the C-5 axial proton can cause a reversal of the C-5 axial/equatorial proton chemical shifts of 1,3-dioxane. One such case is cis 4,6-dimethyl-1,3-dioxane where the two equatorial

methyl groups cause the C-5 axial proton to resonate at higher field than the C-5 equatorial proton.[103] Tavernier and Anteunis[103] looked at these and other substituent effects for a wide range of 1,3-dioxane derivatives and concluded that the substituent effects were additive. This is an analogous situation to the ^{13}C chemical shifts of the ring carbons of the cyclic acetals which could be related to the ^{13}C chemical shifts of 1,3-dioxane by ^{13}C substituent shift effects.

Apart from effects on the chemical shift of the ring protons, substituents can also affect the geometry of the ring. The conformation of the ring for many substituted 1,3-dioxanes has been studied by proton n.m.r. spectroscopy.[35] It is found that for equatorial substituents at the 2,4 or 6 positions there is no significant deviation from the chair form. The conformational analysis was carried out by measurement of coupling constants then relating them to dihedral angles.[35,104]

Apart from having 1,3-dioxanic ring protons the acetals studied in this thesis have several hydroxyl substituents, both in the ring and on side chains. The type and orientation of these hydroxyl functions can be found from the appearance of the hydroxyl proton in an ^{1}H n.m.r. spectrum. The coupling constants for hydroxyl protons are difficult to observe in some solvents due to the presence of very slight traces of acid. This causes a rapid exchange process to be set up leaving the hydroxyl proton resonance as a broad signal.

When the solvent is changed to dimethyl sulphoxide however this rapid exchange is slowed down considerably, presumably due to formation of strong intermolecular hydrogen bonds[105] as shown below (Fig. V-33) for the case of cyclohexanol.[106]

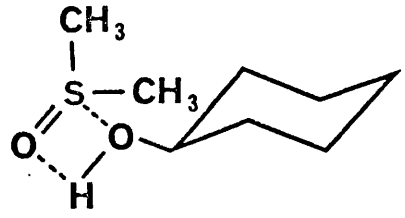
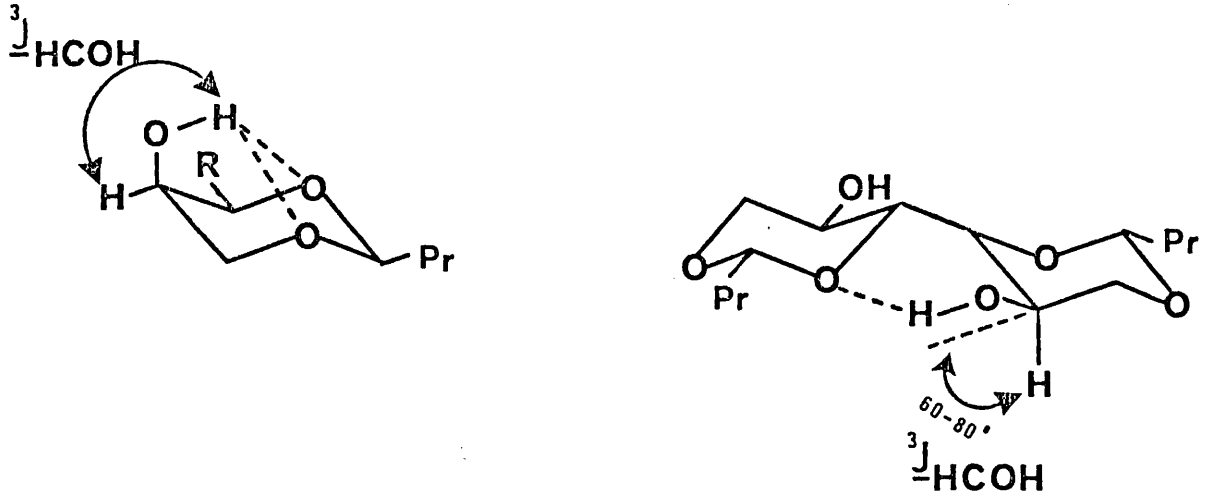


Fig. V-33

This allows observation of any hydroxyl proton couplings present. Under these conditions $-CH_2OH$ hydroxyl protons appear as triplets and -CHOH hydroxyl protons appear as doublets in their ^1H n.m.r. spectra. The magnitude of the coupling with other protons allows the orientation of the hydroxyl function to be ascertained. The size of the coupling follows a Karplus type relationship with dihedral angle.[107] For example, the 1,3:4,6-di-O-butylidene acetal of galactitol showed a large $^3J_{HCOH}$ coupling[108] (12 Hz) suggestive of a trans disposition of the hydroxyl proton and the proton it coupled to (Fig. V-34I).



I II

Fig. V-34

This large coupling can be compared with the small $^{3}J_{HCOH}$ coupling (1.5 Hz) in 1,3:4,6-di-O-butylidene-D-mannitol[108] (Fig. V-34II) where the dihedral angle between the coupled protons is about 60-80° i.e. a *gauche* disposition.

The hydroxyl proton resonances are easily distinguished from other proton signals in an ^{1}H n.m.r. spectrum as they disappear upon addition of a few drops of D_2O to the sample. Apart from the examples cited above hydroxyl proton resonances have been used to obtain structural information for a variety of carbohydrate molecules.[109,110] In the structure proofs of most of the acetals discussed in this thesis strong emphasis is placed upon hydroxyl proton n.m.r. spectroscopy.

Another technique associated with ^{1}H n.m.r. spectroscopy and structure elucidation is computer simulation of spectra. The theoretical spectrum of the molecule is calculated then compared with the experimental spectrum. Marked similarities between the two

usually indicate correct interpretation of the experimental spectrum. Computer simulation of n.m.r. spectra is also used for obtaining the absolute values of spin-spin coupling constants (J values).[111,112] Once the spectrum has been calculated and the coupling constants obtained then the various dihedral angles between the protons can be found by means of the Karplus equation,[113] resulting in a knowledge of the conformation of the molecule.

There are cases where the Karplus equation breaks down, e.g. it does not account for the high J values between vicinal diaxial protons in certain systems. Certain modified Karplus equations have been formulated to overcome this. Lemieux et al[114] have suggested an upward displacement of the Karplus curve by 2.2 Hz to account for certain couplings in 1,3-dioxolanes. Abraham[115] has also pointed out deviations from the Karplus relationship for 1,3-dioxane and 1,3-dioxolane derivatives.

Calculations of ^{1}H n.m.r. spectra of 1,3-dioxane derivatives are routinely performed in order to ascertain molecular geometry.[98,103] The technique was utilised for several of the acetals discussed in this thesis. The calculations were performed using the two programs UEA NMR BASIC and UEA NMR ITERATIVE on the University of London CDC 1700 and CDC 6600 computers respectively. These programs are part of a library of such programs, the manual for their usage is issued by the Science Research Council.[116] The programs were adapted for use at the Royal Holloway College computer terminal by the staff of the Computer Science Department of Royal Holloway College. The procedure for the calculation of the spectra of the acetals was identical to that recently reviewed by Coxon[111] so will not be further elaborated upon.

2. Results and Discussion

The ^1H n.m.r. spectra presented in this section were all run at 220 MHz. Lower field strength spectra (60 or 100 MHz) proved impossible to interpret due to overlapping resonances of similarly shielded protons. This was overcome for some acetals by recourse to the higher field strength, even then some spectra were uninterpretable, particularly those of the diastereoisomeric five membered ring acetals. It proved convenient for discussion purposes to divide the ^1H n.m.r. spectroscopy of the acetals into two categories. The first of these is that concerned with the hydroxyl protons and the acetal protons.

(i) ^1H n.m.r. Spectral Features of the Acetal Protons (Ha) and the Hydroxyl Protons

The chemical shifts and coupling constants of the acetal protons and the hydroxyl protons are tabulated below (table V-8), the first row of numbers associated with a particular acetal is the chemical shift in δ p.p.m., the second row is the chemical shift in Hz, the third row is the coupling constant in Hz. All data was taken direct from the experimental spectra and is not computer simulated. The solvent in all cases was D.M.S.O. (d^6). The superscripts p or s indicate primary or secondary hydroxyl functions respectively, the hydroxyl functions were detected by rerunning the spectra after the addition of a few drops of D_2O then observing which original resonances had disappeared, this is illustrated in Fig. V-35 for 4,6-O-butylidene-2-deoxy-D-arabino-hexitol. The acetal protons were detected in some cases by double resonance methods

Acetal	Ha	OH	OH	OH
1,3-O-Butylidene-2-deoxy-D-arabino-hexitol	4.53 997 5.0	4.27^{p} 939 5.3	4.38^{s} 964 7.5	4.40^{s} 968 5.5
4,6-O-Butylidene-2-deoxy-D-arabino-hexitol	4.43 975 5.1	4.15^{s} 913 7.2	4.36^{p} 959 5.1	4.93^{s} 1084 6.0
1,3-O-Butylidene-2-deoxy-D-erythro-pentitol	4.47 983 5.5	4.42^{p} 972 5.6	4.66^{s} 1030 5.1	-
3,5-O-Butylidene-2-deoxy-D-erythro-pentitol	4.43 975 5.1	4.43^{p} 975 5.1	5.11^{s} 1124 5.2	-
1,3-O-Butylidene-2-deoxy-D-lyxo-hexitol	4.47 983 5.0	4.21^{s} 926 6.4	4.30^{s} 946 7.8	4.44^{p} 977 6.0
4,5-O-Butylidene-2-deoxy-D-lyxo-hexitol	4.95 1089 4.6	4.38^{p} 964 5.0	?	?
4,6-O-Butylidene-2-deoxy-D-lyxo-hexitol	4.50 990 5.2	4.31^{p} 948 5.3	4.49^{s} 988 6.8	4.56^{s} 1003 6.1
2,4-O-Butylidene-3-deoxy-D-ribo-hexitol	4.49 988 5.0	4.40^{p} 968 5.5	4.61^{p} 1014 6.0	4.63^{s} 1019 5.2
1,3-O-Butylidene-4-deoxy-D-xylo-hexitol	4.52 994 5.4	4.45^{s} 979 5.4	4.50^{p} 990 5.8	4.57^{s} 1005 6.8
2,3-O-Butylidene-4-deoxy-D-xylo-hexitol	4.90 1078 ?	?	?	?
2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol	4.61 1014 5.3	4.41^{p} 970 5.6	4.82^{p} 1060 5.7	4.88^{s} 1074 5.9
4,5-O-Butylidene-6-deoxy-6-fluoro-D-galactitol	4.95 1089 4.7	?	?	?

Table V-8 ^{1}H Chemical Shifts (Hz and p.p.m.) and Coupling Constants (Hz) for the Acetal and Hydroxyl Protons of the Deoxy Polyol Butylidene Acetals at 220 MHz.

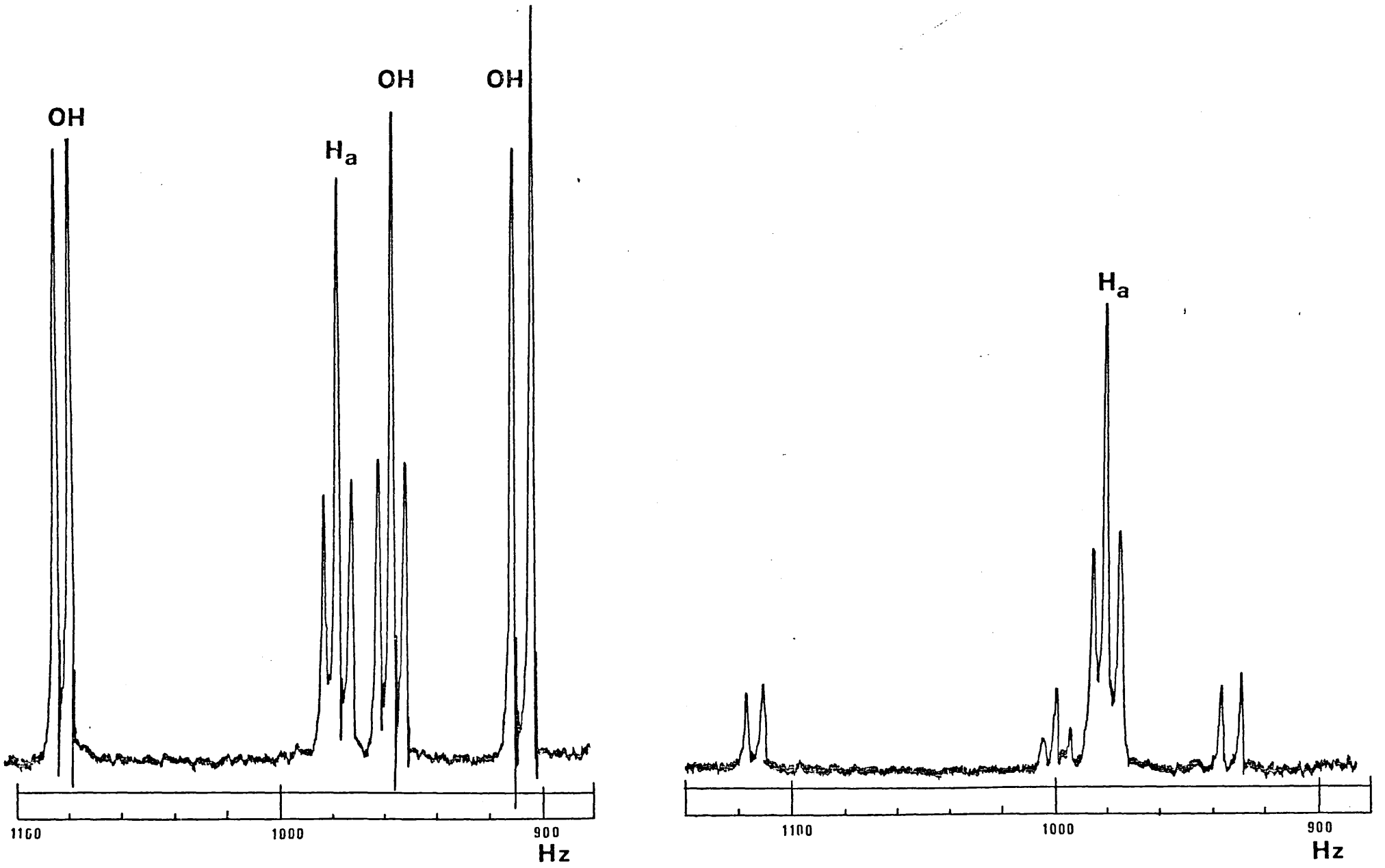
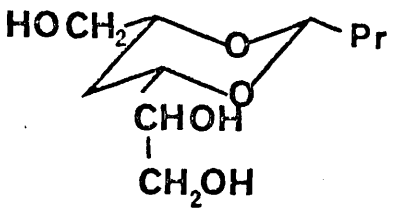


Fig. V-35 Hydroxyl and Acetal ^{1}H n.m.r. Spectral Region of 4,6-O-Butylidene-2-deoxy-D-arabino-hexitol before (left) and after (right) Deuterium Exchange.

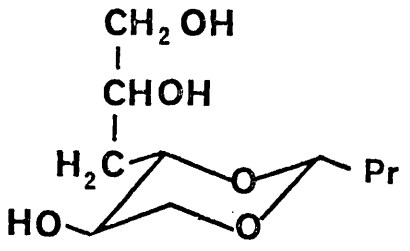
but are also easily recognised on an ^{1}H n.m.r. spectrum due to their low field chemical shift. This is a result of deshielding from two oxygen atoms attached to the acetal carbon.

Looking first of all at the acetal proton data in table V-8 there are two apparently useful points regarding structure elucidation. The shift range of the acetal protons in six membered rings is 4.43 to 4.61 δ , whilst for five membered rings the range is 4.90 to 4.95 δ. This is to be expected from previous studies relating acetal ring size to the acetal proton chemical shift.[95,96] Also, the acetal protons appear as triplets due to couplings with the protons on the adjacent methylene group of the propyl side chain. The magnitude of this coupling is 5.0 to 5.5 Hz for the six membered rings and 4.6 to 4.7 Hz for the five membered rings. This variance in coupling with ring size is also predicted from previous studies.[31] These two features give immediate insight into the size of the acetal ring.

Let us now look at the hydroxyl proton data in table V-8. The multiplicity of the hydroxyl proton resonances allows differentiation between primary and secondary hydroxyl functions. This knowledge of the number and type of hydroxyl functions is extremely useful in structural analysis of the acetals especially when the ring size is known from other n.m.r. data. For example the ^{1}H n.m.r. spectrum of the mono-O-butylidene acetal of 3-deoxy-D-ribo-hexitol showed an acetal proton triplet at 4.49 δ thereby revealing a six membered ring. The only two possibilities for this are the 2,4- and 4,6-rings (Fig. V-36).



2,4

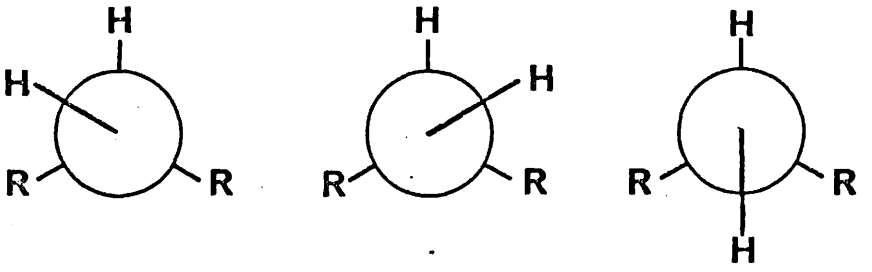


4,6

Fig. V-36

The hydroxyl ^{1}H n.m.r. spectrum of the acetal revealed two primary hydroxyls and one secondary. This eliminated the 4,6-ring thus showing the structure to be the 2,4-acetal. Similar application of these two features to the other acetals discussed in this thesis leads either to definite structure assignments or narrows possibilities down to two or three isomers. Individual cases other than the illustrated example will not be further discussed as they have previously been discussed in those sections dealing with structure elucidation.

Information about structure was not forthcoming from the hydroxyl proton coupling constants. The couplings shown in table V-8 vary between 5.0 and 7.8 Hz. This is presumably because of rotations about the C-O bonds yielding mixtures of rotamers. Of these rotamers only three have favoured staggered conformations of the hydroxyl proton and substituents on the carbon atom (Fig. V-37).



I II III

Fig. V-37

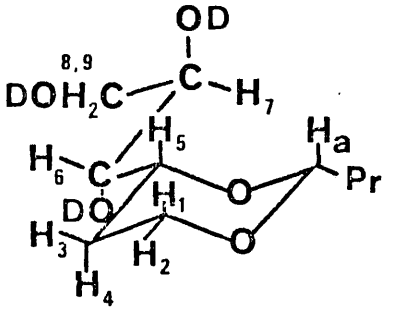
The observed couplings for the hydroxyl protons are probably average couplings with contributions from the above three rotamers. Two of the rotamers (I, II) give gauche couplings, the other one (III) gives a trans coupling. For the situation where one might expect to find a large trans $^{3}J_{HCOH}$ coupling there is no evidence for it. This is for those acetals having an axial hydroxyl function in the acetal ring whereby its orientation may be trans to the other proton on the same carbon due to hydrogen bonding with the ring oxygens (Fig. V-34I). In the present case these acetals would be 4,6-O-butylidene-2-deoxy-D-lyxo-hexitol and 1,3-O-butylidene-4-deoxy-D-xylo-hexitol. If one looks at the values for the hydroxyl couplings in these acetals there are no large (12 Hz) couplings. This means that the OH proton is not predominantly orientated trans to the other proton on the same carbon. This could be caused by the fact that the OH function is strongly intermolecularly bonded to the D.M.S.O. solvent molecules and not strongly intramolecularly bonded to the ring oxygens.

(ii) ^{1}H n.m.r. Spectral Aspects of the Remaining Ring Protons and those of the Side Chains

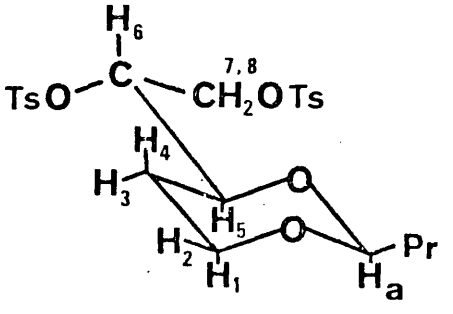
Of these remaining protons the easiest to deal with are those of the propyl chains. The terminal methyl groups appear as first order triplets between 0.81 and 0.91 δ. The adjacent methylene groups appear as complex multiplets centred at 1.30 to 1.38 δ . The methylene groups adjacent to the acetal carbons also appear as complex multiplets between 1.43 and 1.53 δ (Fig. V-39). Double resonance experiments with irradiation at the frequency of these lower field methylene groups resulted in decoupling of the acetal protons on the adjacent acetal carbons thus confirming the assignments. It may be recalled that to distinguish between the deoxy carbon atom and the methylene carbon adjacent to the acetal carbon certain S.F.O.R.D. ^{13}C spectra were taken (section V-A). The protons of the deoxy carbon are usually at a lower field than the protons of this particular methylene group, thus irradiation of this lower field resonance usually resulted in deoxy carbon proton decoupling but no proton decoupling for the methylene carbon adjacent to the acetal carbon. Apart from the decoupling experiments no utility can be made of the propyl chain proton resonances towards structure elucidation.

Let us now look at the ^{1}H n.m.r. spectroscopy of the protons on the acetal rings and the other side chains. This discussion is centred upon those acetals for which a reasonable number of assignments could be made. This excluded the five membered ring acetals and the acetals of the fluoro polyols. The proton chemical shifts in p.p.m.

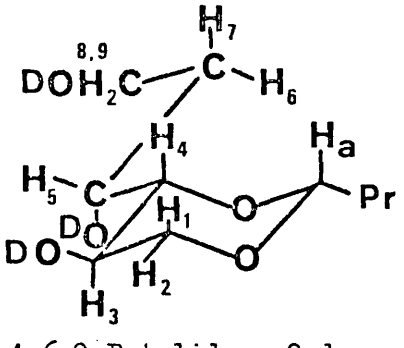
and Hz are listed in table V-10; those shifts with a superscript c are computer simulated chemical shifts otherwise the values were extracted directly from the experimental spectra. The labelling systems used for the protons are illustrated for the appropriate acetals in Fig. V-38. The solvent was D.M.S.O. (d^6) + D_2O for the deoxy hexitol acetals and pyridine (d^5) + D_2O for the deoxy pentitol acetals. The coupling constant values are listed in table V-9, the same usage of the superscript c applies.



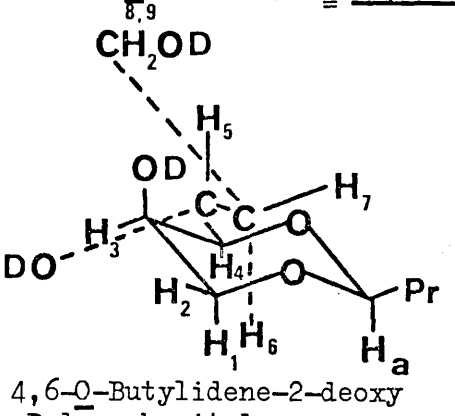
1,3-O-Butylidene-2-deoxy
-D-arabino-hexitol



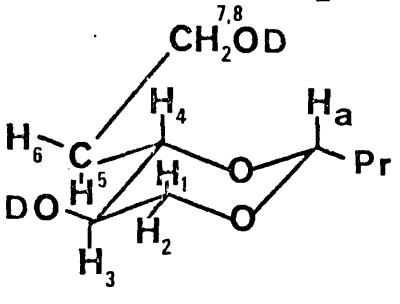
1,3-O-Butylidene-2-deoxy-4,5-di-O-
toluene-p-sulphonyl-D-erythro-pentitol



4,6-O-Butylidene-2-deoxy
-D-arabino-hexitol



4,6-O-Butylidene-2-deoxy
-D-lyxo-hexitol



3,5-O-Butylidene-2-deoxy
-D-erythro-pentitol

Fig. V-38

Acetal	J1,2	J1,3	J1,4	J2,3	J2,4	J3,4	J3,5	J4,5	J4,6	J5,6	J5,7	J6,7	J6,8	J7,8	J7,9	J8,9
1,3-O-Butylidene-2-deoxy-D-arabino-hexitol	-10.9	?	13.0	?	5.1	12.0	?	13.0	0	2.9	0	7.8	0	5.75	?	-10.5
1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol	-11.6[c]	2.8[c]	12.7[c]	1.75[c]	5.1[c]	-12.0[c]	2.8[c]	12.2[c]	0	6.8[c]	0	J6,7+J6,8= 3.7[c]		?	-	-
4,6-O-Butylidene-2-deoxy-D-arabino-hexitol	-10.3[c]	10.3[c]	0	5.5[c]	0	9.1[c]	0	1.5[c]	0	9.0[c]	4.5[c]	-14.2[c]	J6,8=7,8=6,9 =7,9=6.6[c]av			-11.0[c]
4,6-O-Butylidene-2-deoxy-D-lyxo-hexitol	-11.9	1.6	0	1.5	0	1.2	0	8.8	0	?	?	?	?	?	?	?
3,5-O-Butylidene-2-deoxy-D-erythro-pentitol	-10.9[c]	10.1[c]	0	5.1[c]	0	8.9[c]	0	8.9[c]	3.1[c]	-14.2[c]	J5,7 =5,8 =5.0[c]	5.0[c]	11.0[c]	-11.0[c]	-	-

Table V-9 Geminal and Vicinal Coupling Constants (Hz) of some Deoxy Polyol Acetals (Underlined Values are Approximations only)

Acetal	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9
1,3-O-Butylidene-2-deoxy	?	4.02	1.40	1.80	3.85	3.21	?	3.43	?
-D-arabino-hexitol		884	308	396	847	706		755	
1,3-O-Butylidene-2-deoxy-	3.55[c]	3.97[c]	1.48[c]	1.64[c]	4.01[c]	4.94[c]	4.53[c]	4.53[c]	-
4,5-di-O-toluene-p-sulphonyl	781	875	327	361	883	1087	997	997	
-D-erythro-pentitol									
4,6-O-Butylidene-2-deoxy	3.20[c]	3.93[c]	3.58[c]	3.04[c]	3.84[c]	1.68[c]	1.54[c]	3.50[c]	3.50[c]
-D-arabino-hexitol	706	865	788	669	846	370	340	772	772
4,6-O-Butylidene-2-deoxy	3.73	3.90	3.55	3.25	3.72	1.80	1.30	3.55	3.55
-D-lyxo-hexitol	821	858	781	715	818	396	286	781	781
3,5-O-Butylidene-2-deoxy-	3.74[c]	4.45[c]	3.84[c]	3.98[c]	2.10[c]	2.71[c]	4.16[c]	4.16[c]	-
-D-erythro-pentitol	824	980	846	877	463	598	916	916	

Table V-10 ^{1}H Chemical Shifts (Hz and p.p.m.) of some Deoxy Polyol Acetals

(δ p.p.m. top row, Hz 2nd row)

The five acetals listed in the above table can be divided into two categories. The first category contains those acetals having a hydroxyl function in the ring, the second category contains acetals without a ring hydroxyl. These two categories give different types of spectra for the ring protons due to the presence or absence of one ring hydroxyl group. The hydroxyl functions do not contribute towards the ^1H n.m.r. spectra as they have been D_2O exchanged. It is proposed to discuss the ^1H n.m.r. spectra of a representative member of each category rather than a block discussion of all the above acetals' ^1H n.m.r. spectra.

(a) The ^1H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol (Hydroxyl in the Ring)

The 220 MHz ^1H n.m.r. spectrum of 3,5-O-butylidene-2-deoxy-D-erythro-pentitol in D.M.S.O. $(d^6)/D_2O$ is shown in Fig. V-39. There is considerable overlap of the resonances resulting in a second order spectrum. It was decided to try and utilise the anisotropic solvent induced shift effect[117] (A.S.I.S.) for some form of spectral simplification. In this technique the sample is dissolved in another solvent which has some form of anisotropic ring current (usually benzene or pyridine). The solvent/solute interaction then causes the resonances to move relative to their positions in a non anisotropic solvent. The direction and magnitude of the solvent shifts depend on the positions of the particular protons with respect to the anisotropic ring current. In this case the solvent tried was pyridine $(d^5)/D_2O$. The result is shown in Fig. V-40, the A.S.I.S. effect has separated the resonances enough to render interpretation possible.

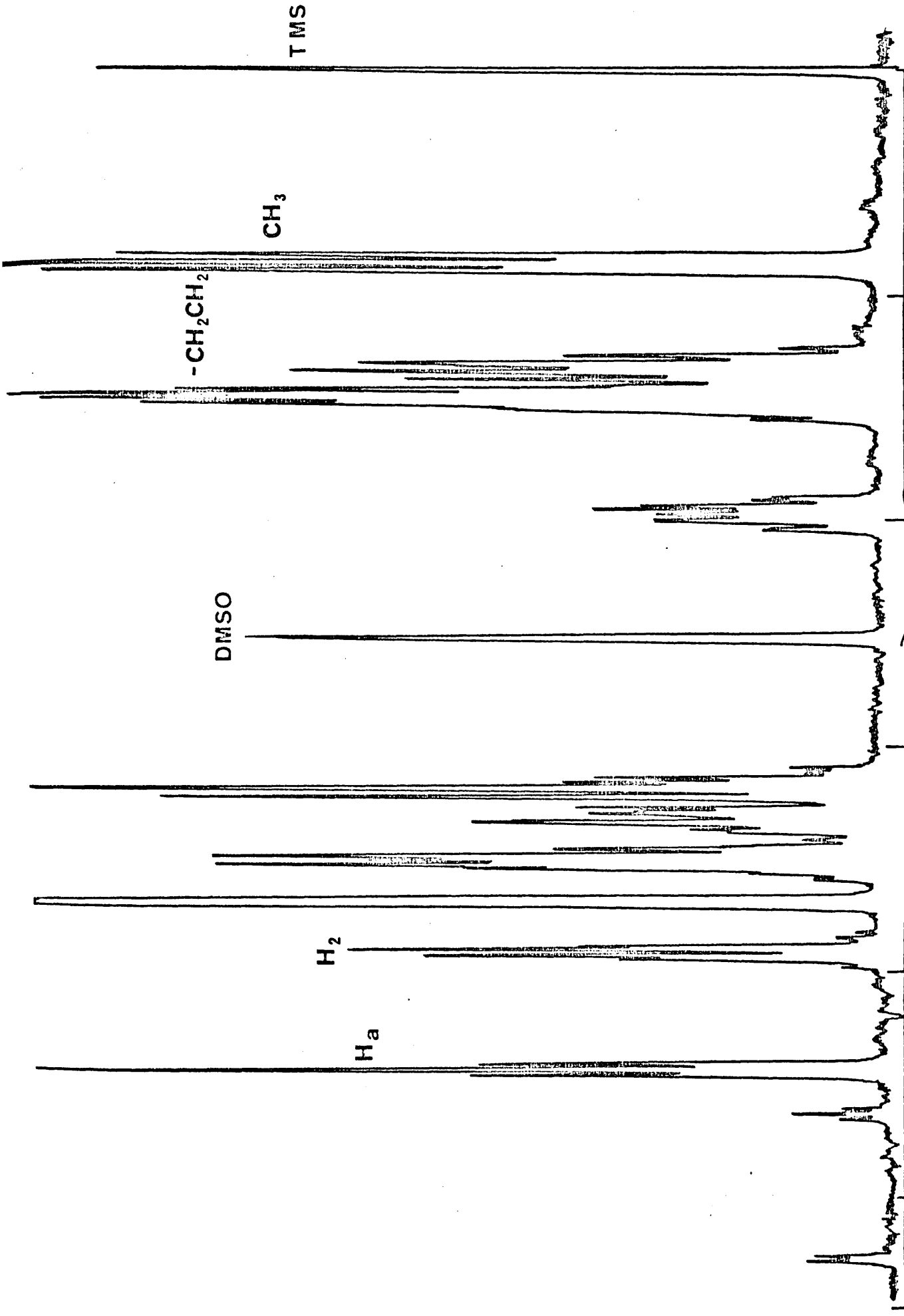


Fig. V-39 220 MHz ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol in D.M.S.O. (d^6)/D_2O.

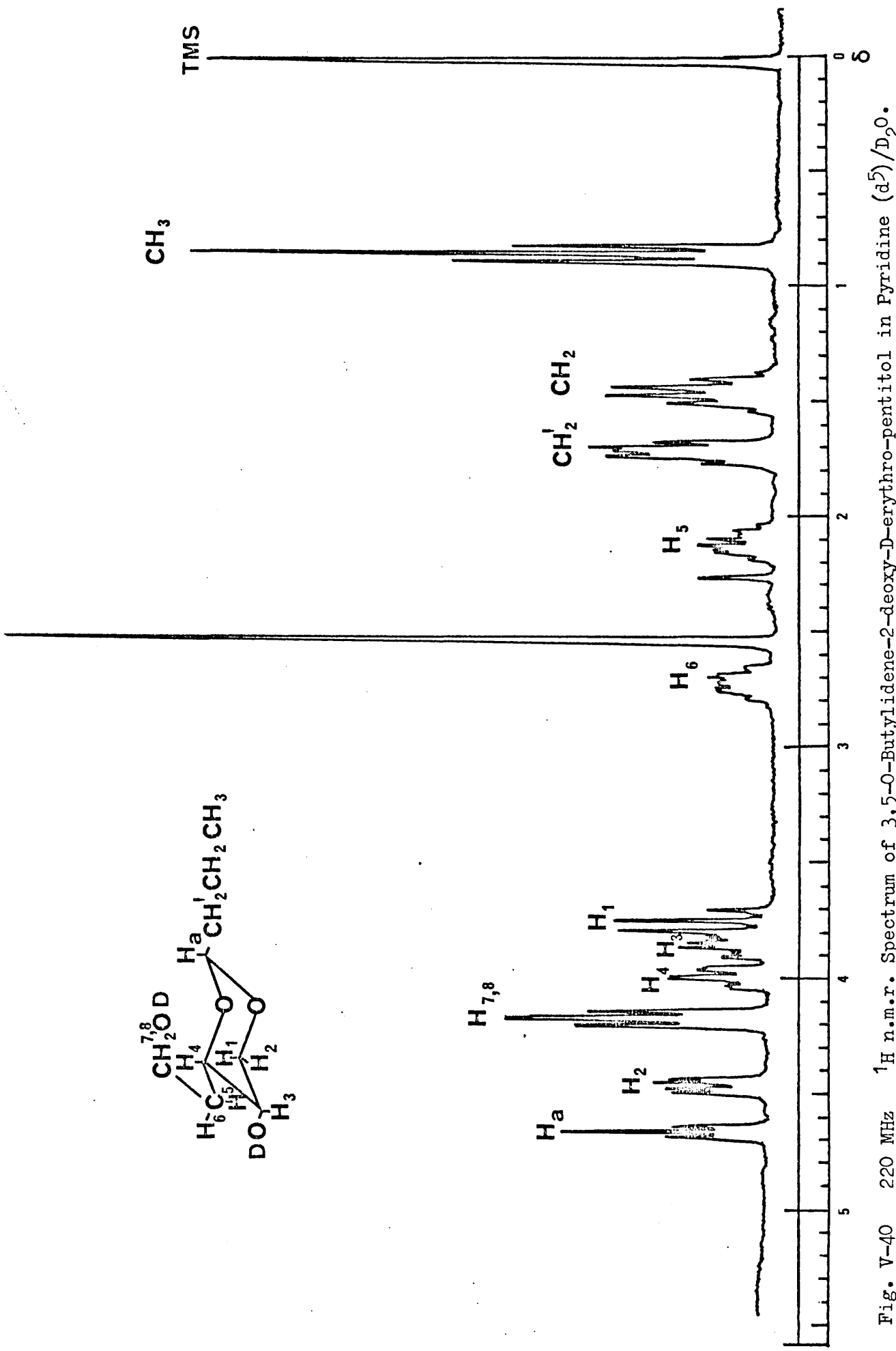


Fig. V-40 220 MHz ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol in Pyridine (d^5)/D_2O.

The low field part of the spectrum between 800 and 1050 Hz (3.61 to 4.77 δ) is shown with the relevant splitting patterns in Fig. V-41. The higher field part between 400 and 650 Hz (1.81 to 2.95 δ) with the relevant splitting patterns is illustrated in Fig. V-43. Considering the low field part first the lowest field signal is that of the acetal proton, its coupling constant and chemical shift value both being indicative of a six membered ring as outlined earlier. The adjacent signal which appears as a quartet centred at 980 Hz (4.45 δ) arises from H_2 of the acetal. Its low field position is because it is flanked by two electron lone pairs on the adjacent oxygen atom. The quartet structure arises from a large geminal coupling of -10.9 Hz to H_1, with a further vicinal axial/equatorial coupling of 5.1 Hz to H_3. The triplet signal centred at 824 Hz (3.74 δ) is due to H_1. The triplet appearance arises because H_1 has a vicinal axial/axial coupling to H_3 of similar magnitude (10.1 Hz) to its geminal coupling to H_2. This results in a set of coincident lines causing the theoretical four line spectrum to appear as a three line spectrum.

Having assigned the H_1 and H_2 signals let us now look at the proton on the adjacent carbon atom, namely H_3. The couplings of H_3 to H_1 and H_2 have been discussed above, there is one further pr oton coupling to H_3 however and that is H_4. The vicinal axial/axial coupling of H_4 to H_3 is 8.9 Hz. The resultant appearance of H_3 is a six line spectrum centred at 846 Hz (3.84 δ), the splitting pattern giving rise to the six lines is shown in Fig. V-41. Moving on now to H_4, apart from its vicinal axial/axial coupling to H_3 it has two further vicinal couplings to H_5 and H_6. The magnitude

of the H_4/H_5 coupling (8.9 Hz) is suggestive of a trans vicinal orientation of these two nuclei, whereas the H_4/H_6 vicinal coupling of 3.1 Hz suggests H_4 and H_6 to be gauche to one another. The H_4 n.m.r. spectrum consists of six lines centred at 877 Hz (3.98 δ) the origin of the six line spectrum is illustrated by the splitting pattern in Fig. V-41. This covers the ring protons, let us now look at the ^1H n.m.r. spectra of the protons in the side chain.

The pair of protons on the carbon directly attached to the acetal ring are H_5 and H_6 comprising the 2-deoxy function of the original polyol. Their respective couplings to H_4 of the ring were discussed above. There are however two further couplings to consider for each of these protons. They have a mutual geminal coupling of -14.2 Hz; H_5 has a vicinal coupling to the $H_{7,8}$ pair of protons of 5.0 Hz and H_6 has vicinal couplings to the $H_{7,8}$ protons of 5.0 and 11.0 Hz. Both H_5 and H_6 appear as complex multiplets in their n.m.r. spectra centred at 463 and 598 Hz (2.10 and 2.71 δ) respectively. These multiplets were resolved however to give the splitting patterns illustrated in Fig. V-43. The only remaining protons to assign are the $H_{7,8}$ protons of the $-CH_2OD$ function. Their vicinal couplings of 5.0 Hz to H_5 and 5.0 and 11.0 Hz to H_6 have been outlined above, these couplings give rise to the four line spectrum centred at 916 Hz (4.16 δ).

In order to check the accuracy of the above assignments the ^1H n.m.r. spectrum of 3,5-O-butylidene-2-deoxy-D-erythro-pentitol was calculated using the University of London CDC 6600 computer.

The input data of chemical shifts and coupling constants were taken directly from the experimental spectrum and used for a basic calculation. The results of the basic calculation were used for an iterative analysis, the appropriate spectral ranges showing the calculated ^1H n.m.r. spectrum are illustrated in Fig. V-42 (800 to 1050 Hz) and Fig. V-44 (400 to 650 Hz). Comparison of these calculated spectra with the experimental spectra shows marked similarities tending to give confidence about the spectral interpretation.

There are two sets of signals missing from the computed spectra however, namely H_a the acetal proton and the $H_{7,8}$ pair of protons. The program used to calculate the spectrum had a capacity of seven spin systems, i.e. seven magnetically unequivalent nuclei hence it was not possible to put in data for all the protons. As the acetal proton H_a was not coupled to any of the other protons shown in Figs. V-41 and 43 it was decided to exclude it from the calculation. As far as the $H_{7,8}$ pair of protons were concerned the program could not plot their spectrum at the same time as the remaining protons. This is an inherent feature of the program and plotting routine arising from multiplicity values, i.e. the $H_{7,8}$ pair of protons have a multiplicity value of 3 whereas all the other protons have a multiplicity value of 2, output only being available for one type of multiplicity at a time.

The ^1H n.m.r. data obtained from the acetal readily gives information regarding the conformation. The vicinal coupling constants suggest a chair form for the acetal ring in agreement with

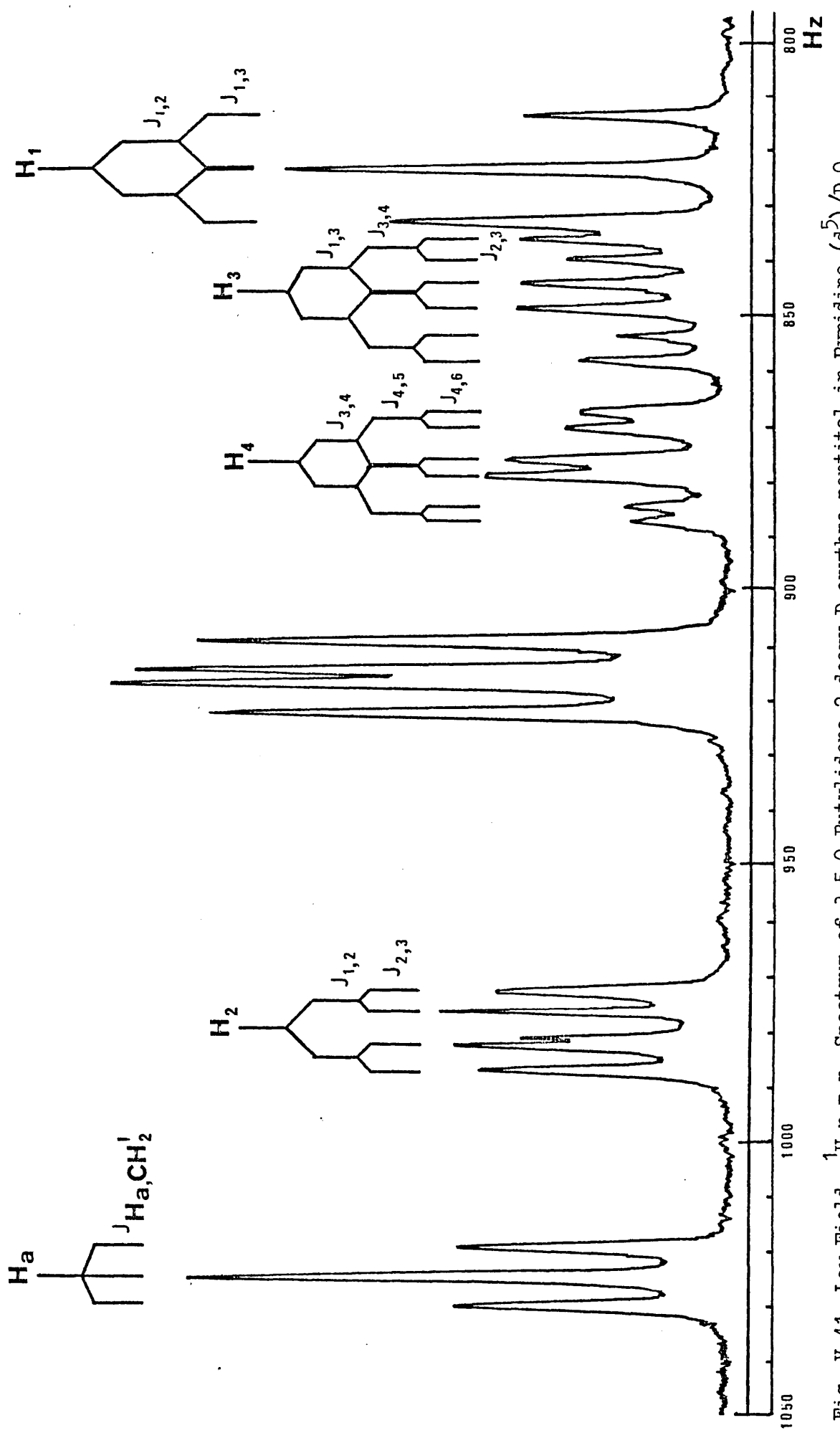


Fig. V-41 Low Field ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol in Pyridine (d^5)/D_2O.

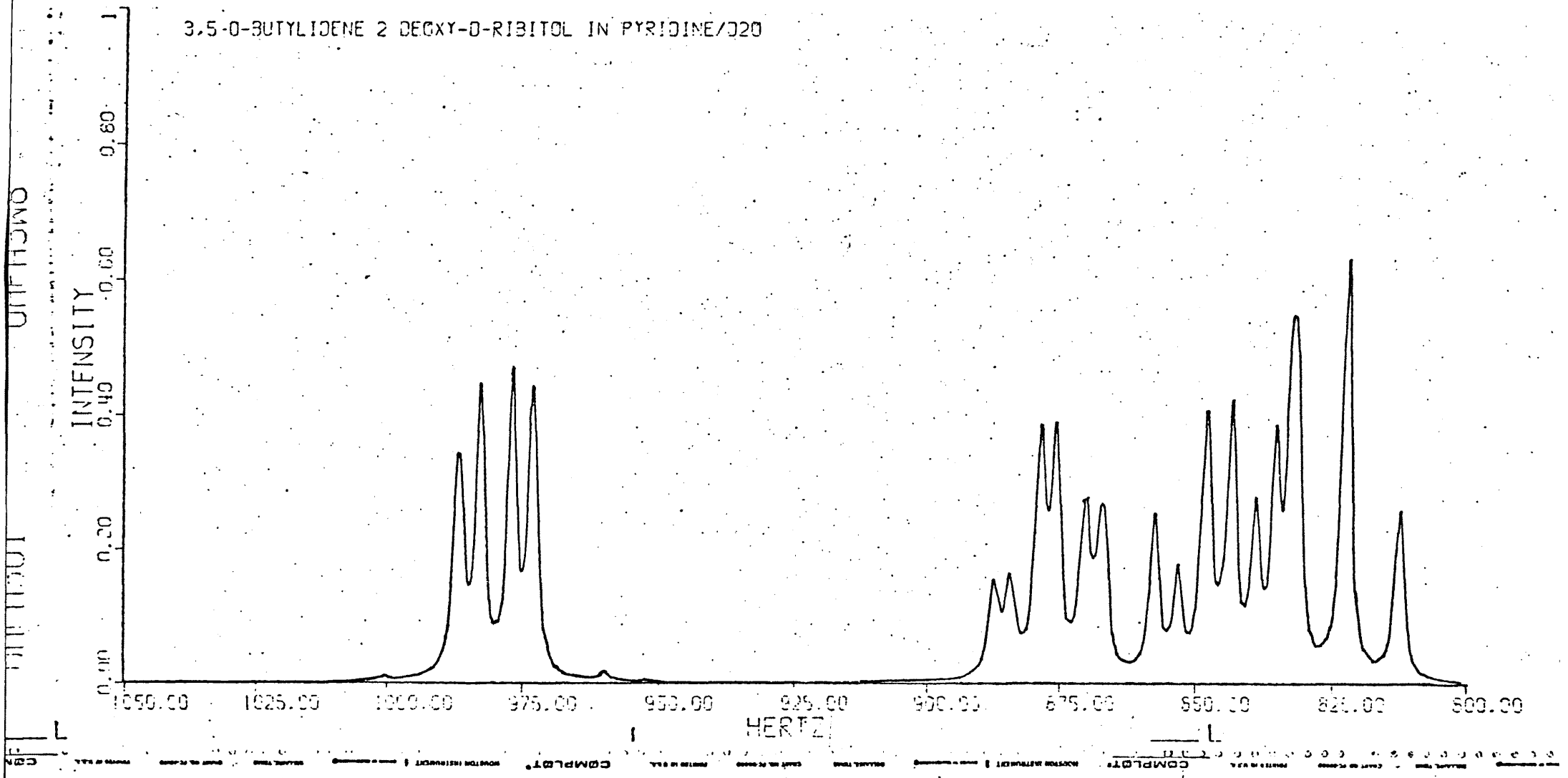


Fig. V-42 Computer Simulated ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol (800-1050 Hz)

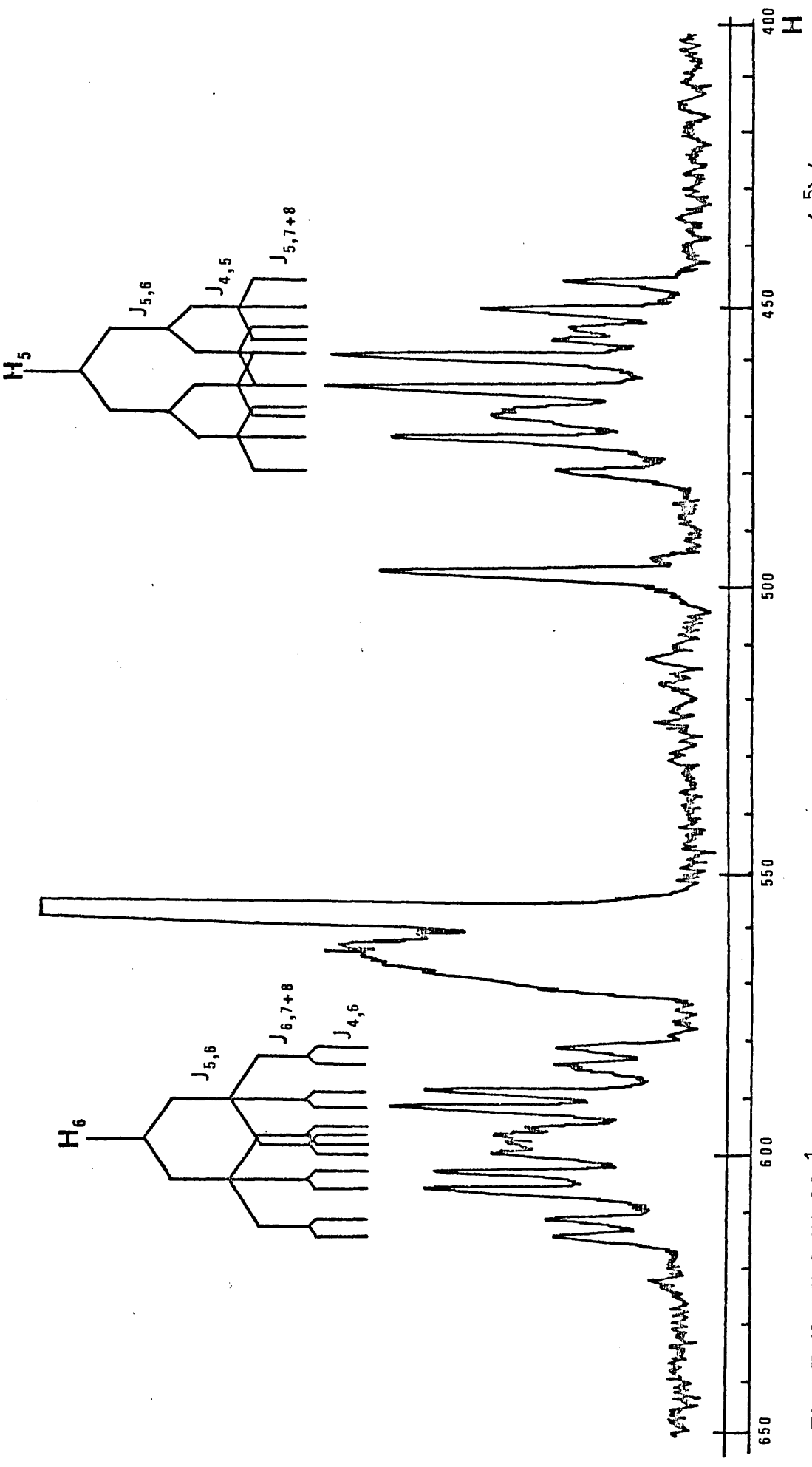


Fig. V-43 High Field ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol in Pyridine (d^5)/D_2O.

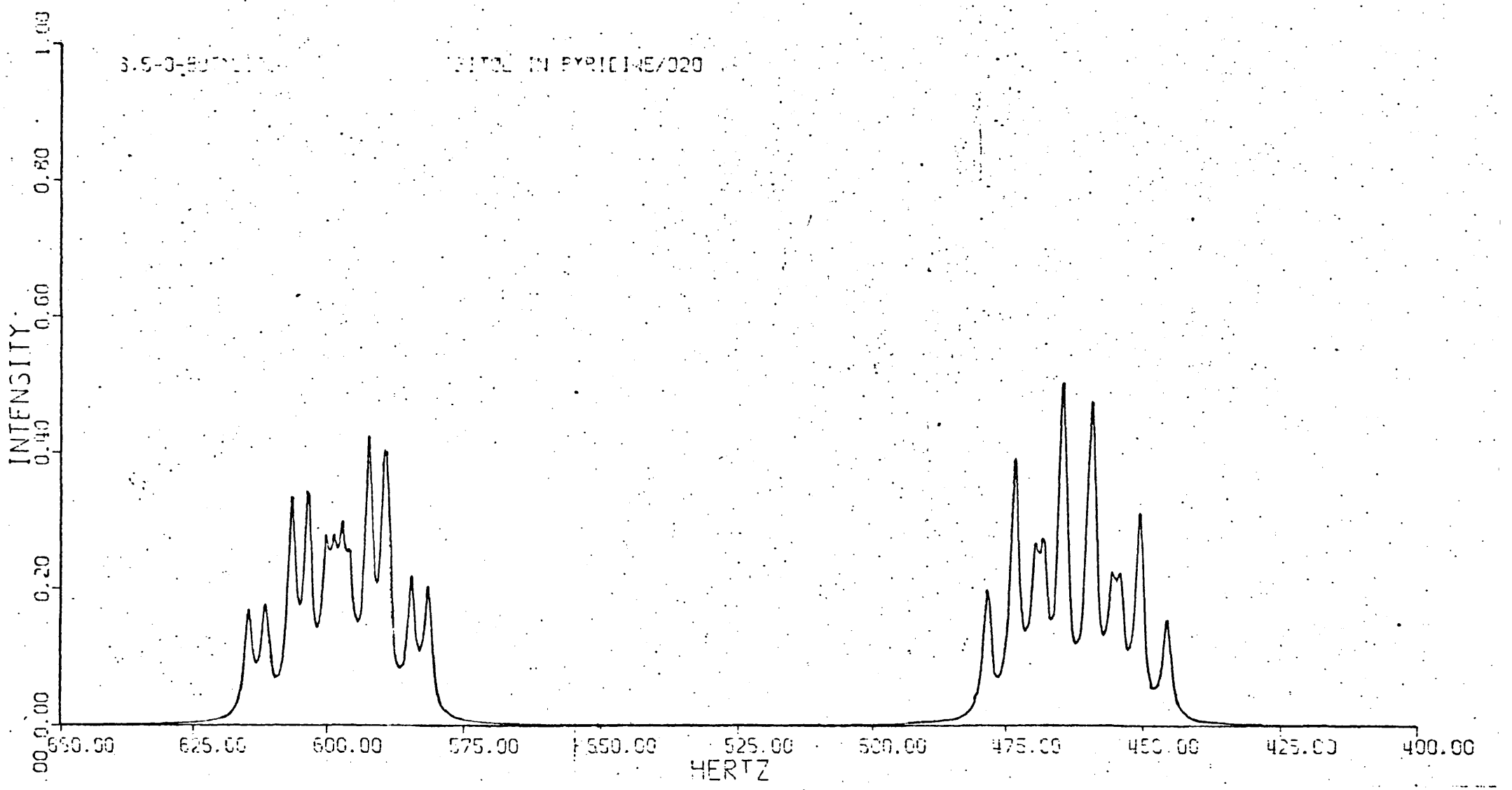


Fig. V-44 Computer Simulated ^{1}H n.m.r. Spectrum of 3,5-O-Butylidene-2-deoxy-D-erythro-pentitol(400-650 Hz)

data found by many other workers for 1,3-dioxane systems.[35] The vicinal coupling constants of the protons in the $-CH_2-CH_2OD$ side chain indicate that this side chain is part of a continuous planar zig-zag, the remainder of which is comprised of the three consecutive ring carbons. That is to say the expected planar zig-zag conformation of the carbon chain of the deoxy polyol is not altered upon cyclic acetal formation across the 3 and 5 hydroxyl functions.

For the remaining two acetals in the present category (having a ring hydroxyl) it was possible to fully interpret and computer simulate the ^1H n.m.r. spectrum for 4,6-O-butylidene-2-deoxy-D-arabino-hexitol only. The coupling constant data shown in table V-9 are consistent with a chair form for the 1,3-dioxane ring part of this acetal, and a planar zig-zag conformation for the $-CHOD-CH_2-CH_2OD$ chain and the three consecutive ring carbons. The experimental spectrum for the molecule is shown in Fig. V-45. The remaining member of this category 4,6-O-butylidene-2-deoxy-D-lyxo-hexitol has ^1H n.m.r. spectral features consistent with its structure but it proved impossible to fully interpret its spectra.

(b) The ^1H n.m.r. Spectrum of 1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol (no Ring Hydroxyl)

The low field part of the ^1H n.m.r. spectrum of the acetal between 3.06 and 5.34 δ (675 to 1175 Hz) is illustrated in Fig. V-46 with the relevant splitting patterns. The appearance of the resonances of the ring protons is similar to those acetals having a

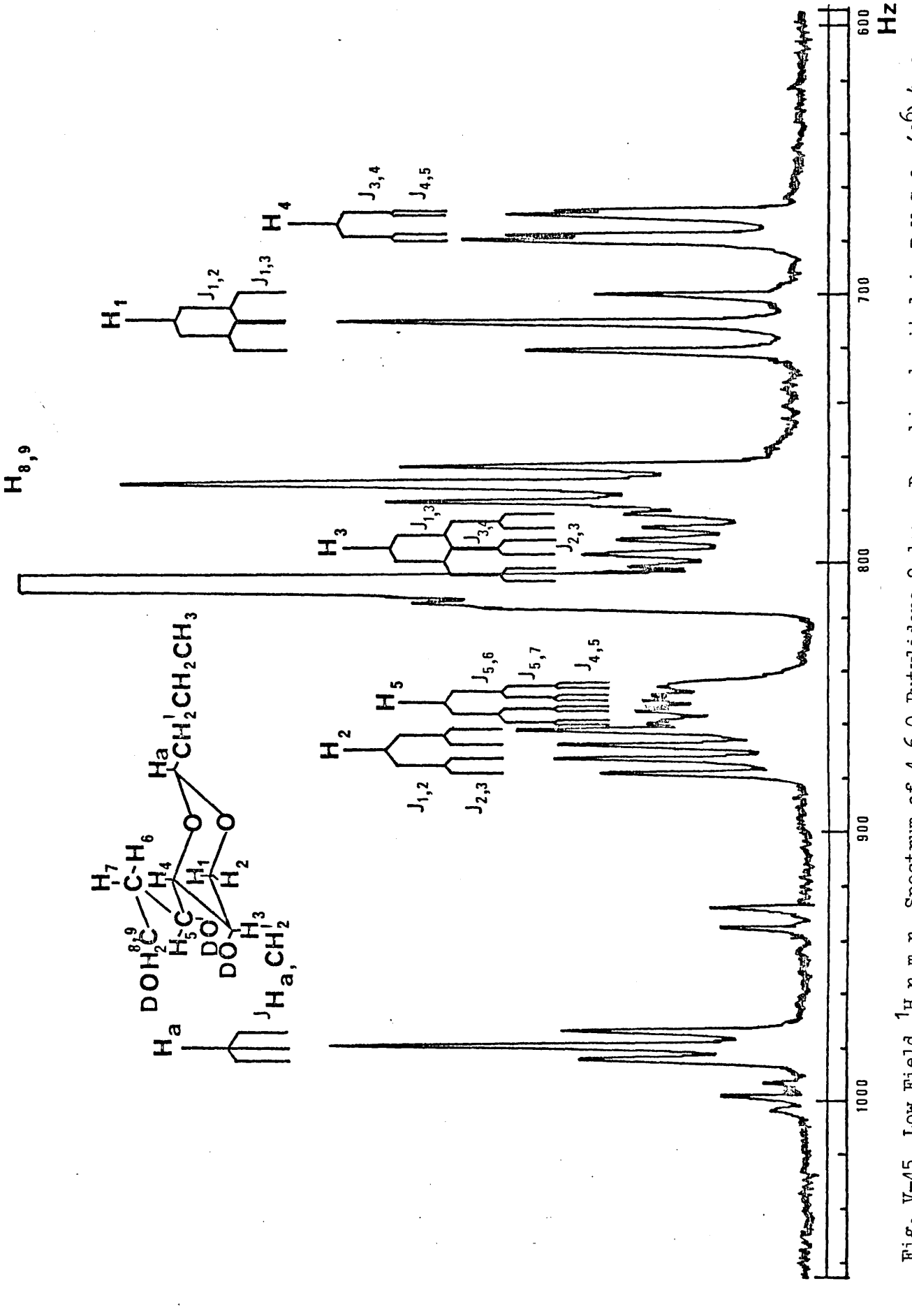


Fig. V-45 Low Field ^{1}H n.m.r. Spectrum of 4,6-O-Butylidene-2-deoxy-D-arabino-hexitol in D.M.S.O. $(d^6)/D_2O$.

ring hydroxyl. One difference is that the ring protons apart from the acetal proton contain an additional coupling to the proton H_3 which has replaced the ring hydroxyl. For example H_1 appears as a six line signal centred 781 Hz (3.55 δ) whereas previously it was a three line signal. The additional signals are caused by vicinal axial/equatorial coupling between H_1 and H_3. The remaining couplings in the H_1 signal are a geminal coupling of -11.6 Hz to H_2 and a vicinal axial/axial coupling of 12.7 Hz to H_4. The similar magnitude of the geminal and axial/axial couplings causes coincidences in the distribution of the lines as described previously for H_1.

The resonances arising from H_2 are partially obscured by those of H_5. The geminal coupling between H_2 and H_1 is known however and the vicinal axial/equatorial coupling between H_4 and H_2 (5.1 Hz) can be found in the resonances arising from H_4 at higher field (Fig. V-47). The only coupling of H_2 which is not directly observable in the spectrum is to H_3. This is a vicinal equatorial/equatorial coupling and as such is expected to be small, in the region of 0.6 - 3.5 Hz.[92] In order to obtain a value for this coupling constant a guess was made at it and the spectrum computer simulated. It proved possible to simulate the experimental spectrum using a value of 1.75 Hz for $^3J_{2,3}$ with a chemical shift centred at 875 Hz (3.97 δ).

Looking now at the adjacent carbon atom one sees the absence of an oxygen substituent, this results in a shielding of the appended

protons. Fig. V-47 shows the high field portion of the spectrum between 250 and 400 Hz (1.13 and 1.82 δ). Unfortunately the resonances from H_3 and H_4 have some overlap with the methylene functions of the propyl chain, resulting in H_3 being obscured. However H_4 is still visible as it is the lower field resonance of the two. This lower field position of H_4 at 361 Hz (1.64 δ) relative to H_3 is to be expected as H_4 is the axial proton and is deshielded by the electron lone pairs of the ring oxygens. The H_4 resonance constitutes eight observed lines, these lines arise through the previously described H_1/H_4 vicinal axial/axial coupling and the H_2/H_4 vicinal axial/equatorial coupling, together with a further vicinal axial/axial coupling to H_5 (12.2 Hz) and a geminal coupling (-12.0 Hz) to H_3. The splitting pattern for the H_4 proton is shown in Fig. V-47. The values for the H_4/H_5 and H_3/H_4 coupling constants were obtained by making a guess at their size then computer simulation of the spectrum until a good fit with the experimental spectrum was obtained. It proved impossible to illustrate any splitting pattern for H_3 as it is totally obscured by the methylene protons of the propyl side chain.

The remaining proton of the acetal ring is H_5. Its vicinal axial/axial coupling to H_4 has been described, it also has a vicinal axial/equatorial coupling of 2.8 Hz to H_3 and a vicinal coupling of 6.8 Hz to H_6. The H_5 resonances are overlapping with another set of resonances (H_2) so the coupling values just mentioned were obtained by trial and error computation of the spectrum until a reasonable fit with the experimental spectrum was obtained. For a reasonable fit a chemical shift of 883 Hz (4.01 δ) was needed for H_5.

The remaining protons of the acetal to discuss are H_6 and the pair of $H_{7,8}$ protons, both being on the side chain bearing O-tosyl functions. These protons constitute an ABX spin system, $H_{7,8}$ being the AB part. However the spectrum of the $H_{7,8}$ protons appears as a doublet and not the eight lines expected from the AB part of a true ABX system. This is the case of a deceptively simple ABX spectrum where the AB part appears as an A_2 system. This occurs when the chemical shift difference between the AB protons is very small and the expression L/J_{AB} tends towards zero $[L = \frac{1}{2}(J_{AX} - J_{BX})]$, conditions which are presumably fulfilled here.[118] In this deceptively simple case the spacing between the $H_{7,8}$ doublet is the sum of the $J_{6,7}$, $J_{6,8}$ couplings, the geminal coupling is not observed in the spectrum. The X part of the deceptively simple ABX spectrum appears a a triplet and not the four line signal predicted for it. The spectrum of the H_6, $H_{7,8}$ protons is thus appearing as an A_2X system whereas its correct classification is as an ABX system. A vicinal coupling of 6.8 Hz is observed between H_6 and H_5, and a coupling of 3.7 Hz is observed for $J_{6,7} + J_{6,8}$. These couplings result in the five line spectrum of H_6 centred at 1087 Hz (4.94 δ) (Fig. V-46) and the doublet $H_{7,8}$ spectrum centred at 997 Hz (4.53 δ). As has been indicated in the discussion of the experimental spectrum of the acetal it proved possible to calculate the spectrum by computer. The low field and high field computed spectra are shown in Fig. V-48. Taking the lower field portion first, the acetal proton triplet at 968 Hz (4.4 δ) is absent along with the $H_{7,8}$ doublet at 997 Hz (4.53 δ). This is due to the same reasons given before, i.e. the acetal proton

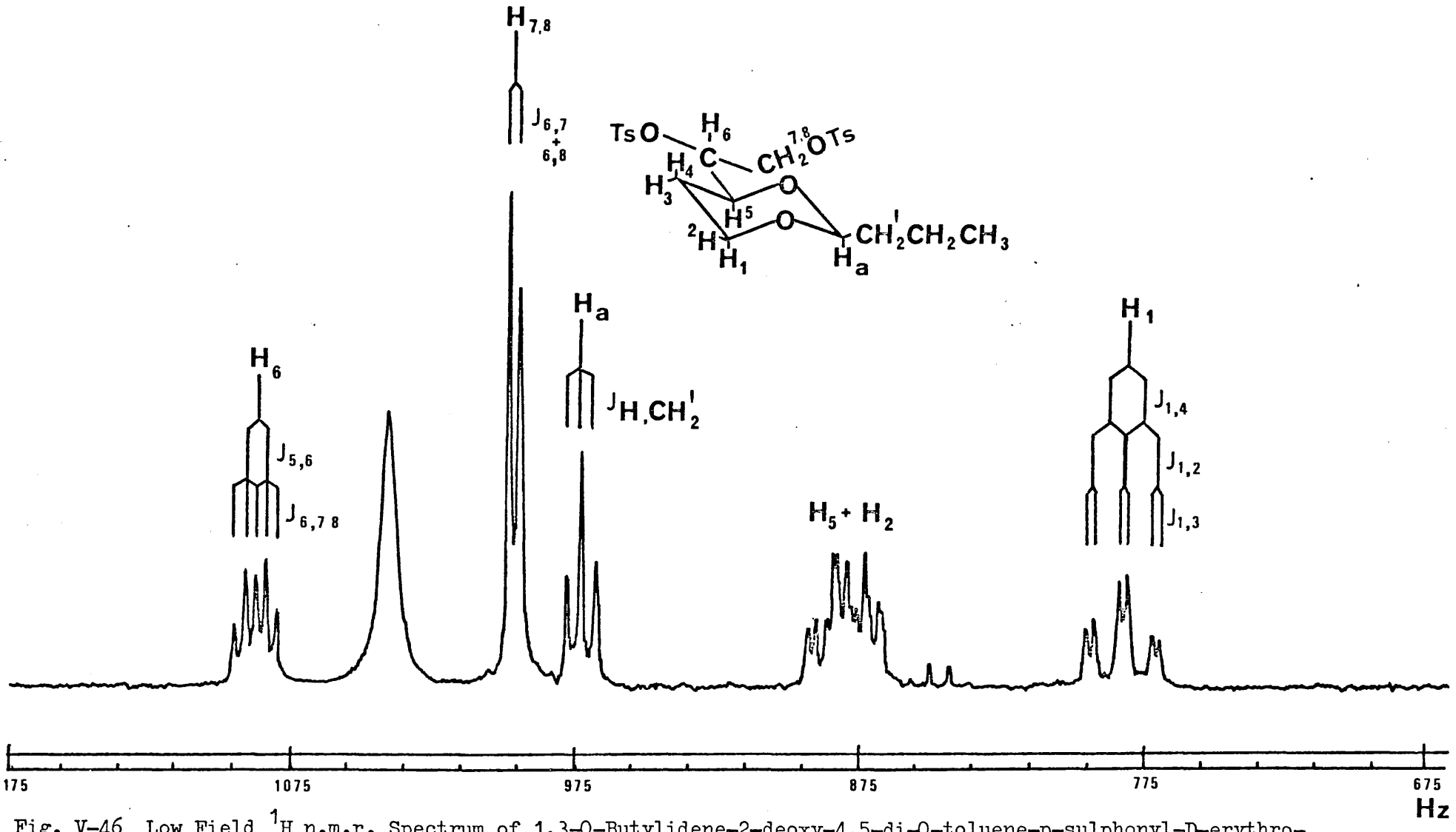


Fig. V-46 Low Field ^{1}H n.m.r. Spectrum of 1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol in Pyridine (d^5).

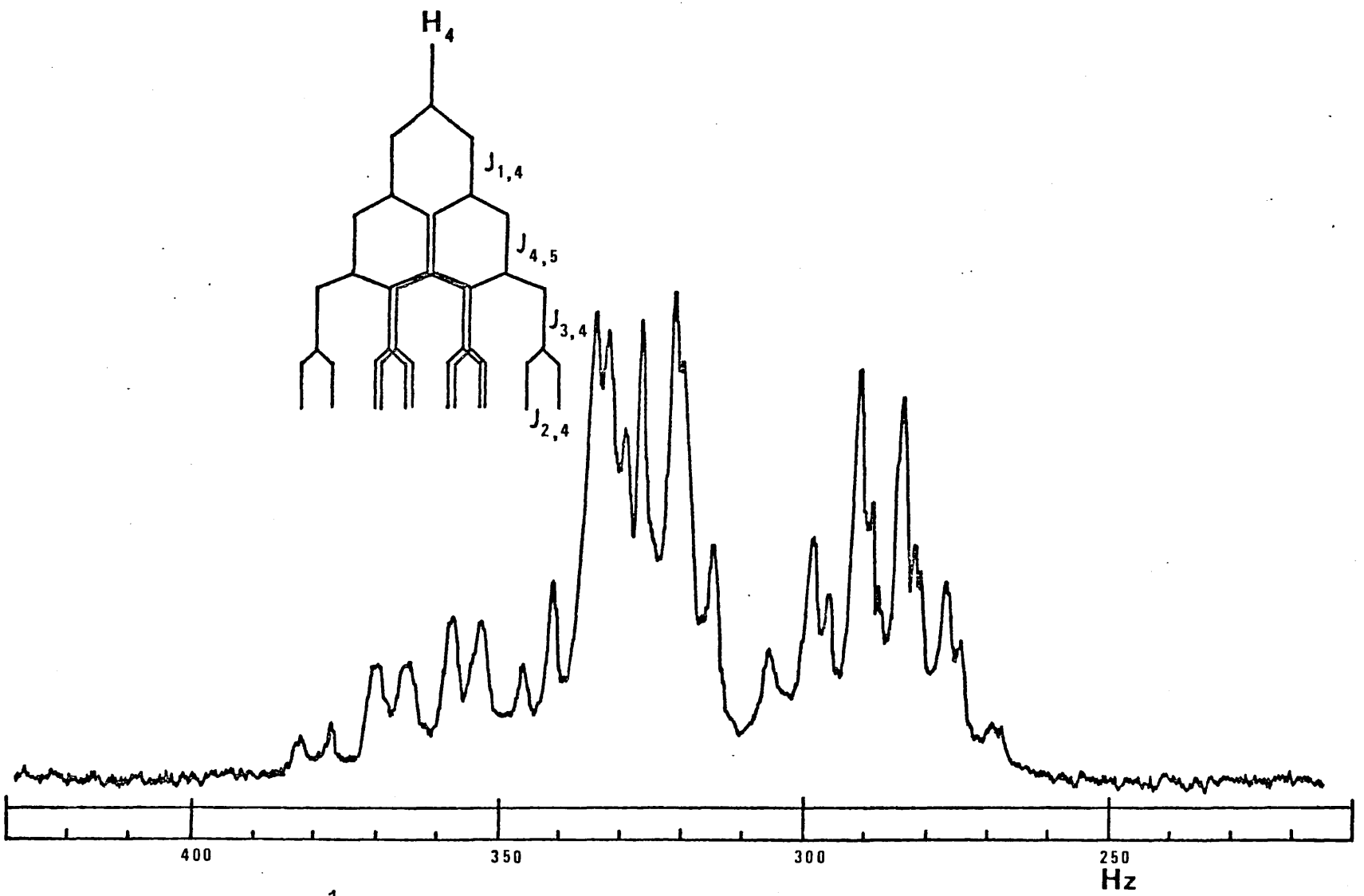


Fig. V-47 High Field ^{1}H n.m.r. Spectrum of 1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol in Pyridine (d^{5}).

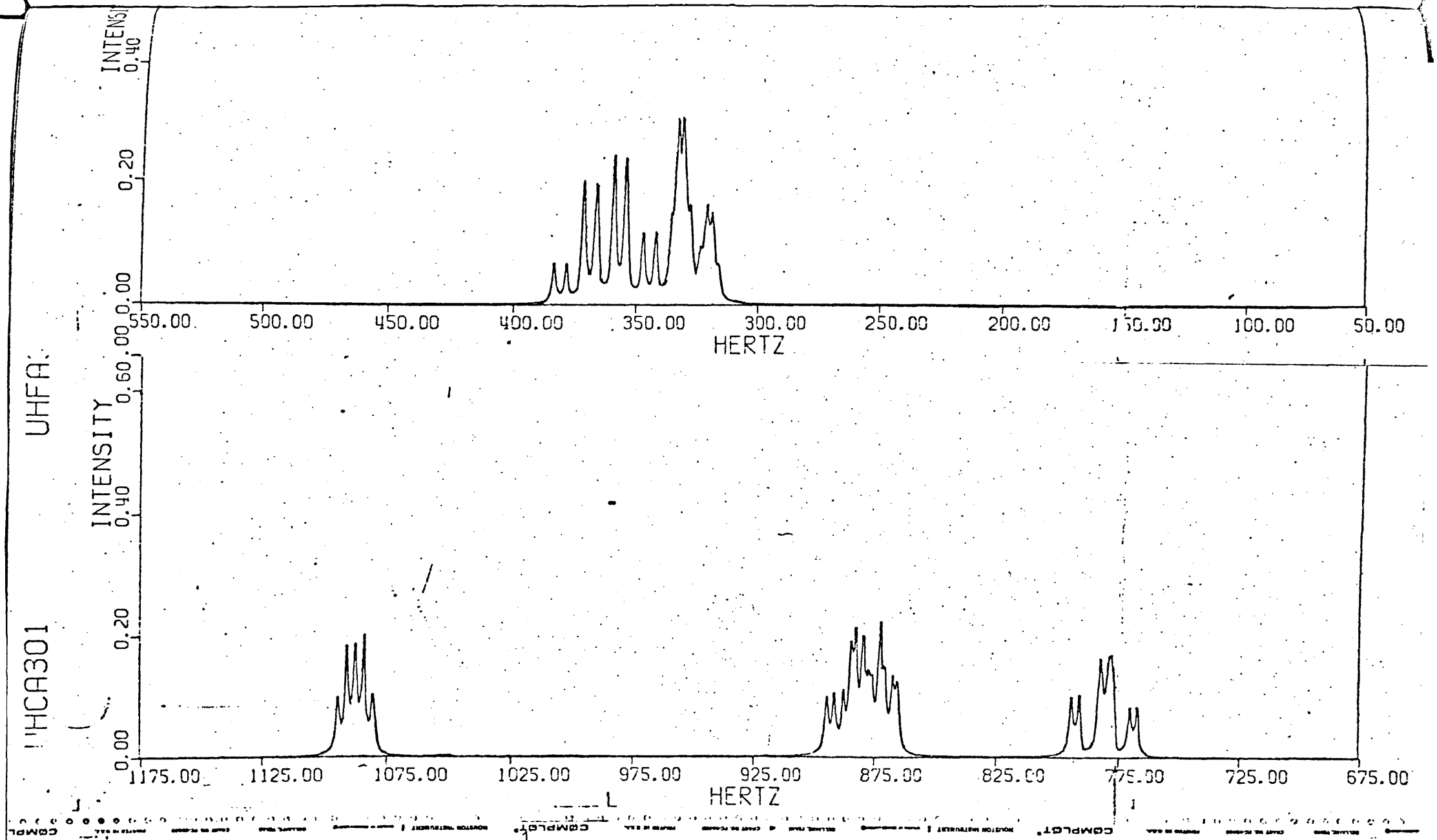


Fig. V-48 Computer Simulated H n.m.r. Spectra of 1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol (50-550 Hz, 675-1175 Hz).

is left out because it would exceed the capacity of the computer program to include it and the $H_{7,8}$ signal is not plotted for multiplicity reasons. The rather broad signal adjacent to the $H_{7,8}$ signal in the experimental spectrum is absent from the computed spectrum as it is a solvent impurity. The higher field part of the computed spectrum shows the H_3 and H_4 resonances. The accuracy of the H_3 resonances cannot be checked as they are obscured in the experimental spectrum, the H_4 resonances however show reasonable compatability to the experimental spectrum as do those other resonances computed in the lower field part.

The coupling constant data again indicate a chair form for the 1,3-dioxane ring part of the molecule. The side chain containing the H_6 and $H_{7,8}$ protons appears to be part of a planar zig-zag chain with the three adjacent ring carbons. This information also coming from coupling constant values. Thus for both categories of acetal studied the conformation is the same, this conformation can hopefully be extended to the remaining acetals where a full analysis was not possible.

(iii) Miscellaneous ^{1}H n.m.r. Spectral Features of the Acetals

This small section is devoted to any small points of interest whereby ^{1}H n.m.r. spectroscopy can be utilised for structure elucidation. The first application arises from the ^{1}H n.m.r. spectrum of 1,3-O-butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol. It may be recalled that H_4 was the axial proton

in the 1,3-dioxane ring system with an eight line ^1H n.m.r. spectrum. Now the other 1,3-acetals of the remaining 2-deoxy polyols also have exactly the same ring proton system as the above mentioned acetal so should exhibit similar ^1H n.m.r. spectral features. For these other acetals however there was some difficulty in spectral interpretations. But, the 1,3-acetal of 2-deoxy-D-arabino-hexitol shows an eight line set of resonances with correct chemical shift for the H_4 type of proton. The same type of proton signal was not observable for 1,3-O-butylidene-2-deoxy-D-lyxo-hexitol as it was obscured under the propyl chain signals. Provided this type of signal is separated enough from other resonances to be visible then strong evidence is obtained for the type of ring shown below (Fig. V-49).

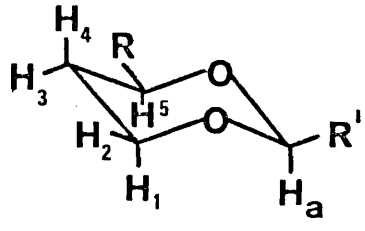
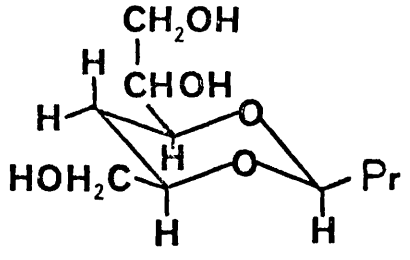


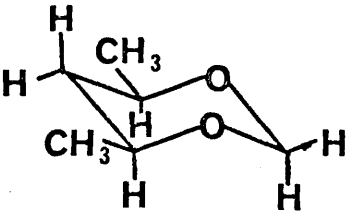
Fig. V-49

The second of these miscellaneous examples incorporates the substituent effect of cis equatorial methyl groups at C-4 and C-6 of 1,3-dioxane derivatives. It may be recalled that substituents of this type can cause reversal of the axial/equatorial chemical

shifts of the C-5 protons of a 1,3-dioxane derivative. The high field ^{1}H n.m.r. spectrum of 2,4-O-butylidene-3-deoxy-D-ribo-hexitol in pyridine (d^5)/D_2O (Fig. V-50) showed what appeared to be a reversal of the axial/equatorial proton chemical shifts, i.e. the axial proton is to higher field than the equatorial proton. If one looks at the structures of this acetal (Fig. V-51I) and cis-dimethyl-1,3-dioxane (Fi.g V-51II) one sees very similar ring structures.



I



II

Fig. V-51

The $-CH_2OH$ and $-CHOHCH_2OH$ substituents are acting in a similar manner as the methyl substituents by causing a reversal of the axial/equatorial proton chemical shifts. This is helpful for structure elucidation as it only happens for the types of acetals shown above. The axial/equatorial protons in Fig. V-50 were distinguished on the basis of their coupling constant values.

Finally certain features of the ^{1}H n.m.r. spectrum (Fig. V-53) of 2,6-anhydro-1,3-O-butylidene-D-galactitol (Fig. V-52)

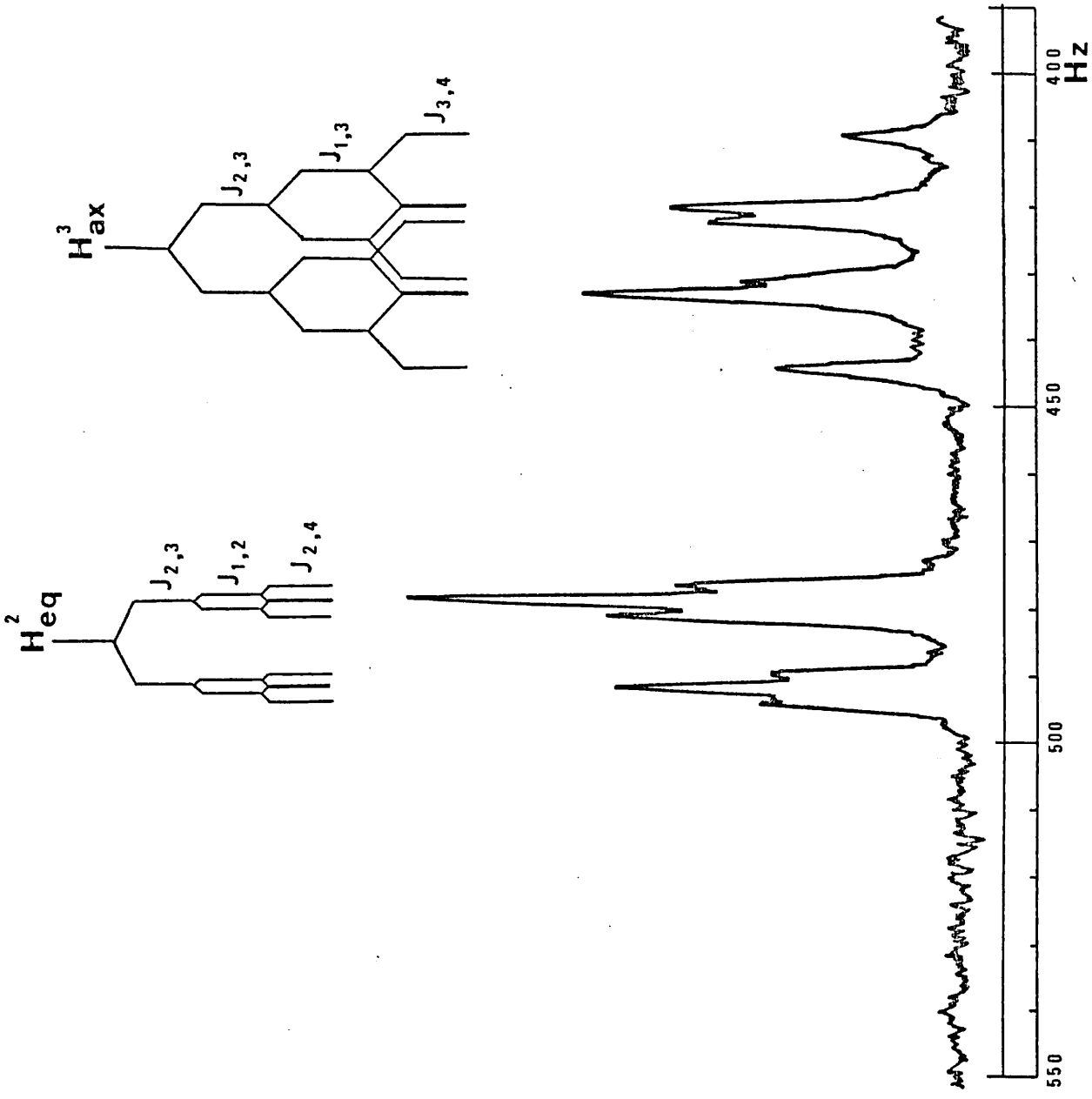


Fig. V-50 High Field ^1H n.m.r. Spectrum of 2,4-O-Butylidene-3-deoxy-D-ribo-hexitol in Pyridine (d^5)/D_2O.

consistent with its structure will be discussed. The acetal proton triplet is centred at 4.52 δ with a coupling of 5.0 Hz to the methylene group of the propyl chain. Both facts are consistent with a six membered acetal ring. Also, there is a triplet resonance centred at 656 Hz (2.98 δ) very similar in appearance to the triplet signal found for H_1 of 3,5-O-butylidene-2-deoxy-D-erythro-pentitol. This would suggest it to be actually a four line signal with coincident lines. If the triplet is analysed as a four line signal then the two couplings causing the splitting are approximately 10.5 Hz each. Examination of the structure of the anhydro acetal (Fig. V-52) shows a possible contender for this proton is H_4.

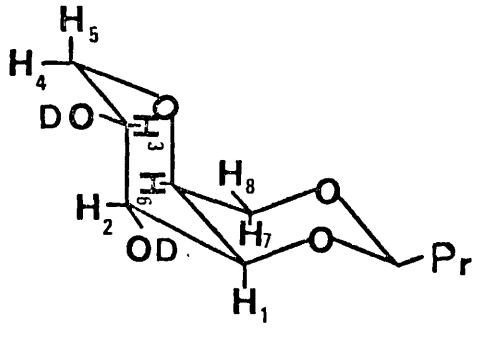


Fig. V-52

It has a geminal coupling to H_5 and a vicinal axial/axial coupling to H_3, the magnitude for both couplings will be of the order predicted above. The H_3 proton has a vicinal axial/axial coupling

to H_2 as well as H_4, it also has a vicinal axial/equatorial coupling to H_5. A proton with such an environment was H_3 in 3,5-O-butylidene-2-deoxy-D-erythro-pentitol, in that case it had a six line ^1H n.m.r. spectrum as shown in Fig. V-41. The ^1H n.m.r. spectrum of the anhydro acetal shows an almost identical sextet spectrum centred at 785 Hz (3.57 δ).

Although the two spectral features mentioned above do not conclusively prove the structure of the molecule they contribute to that evidence previously discussed in the ^{13}C n.m.r. section. It is worth noting that the acetal ring protons of the molecule cannot possibly give rise to such spectral features whereas those of the anhydro ring can.

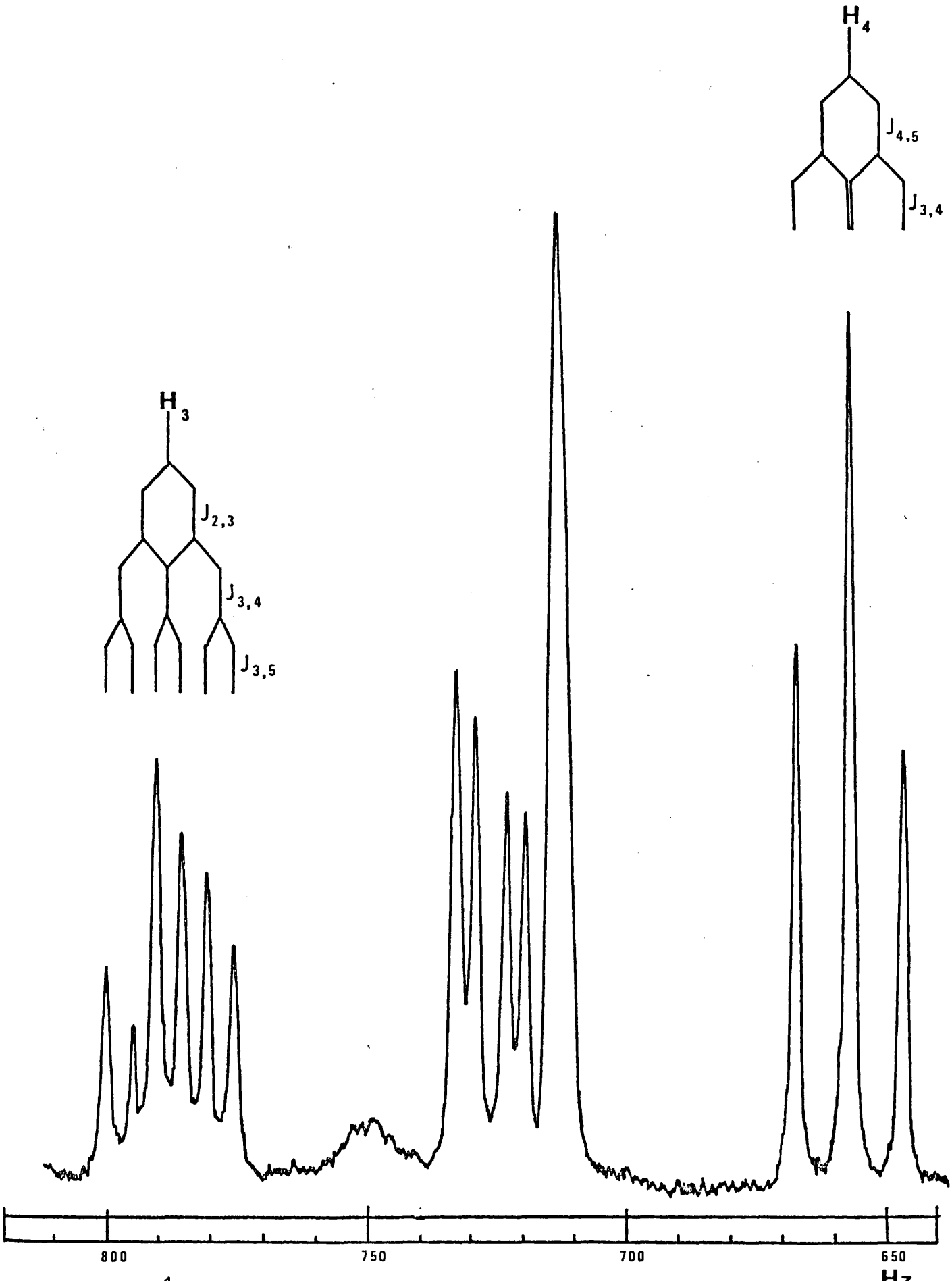


Fig. V-53 ^{1}H n.m.r. Spectrum (650–800 Hz) of 2,6-Anhydro-1,3-O-butylidene-D-galactitol.

V-C Fluorine (^{19}F) n.m.r. Spectroscopy of the Fluoro Polyols and their Butylidene Acetals

1. Introduction

In this section the ^{19}F chemical shifts and $^{19}F-^{1}H$ coupling constants of the two fluoro polyols and their acetals are discussed. It is shown that utilisation of these two parameters gives reasonable insight into the conformation of these compounds. Prior to the results and discussion section some relevant aspects of ^{19}F n.m.r. spectroscopy are introduced.

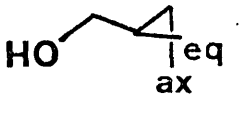
All the ^{19}F chemical shifts discussed are relative to trichlorofluoromethane ($CFCl_3$), i.e. the ϕ scale. It has been found that the chemical shift of the fluorine atom is dependent upon its environment. The ^{19}F nucleus in a $-CH_2F$ function has a shift range of 213-235 ϕ whereas the ^{19}F shift range for a -CHF- function is 193-208 ϕ .[119] For deoxy fluoro carbohydrates the ^{19}F chemical shifts within a particular range are affected by the orientation of certain types of bonds and substituent atoms to the fluorine atoms.[120]

Slightly more useful as far as conformational work is concerned are those studies dealing with $^{19}F-^{1}H$ coupling constants, particularly vicinal coupling constants. It has been shown that the magnitude of vicinal $^{19}F-^{1}H$ coupling constants ($^{3}J_{FH}$) varies with the dihedral angle between the coupled nuclei in a similar manner to the Karplus relationship for $^{1}H-^{1}H$ couplings.[121] This observation has been tested and verified for a wide range of derivatives, notably

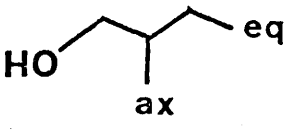
deoxy fluoro carbohydrates.[122-124] Phillips and Wray[120] have examined $^{3}J_{FH}$ values for several fluorinated carbohydrates and interpreted these couplings in terms of stereospecific electronegative effects. They found that $^{3}J_{FH}$ values could be calculated by addition or subtraction of appropriate substituent effects to an unperturbed vicinal coupling constant value. They took values of 43.5 Hz and 16.0 Hz as unperturbed $^{3}J_{FH}$ values for trans and gauche environments respectively of the coupled nuclei.

The trans situation is quite straightforward, for each oxygen substituent on the coupling fragment approximately 10 Hz is subtracted from the unperturbed value. The gauche situation is more complex, the contributions to be considered with the unperturbed value are as outlined below.

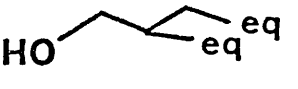
(i)	Oxygen substituent	-2.5 Hz
(ii)	Ring oxygen or OH trans to F via the C-C bond	-7.0 Hz
(iii)	OH trans to C-C in the sense (X) or (Z)	-2.0 Hz
	OH trans to C-C in the sense (Y)	+2.0 Hz



(X)



(Y)



(Z)

By application of these substituent effects Phillips and Wray[120] were able to rationalize the $^{3}J_{FH}$ values found in a wide range of deoxy fluoro carbohydrates.

Phillips and Wray have also looked at geminal $^{19}F-^{1}H$ couplings ($^{2}J_{FH}$), and in a similar manner as above formulated substituent increments enabling $^{2}J_{FH}$ values to be calculated.[125] The unperturbed $^{2}J_{FH}$ value was given as 50 Hz then the following increments were given.

(i) Replacement of C α to the C bearing H and F by O. +1Hz

(ii) Substituent effects for X = (OH,OR) groups vicinal to H,F

F axial	X	equatorial	+1Hz
F equatorial	X	equatorial	
F axial	O	in ring	
F equatorial	X	axial	-2Hz
F axial	X	axial	
F equatorial	O	in ring	

Again, the substituent effects were valid for a wide range of fluorinated carbohydrates.

Apart from the above discussed methods for calculation of $^{19}F-^{1}H$ coupling constants further studies relevant to this section are those dealing with the ^{19}F n.m.r. spectral parameters of 5-fluoro-1,3-dioxane[126,127] (Fig. V-54). This compound has a similar structure to one of the butylidene acetals discussed later.

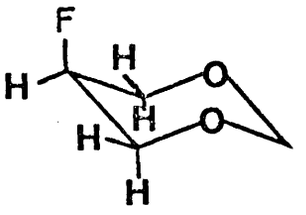


Fig. V-54

Both studies independently came to the conclusion that the fluorine atom prefers an axial position in the dioxane ring. The $^{2}J_{FH}$ value was found to be approximately 47 Hz, the trans $^{3}J_{FH}$ values ranged from 32-37 Hz and the gauche $^{3}J_{FH}$ values ranged from 12-17 Hz.

2. Results and Discussion

(i) 3-Deoxy-3-fluoro-D-glucitol and its 2,4-O-Butylidene Acetal

The ^{19}F n.m.r. spectrum of 3-deoxy-3-fluoro-D-glucitol in D_2O is shown in Fig. V-55. The conformation of the polyol was previously elucidated in section V-A using ^{13}C n.m.r. spectroscopy. The conformation was shown to be a "sickle" as illustrated in Fig. V-15I. The ^{19}F n.m.r. spectral parameters of the polyol are also consistent with this conformation.

The chemical shift of the ^{19}F nucleus is 212.9 ϕ , a value quite close to the previously described range for a -CHF- function. The $^{19}F-^{1}H$ coupling constant data are much more indicative of conformation however. First of all the trans vicinal coupling of F on C-3 with H on C-4 (see Fig. V-15I or Fig. V-55) can be calculated using Phillips and Wray's[120] work on $^{3}J_{FH}$ values in deoxy fluoro

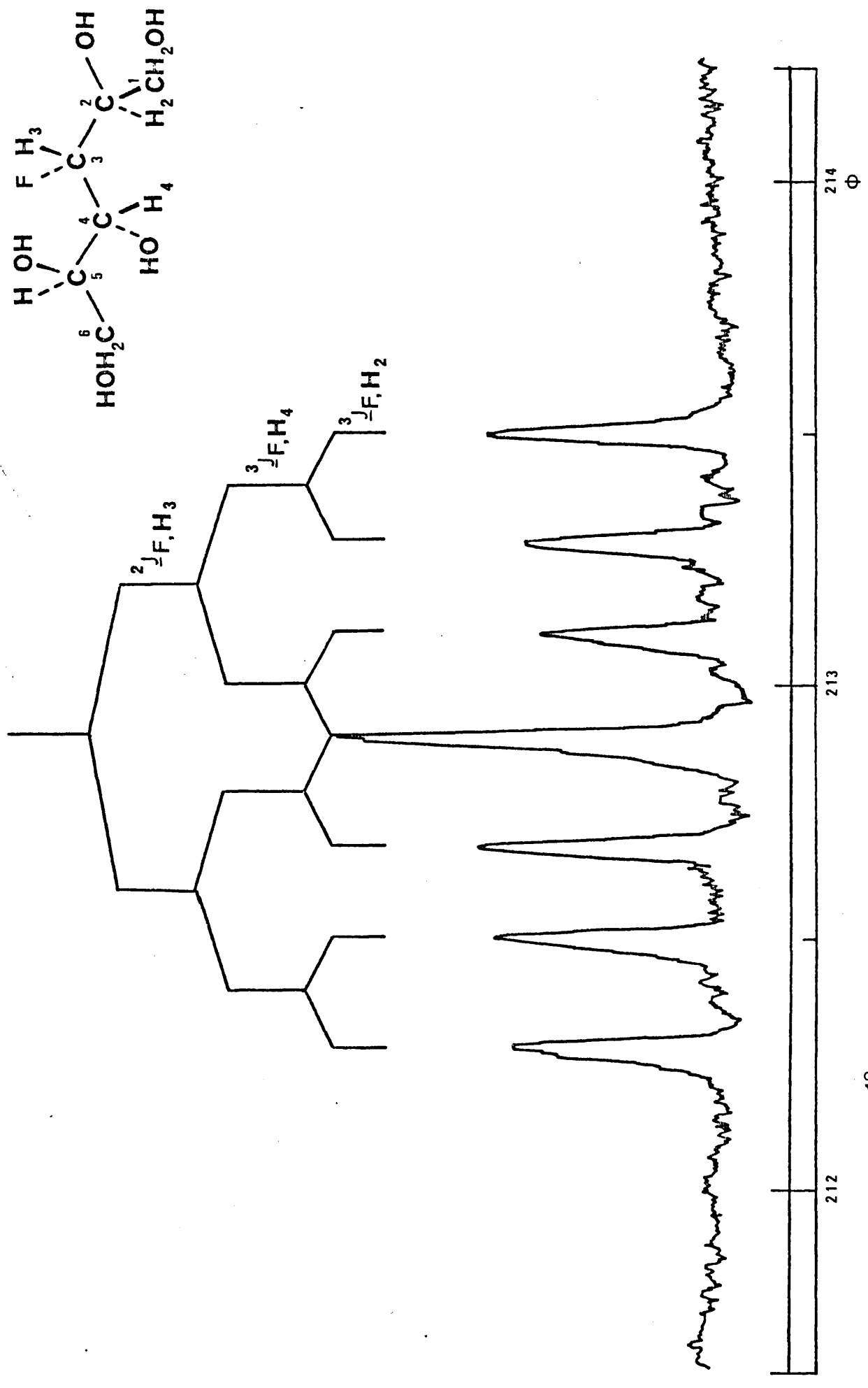


Fig. V-55 ^{19}F n.m.r. Spectrum of 3-Deoxy-3-fluoro-D-glucitol in D_2O.

carbohydrates. The unperturbed value they used was 43.5 Hz for a trans $^{3}J_{FH}$ coupling. However, for this polyol 10 Hz should be subtracted for an oxygen substituent on the coupled fragment giving a value of 33.2 Hz. This compares favourably with the observed trans $^{3}J_{FH}$ value of 31.1 Hz.

Let us now consider the gauche $^{3}J_{FH}$ value in terms of the work by Phillips and Wray.[120] The gauche $^{3}J_{FH}$ coupling is between F on C-3 and H on C-2. Phillips and Wray used an unperturbed gauche $^{3}J_{FH}$ value of 16 Hz, however 2.5 Hz must be subtracted from this for the oxygen substituent at C-2 which is part of the coupling fragment. This gives a value of 13.5 Hz. The observed $^{3}J_{FH}$ value is between 16-17 Hz when taken directly from the spectrum. This is slightly higher than calculated. Any factors which would marginally increase the calculated gauche $^{3}J_{FH}$ value to that observed are not clear at present.

As far as calculation of the $^{2}J_{FH}$ coupling is concerned the procedure of Phillips and Wray[125] cannot be confidently followed here. This is because they considered stereochemical electronegative effects associated with definite axial/equatorial environments from cyclic compounds. The polyol here is acyclic and the substituent groups do not occupy such positions. However, Phillips and Wray[125] assumed an unperturbed $^{2}J_{FH}$ value of 50 Hz. Then using their coupling increments they found a range of 44-53 Hz for $^{2}J_{FH}$ values in deoxy fluoro carbohydrates. The observed value of 47.6 Hz for $^{2}J_{FH}$ in 3-deoxy-3-fluoro-D-glucitol is within this range.

Let us now look at the changes in ^{19}F n.m.r spectral parameters caused by acetalation of 3-deoxy-3-fluoro-D-glucitol. The ^{19}F n.m.r. spectrum of 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol in $CDCl_3$ is shown in Fig. V-56. The chemical shift of the ^{19}F nucleus in the acetal is 220.5 ϕ as taken direct from the experimental spectrum. The chemical shift of the ^{19}F nucleus in the polyol was 212.9 ϕ, hence acetalation has caused a shielding of 7.6 p.p.m. A shielding is described as all the ϕ values in this section are to higher field than $CFCl_3$ at 0 ϕ. The previous studies on 5-fluoro-1,3-dioxane in $CFCl_3$ with an axial fluorine atom in the ring showed chemical shifts of 191 ϕ [127] and 194 ϕ [126] for the ^{19}F nucleus. There is no reason to assume that the change of solvent from $CFCl_3$ to $CDCl_3$ will cause any significant change in ^{19}F chemical shift.[126,127] The ^{19}F nucleus is expected to adopt an axial orientation in the ring of 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol in order to accommodate the ring substituents in equatorial environments. Therefore, there is a discrepancy in the ^{19}F chemical shifts of the axial fluorine atoms of 5-fluoro-1,3-dioxane and 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol even though they both have the same basic ring structure.

The difference in ^{19}F chemical shift of approximately 25-30 p.p.m. between the two types of fluoro dioxanes may be due to the substituents present in 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol. Here the fluoro dioxane ring has equatorial $-CH_2OH$ and $-CHOH-CH_2OH$ substituents on the carbons α to that bearing the fluorine atom. A compound which goes some way to testing this substituent theory is 4-deoxy-4-fluoro-D-galactose (Fig. V-57I).

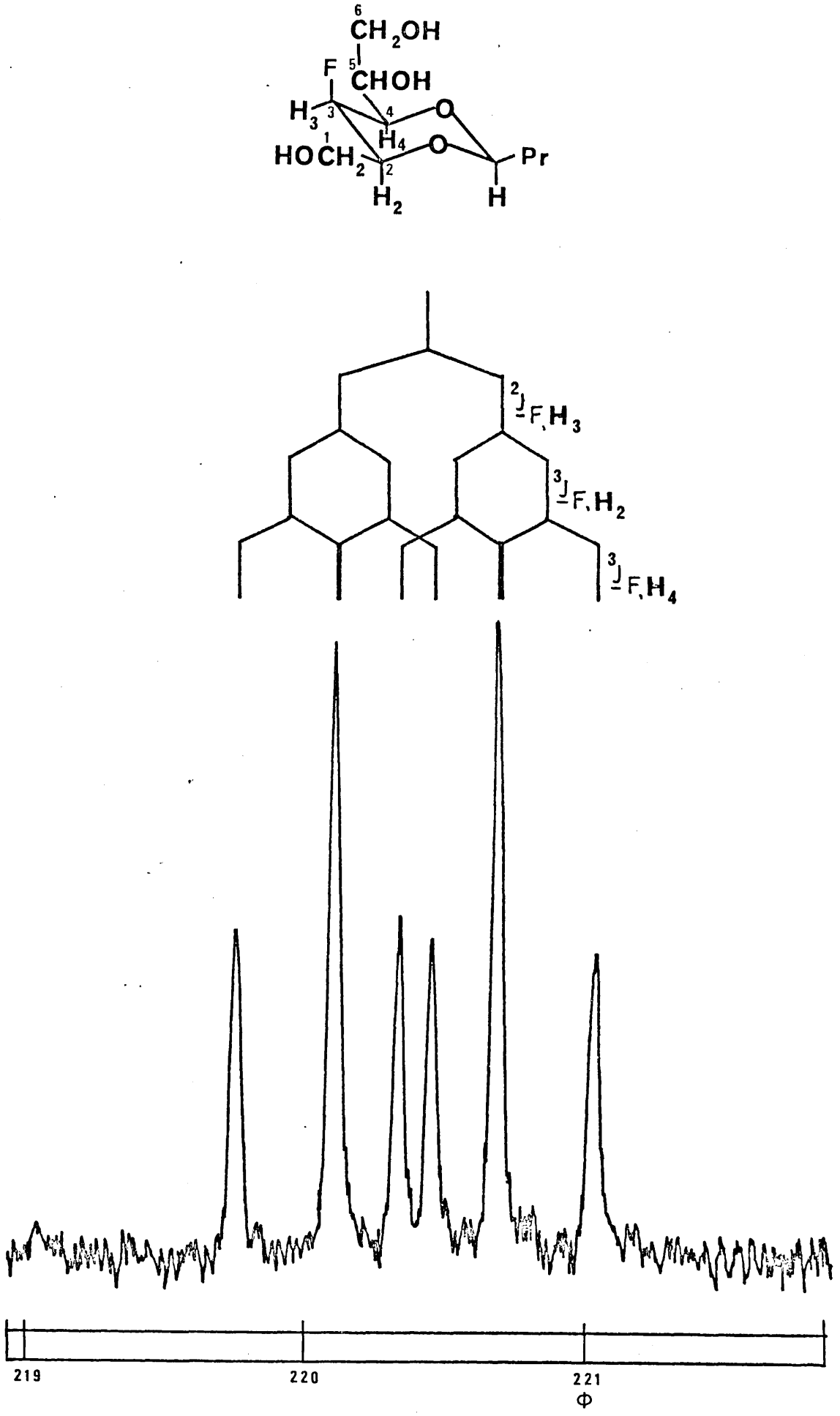
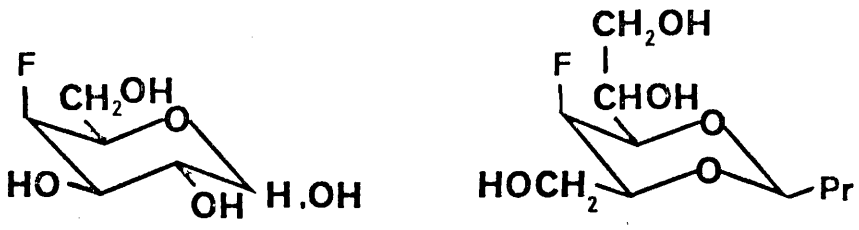


Fig. V-56 ^{19}F n.m.r. Spectrum of 2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol in $CDCl_3$.



I II

Fig. V-57

Although the two structures above look only vaguely comparable there are quite definite similarities regarding the positions of atoms relative to the fluorine. For example I above has a $-CH_2OH$ function gauche to the axial fluorine as does II. On the same carbon as this there is also an oxygen atom gauche to the axial fluorine in both I and II. On the other carbon α to that bearing the fluorine I has a gauche oxygen and a gauche oxygenated carbon with respect to the fluorine. The same substitution pattern of oxygen and oxygenated carbon are to be found in II. It would seem reasonable therefore to compare the chemical shifts of the fluorine nuclei in the two compounds.

The ^{19}F chemical shift of 4-deoxy-4-fluoro-D-galactose in D_2O is about 214 ϕ[128] (α anomer 213 ϕ, β anomer 215 ϕ) whereas the ^{19}F chemical shift of 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol is 220.5 ϕ. As perhaps expected there is reasonable compatibility between the two. This seems to support the statement that the discrepancy between the ^{19}F chemical shifts of 5-fluoro-1,3-dioxane and 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol is caused by the equatorial substituents in the dioxane ring of the latter.

Having considered shift differences let us now look at the changes in $^{19}F-^{1}H$ coupling constants caused by acetalation. In the fluoro polyol the two $^{3}J_{FH}$ couplings are comprised of one gauche $^{3}J_{FH}$ coupling and one trans $^{3}J_{FH}$ coupling. When the 2,4-acetal is formed however the conformation of the polyol backbone is altered. This modification results in the two $^{3}J_{FH}$ couplings both becoming trans $^{3}J_{FH}$ couplings, as illustrated in Fig. V-56. Calculation of these trans $^{3}J_{FH}$ couplings by the method of Phillips and Wray[120] gives a value of 33.2 Hz, i.e. the unperturbed 43.2 Hz value minus 10 Hz for the oxygen substituent on the appropriate coupling fragment. The observed value of the two $^{3}J_{FH}$ couplings is 29.1 Hz, slightly below that calculated but still reasonable. This observed $^{3}J_{FH}$ value also compares reasonably with the 32.2 Hz found for the trans $^{3}J_{FH}$ in 5-fluoro-1,3-dioxane by Hall and Johnson.[126]

The $^{2}J_{FH}$ value for the acetal can be calculated using the method of Phillips and Wray.[125] The unperturbed value of 50 Hz receives two 1 Hz increments for the situation of F axial, O in ring due to the oxygens on C-2 and C-4 of the acetal. This gives a calculated $^{2}J_{FH}$ value of 52 Hz. The observed $^{2}J_{FH}$ value of 48.6 Hz is a reasonable fit with the calculated value. Hall and Johnson[126] and Mager and Eliel[127] found values of 46.8 Hz and 47 Hz respectively for the $^{2}J_{FH}$ values in 5-fluoro-1,3-dioxane, both very similar to that observed for 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol.

(ii) 6-Deoxy-6-fluoro-D-galactitol and its 4,5-O-Butylidene Acetals

The ^{19}F n.m.r. spectrum of 6-deoxy-6-fluoro-D-galactitol in D_2O is illustrated in Fig. V-58. The spectrum appears as a "doubletted-triplet". The triplet structure arising from the $^2J_{FH}$ coupling, and doublet structure arising from the $^3J_{FH}$ coupling. The less intense signals appearing in Fig. V-58 are spinning side bands of the main signals.

The ^{19}F chemical shift of the $-CH_2F$ function in 6-deoxy-6-fluoro-D-galactitol is 227.9 ϕ. This is within the previously described range for the $-CH_2F$ function.[124] The $^2J_{FH}$ value is 46.7 Hz which is also in agreement with $^2J_{FH}$ values found for other compounds containing a CH_2F function[124] and other fluorinated carbohydrates. Calculation of the $^2J_{FH}$ value by the method of Phillips and Wray[125] cannot be carried out for this polyol as the atoms involved do not occupy specific axial/equatorial environments. This does not apply to the $^3J_{FH}$ values however.

The observed $^3J_{FH}$ value for 6-deoxy-6-fluoro-D-galactitol is approximately 16.5-17 Hz as measured direct from the experimental spectrum. Couplings of a very similar nature have been studied by Evelyn and Hall[124,129] and Phillips and Wray[120] in 6-deoxy-6-fluoro-D-galactose. Evelyn and Hall subscribe to the view that the $^3J_{FH}$ value is due to gauche orientations of the coupled nuclei. Phillips and Wray[120] consider the observed coupling to be the average of three couplings arising from the favoured rotamers of the C-5/C-6 bond. In the discussion of the $^3J_{FH}$ value of 6-deoxy-6-fluoro-D-galactitol both

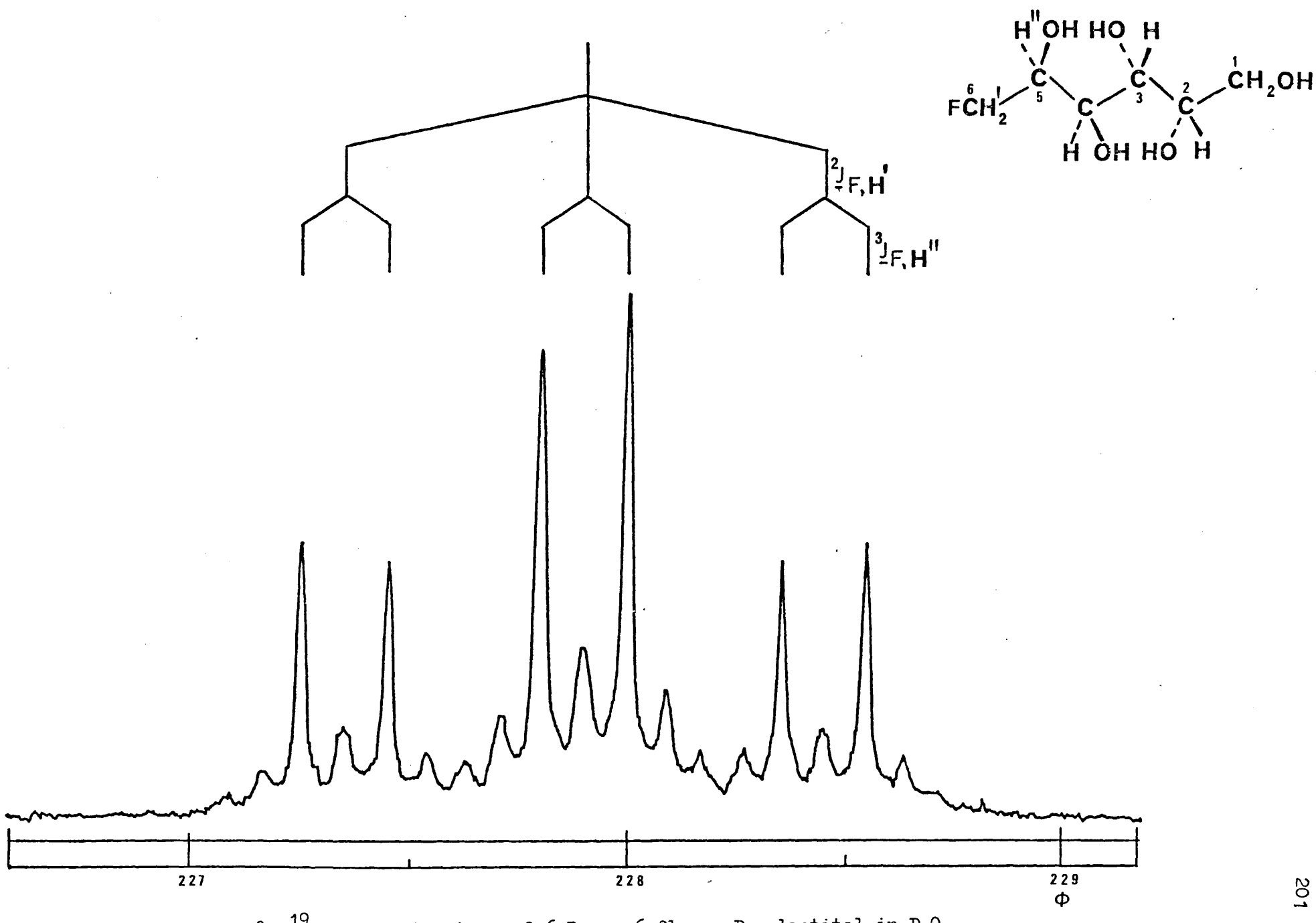
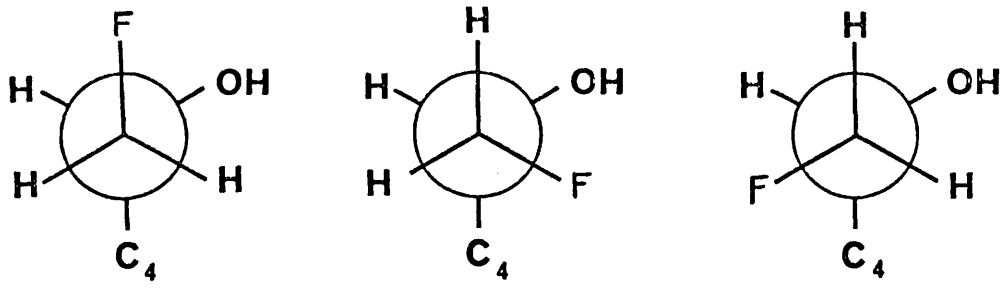


Fig. V-58 ^{19}F n.m.r. Spectrum of 6-Deoxy-6-fluoro-D-galactitol in D_2O.

viewpoints are considered as they can both lead to the same calculated average coupling.

The three favoured rotamers about the C-5/C-6 bond of 6-deoxy-6-fluoro-D-galactitol are illustrated below (Fig. V-59).



$^3J_{FH}$ = 13.5 Hz $^3J_{FH}$ = 33.2 Hz $^3J_{FH}$ = 6.5 Hz

A B C

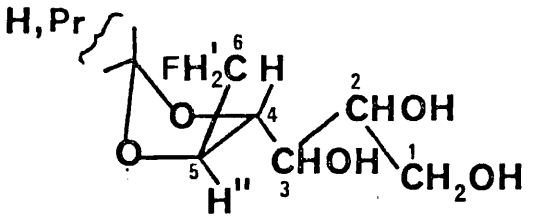
Fig. V-59

Rotamer A has a gauche $^3J_{FH}$ coupling, the maximum unperturbed value used by Phillips and Wray[120] being 16 Hz. However, 2.5 Hz must be subtracted for the oxygen substituent on C-5. This gives a calculated value of 13.5 Hz. Rotamer B has a trans $^3J_{FH}$ coupling, the maximum unperturbed value of which is 43.2 Hz. The oxygen substituent on C-5 requires 10 Hz to be deducted. This gives a calculated $^3J_{FH}$ value of 33.2 Hz. Rotamer C has a gauche $^3J_{FH}$ coupling hence 16 Hz minus 2.5 Hz for the oxygen on C-5 gives 13.5 Hz. However, there is an additional parameter to be considered for rotamer C and that is the OH

on C-5 is trans to the F on C-6. Phillips and Wray[120] give this as further decreasing the gauche $^{3}J_{FH}$ value by 7.0 Hz. This gives a final calculated $^{3}J_{FH}$ value of 6.5 Hz for rotamer C.

If the three rotamers shown in Fig. V-59 are equally populated then the $^{3}J_{FH}$ value observed in the spectrum should be the average of the calculated values. This average value is $(33.2 + 13.5 + 6.5)/3 = 17.6$ Hz. This compares favourably with the observed $^{3}J_{FH}$ value of approximately 16.5 - 17 Hz. The extent to which the rotamer population is altered through the "gauche" effect[130] is uncertain. The "gauche" effect would favour rotamers A and B. Rotamer B however is slightly disfavoured on steric grounds. Here the F atom on C-6 experiences an unfavourable 1,3-interaction with the OH function on C-4. The result of the "gauche" effect and this 1,3-interaction would be to give a higher population of rotamer A and lower populations of rotamers B and C. This situation could conceivably give an average $^{3}J_{FH}$ value in the region of 16.5 - 17 Hz.

The ^{19}F n.m.r. spectrum of 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol in D_2O (Fig. V-61) consists of two sets of signals. These two sets arise from the presence of diastereoisomers. Just as the ^{13}C n.m.r. spectrum of the acetal contained diastereoisomeric carbons then the ^{19}F n.m.r. spectrum shows diastereoisomeric fluorine nuclei. The multiplicity of each diastereoisomeric set of ^{19}F signals is the same, i.e. they are both "doubletted-triplets". The diastereoisomerism of the fluorine atom arises from the cis/trans options between the propyl side chain and the $-CH_2F$ function (Fig. V-60).



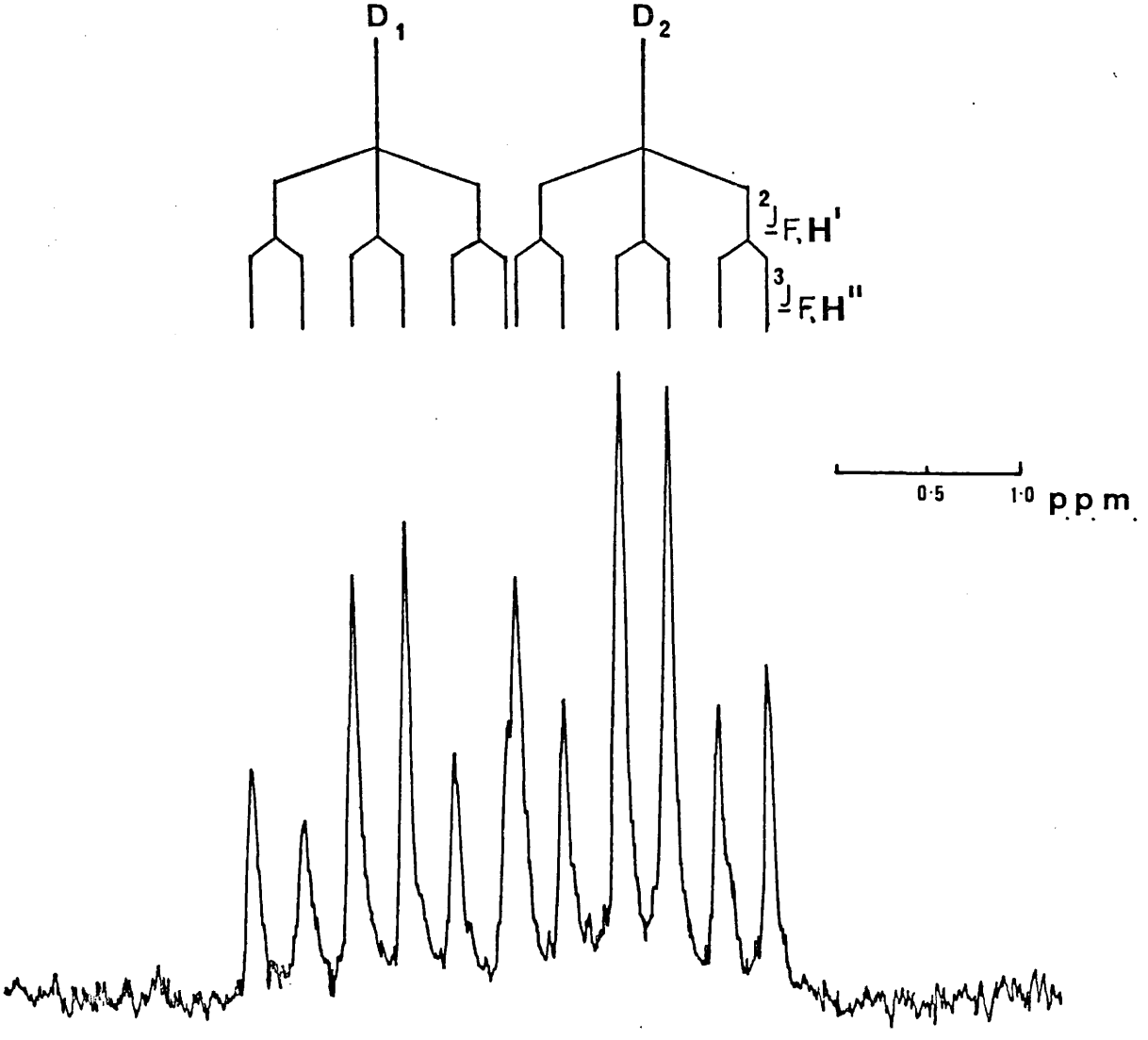
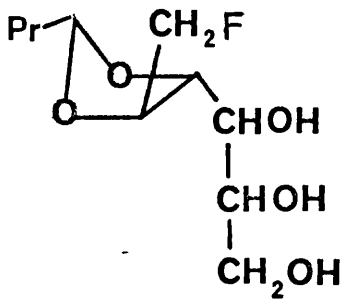
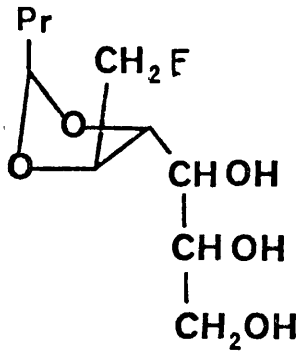


Fig. V-61 ^{19}F n.m.r. Spectrum of 4,5-O-Butylidene-6-deoxy-6-fluoro-D-galactitols in D_2O.



trans



cis

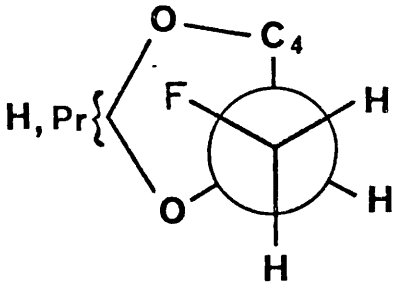
Fig. V-60

For convenience the cis/trans isomers are illustrated as envelope forms but the possibility of half chair forms must be considered. Apart from having different ^{19}F chemical shifts the diastereoisomers also have slightly different $^{2}J_{FH}$ and $^{3}J_{FH}$ values. In the remaining discussion the diastereoisomers giving rise to the lower field and higher field multiplets are labelled D_1 and D_2 respectively.

The ^{19}F chemical shifts of D_1 and D_2 were incorrectly measured when the spectrum was recorded at P.C.M.U. hence the ^{19}F shift effect caused by acetalation of the polyol cannot be ascertained. The shift difference between D_1 and D_2 was measured however, this being 1.4 p.p.m.. Also unknown is the relationship between D_1 and D_2 and the cis and trans diastereoisomers. The $^{2}J_{FH}$ values for D_1 and D_2 are 46.4 Hz and 45.9 Hz respectively. The $^{3}J_{FH}$ values are 24.9 Hz for D_1 and 22.4 Hz for D_2.

The $^{3}J_{FH}$ values can be calculated on exactly the same basis as done for the original fluoro polyol. That is by consideration

of the coupling present in each rotamer of the C-5/C-6 bond then averaging these values. This gives an average calculated value of 17.6 Hz which is some way below that observed for D_1 and D_2. This lower calculated $^3J_{FH}$ value indicates that equal population of the three rotamers is not achieved. Rather, a higher population of that rotamer in which the $^3J_{FH}$ coupling is <u>trans</u> (type B Fig. V-59) is probable. Rotamers of the type A and C must be populated to be a lesser extent however, otherwise the observed $^3J_{FH}$ value would be higher than it is. The high preference for a <u>trans</u> $^3J_{FH}$ value leaves the fluorine atom positioned over the dioxolane ring (Fig. V-62).



<u>Fig. V-62</u>

In a study on conformational preferences of halogenomethyl groups attached to a 1,3-dioxolane ring Borremans et al[31] suggested a similar orientation for the fluorine in a $-CH_2F$ function. The suggestion by Borremans et al[31] on the position of the fluorine was

based upon ^{1}H n.m.r. spectroscopy and not ^{19}F n.m.r. spectroscopy. Examination of their coupling constant data for cis and trans 2-methyl-4-fluoromethyl-1,3-dioxolane shows $^{3}J_{FH}$ values of 17.8 and 19.2 Hz respectively in CS_2. These $^{3}J_{FH}$ values are smaller than expected if the fluorine atom were positioned over the 1,3-dioxolane ring as in Fig. V-62. The cause of their anomalously low $^{3}J_{FH}$ values is not clear. The probable reason for the positioning of the fluorine atoms in the compounds studied by Borremans et al and in this thesis is the "gauche" effect.[130] The "gauche" effect has also been reported as being responsible for the preferred axial environment of the fluorine atom in 5-fluoro-1,3-dioxane.[126,127]

The $^{2}J_{FH}$ values of 46.4 Hz and 45.9 Hz found in D_1 and D_2 respectively agree with those found by Borremans et al[31] for their fluoro dioxolanes (47 Hz and 47.2 Hz for cis and trans isomers respectively). Calculations on the magnitude of the $^{2}J_{FH}$ values are omitted for similar reasons as mentioned for previous fluoro compounds.

VI Mass Spectrometry of Acetylated Methylated Polyols obtained from the Deoxy Fluoro Acetals

1. Introduction

Mass spectrometry is commonly used to find out information regarding the structure of partially methylated alditol acetates.[46,131-134] There are two ways of using the technique. One way is to compare the mass spectrometric fragmentation pattern of such a compound to the mass spectra of authentic samples. The other way is to elucidate the acetoxy and methoxy substitution pattern using principles derived from examination of mass spectra of a wide range of methylated alditol acetates. The latter method is used for those compounds discussed in this section, hence a brief discussion of the principles involved in this is presented.

The molecules of the methylated alditol acetate are bombarded in the ion source of the spectrometer with electrons. This results in removal of one electron from the molecule to give a positively charged species (the molecular ion). However, the molecular ions are not observed in the mass spectra of methylated alditol acetates. Rather, they undergo rapid breakdown to other fragments. Breakdown results in two types of fragments. Those fragments formed by cleavage of the C-C bonds of the alditol chain are called primary fragments. Secondary fragments are subsequently formed from the primary fragments by elimination reactions.

Certain observations have been made on the modes of fission resulting in primary fragments. The three possible types of

fission for a methylated alditol acetate are illustrated below (Fig. VI-1).

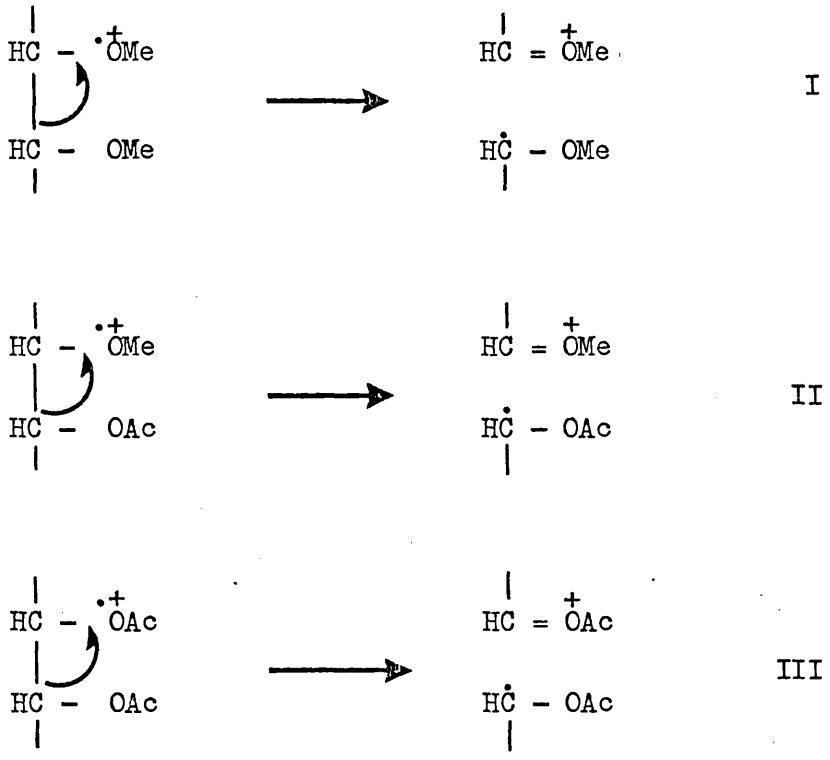
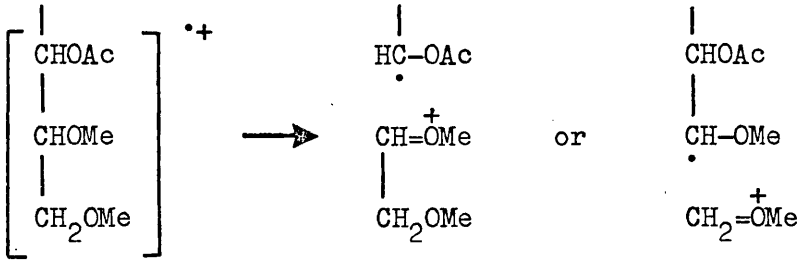


Fig. VI-1

Of these three types, that between adjacent methoxylated carbons (I) is most preferred. Of the two remaining types fission between acetoxyl and methoxyl carbons (II) is preferred over fission between adjacent acetoxylated carbons (III). In type II above the formal positive charge can be located on the acetoxyl or methoxyl oxygen. It is usually located on the methoxyl oxygen however. One important exception to the above observations is the fragmentation pattern of the group shown in Fig. VI-2,I .



I II III

Fig.VI-2

From the discussion above one would expect fission to occur between the methoxyl functions with observation of a large m/e 45 peak from the positively charged species in III. However the favoured fission occurs between the acetoxy and methoxy functions to give a large m/e 89 peak (II). Fission between these adjacent methoxyl functions can occur but is not as frequent as that between acetoxy and methoxy functions.

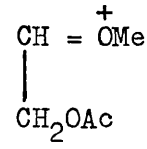
Mass spectral studies of acetylated deoxy fluoro glucitols[135] have shown that primary fission adjacent to C-F bonds is unfavoured. The introduction of methoxy functions into the alditol may increase the likelihood of such cleavage. Secondary fragments of methylated alditol acetates are formed from primary fragments by eliminations of formaldehyde (30), methanol (32), ketene (42), acetic acid (60), methyl acetate (74), methoxymethyl acetate (104), or acetoxymethyl acetate (132). Such eliminations are dependent upon the structure of the primary fragments. Due to the variety of ways in which these secondary fragments may be formed the illustrated examples are confined to those relevant to this section and are presented shortly.

The base peak, i.e. the most intense peak in the mass spectra of methylated alditol acetates is usually at m/e 43 caused by the acetylium ion. It is customary when presenting spectra to consider only those peaks with at least 5 or 10% the intensity of the base peak. This custom is followed here except the m/e 43 peak is not considered. Rather, the base peak has been chosen as the most intense peak other than that of the acetylium ion and only those peaks with 10% or more the base peak intensity considered.

2. Results and Discussion

(i) Mass Spectra of the Methylated Alditol Acetate obtained from the Unknown Monoacetal of 3-Deoxy-3-fluoro-D-glucitol

The mass spectra of the title compound and of its C-1/^{2}H derivative are illustrated in Figs. VI-3 and VI-4 respectively. Let us consider the non deuterated spectrum first. The base peak at m/e 117 is indicative of adjacent acetoxy and methoxy functions, the acetoxy function being on a terminal carbon of the alditol chain (Fig. VI-5).



m/e 117

Fig. VI-5

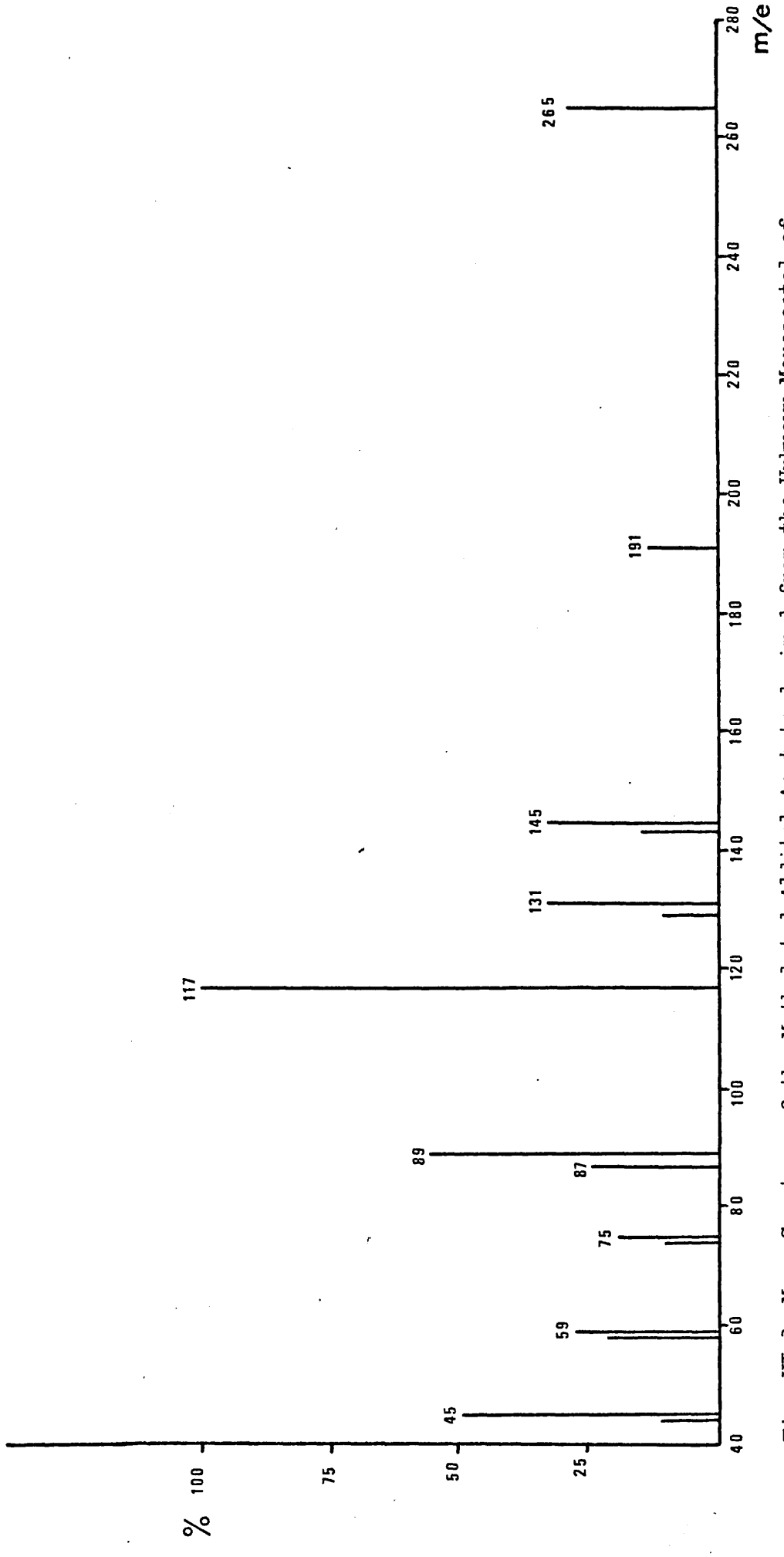


Fig. VI-3 Mass Spectrum of the Methylated Alditol Acetate derived from the Unknown Monoacetal of 3-Deoxy-3-fluoro-D-glucitol.

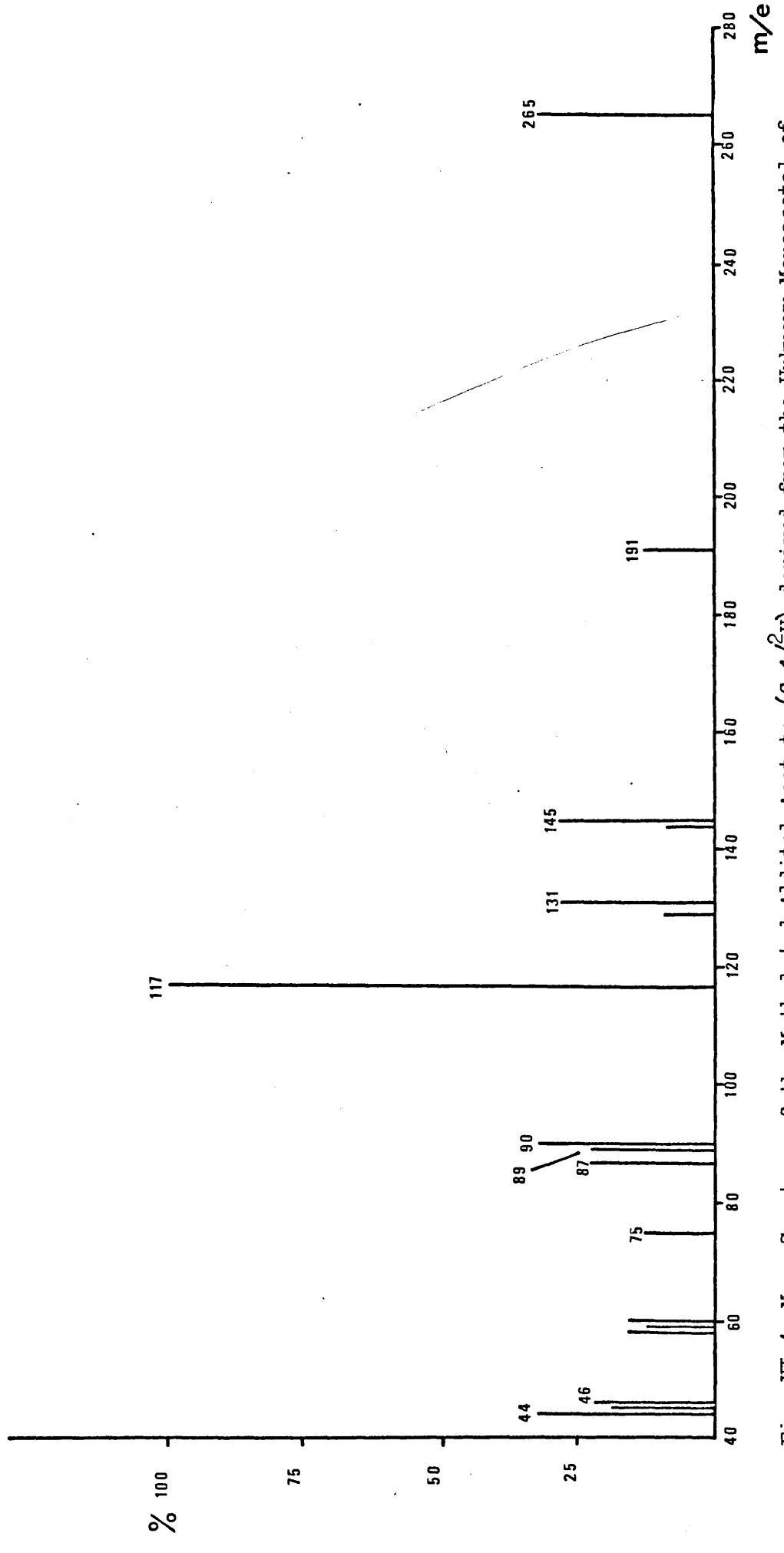
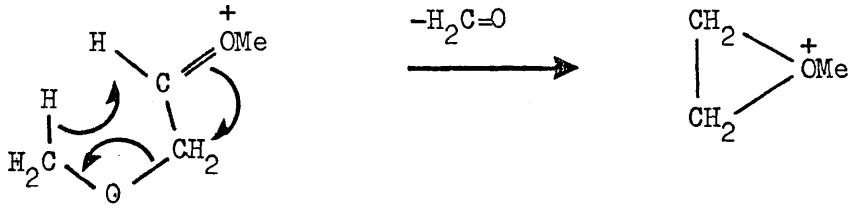


Fig. VI-4 Mass Spectrum of the Methylated Alditol Acetate (C-1/^{2}H) derived from the Unknown Monoacetal of 3-Deoxy-3-fluoro-D-glucitol.

The sequence of events leading to the methylated alditol acetate were methylation, hydrolysis then acetylation reactions starting from the acetal. This results in the two carbons of the polyol which carried the acetal ring oxygens ending up as carbons bearing acetoxy groups. The observation of an m/e 117 peak therefore shows the ring to have been on either C-1 or C-6.

The next most intense peak is at m/e 89. This is indicative of adjacent methoxyl functions, one of which is on a terminal carbon (Fig. VI-6,I).



m/e 89 m/e 59

I II

Fig. VI-6

The secondary fragment of m/e 59 (Fig. VI-6, II) is derived from the primary fragment by elimination of formaldehyde. Observation of the m/e 117 and 89 peaks enables identification of C-1, C-2, C-5 and C-6 of the alditol chain. Of the remaining carbons C-3 is the deoxy fluoro carbon hence C-4 must carry the

remaining acetoxy function. This gives the structure of the diacetate as being 1,4 or 4,6 (Fig. VI-7).

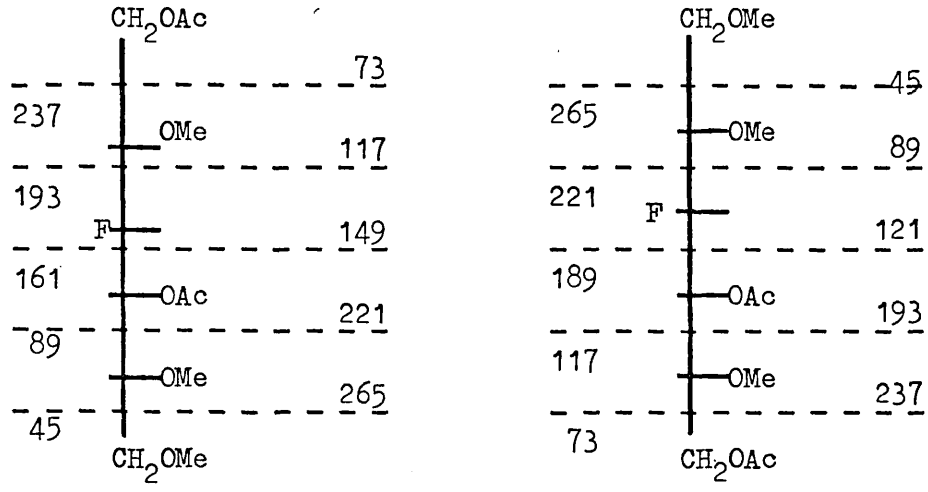
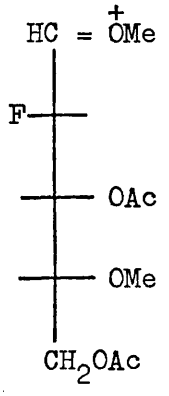


Fig. VI-7

The only other observed primary fragments are at m/e 45 and 265. These fragments can both result from either the 1,4 or 4,6-diacetates. Examination of the mass spectrum of the C-1/^{2}H methylated alditol acetate (Fig. VI-4) obtained from the acetal showed the 4,6-diacetate structure as being correct.

The base peak is still at m/e 117 consistent only with the 4,6-diacetate. The 1,4-diacetate should have the base peak at m/e 118. Similarly the primary fragment at m/e 265 is unaltered by monodeuteration at C-1 (Fig. VI-8).



m/e 265

Fig. VI-8

The m/e 265 primary fragment for a 1,4-diacetate should appear at m/e 266 in the C-1/^{2}H derivative. Peaks affected by deuteration are at m/e 90 and 60. They result from the adjacent methoxyl functions and the oxironium ion obtained therefrom by elimination of formaldehyde. Both peaks are consistent with a 4,6-diacetate as a 1,4 diacetate would have this pair of peaks unaltered by deuteration. On the basis of the mass spectral data it seems reasonable to conclude that the original acetal was 4,6-O-butylidene-3-deoxy-3-fluoro-D-glucitol.

(ii) Mass Spectra of 2,4-Di-O-acetyl-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol

The mass spectra of the title compound and its C-1/^{2}H derivative are shown in Figs. VI-9 and VI-10 respectively. The possible primary fragmentation pattern for the two compounds is shown below (Fig. VI-11).

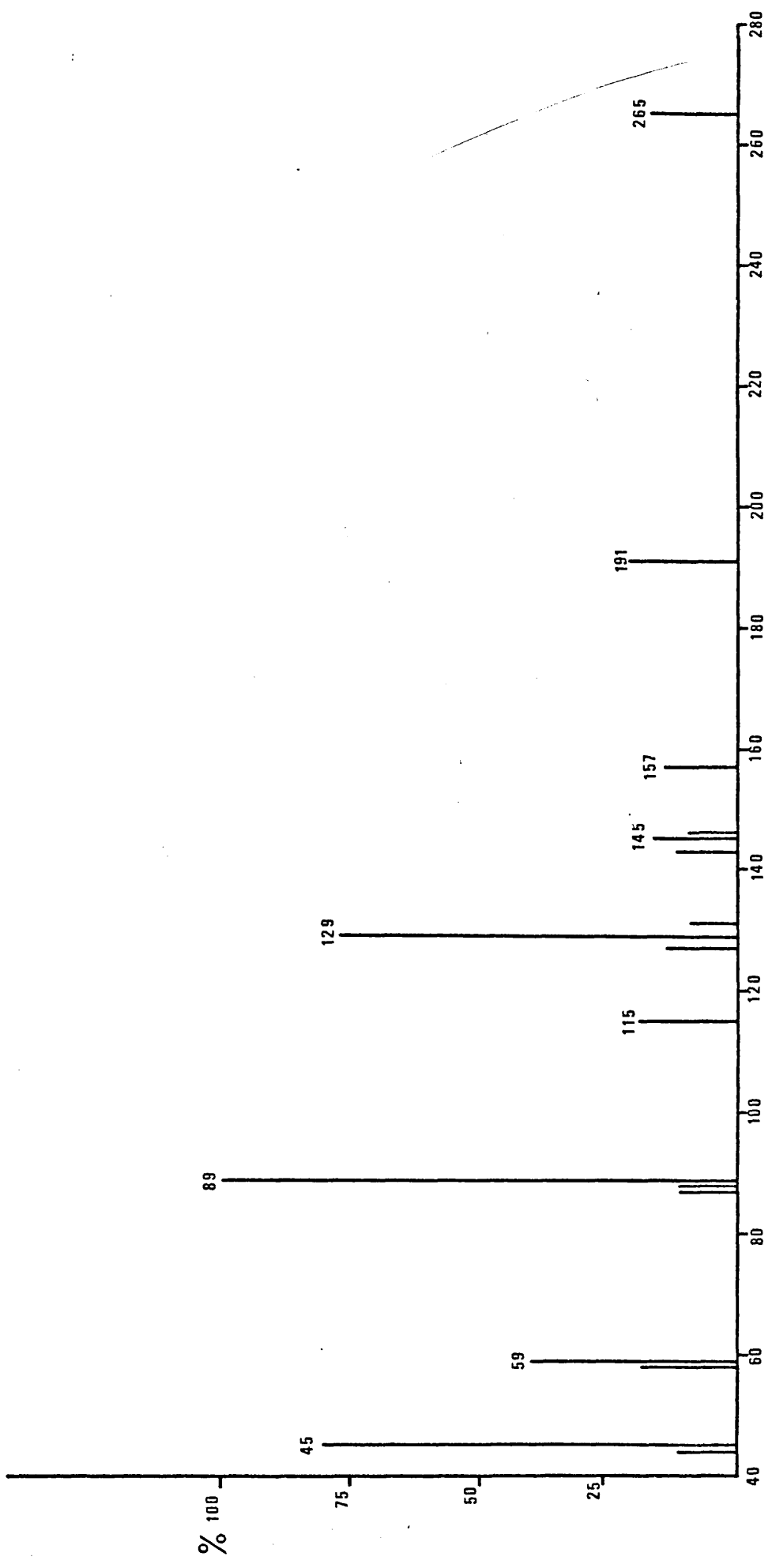


Fig. VI-9 Mass Spectrum of 2,4-Di-O-acetyl-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol.

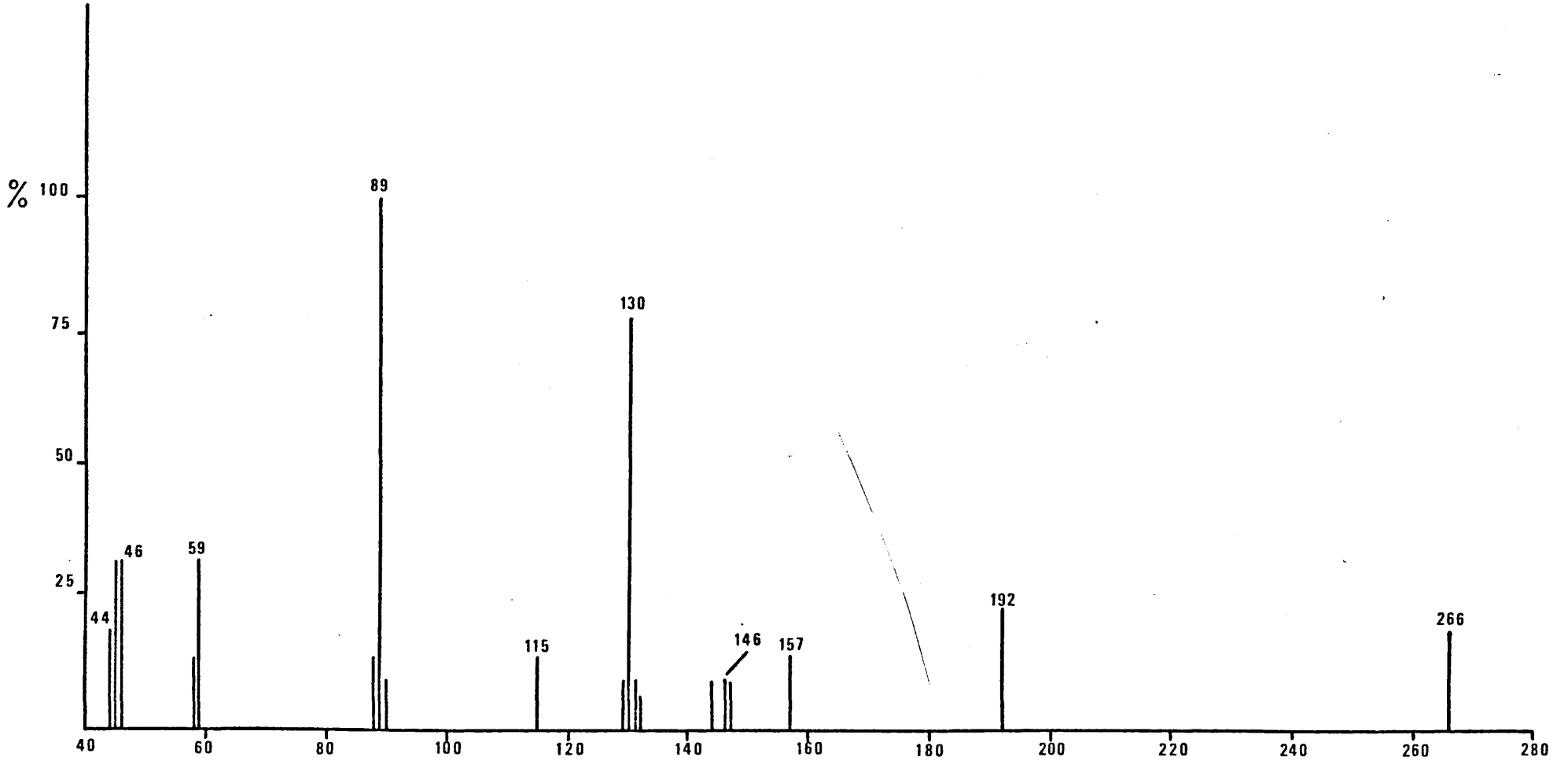


Fig. VI-10 Mass Spectrum of 2,4-Di-O-acetyl-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol (C-1/^{2}H).

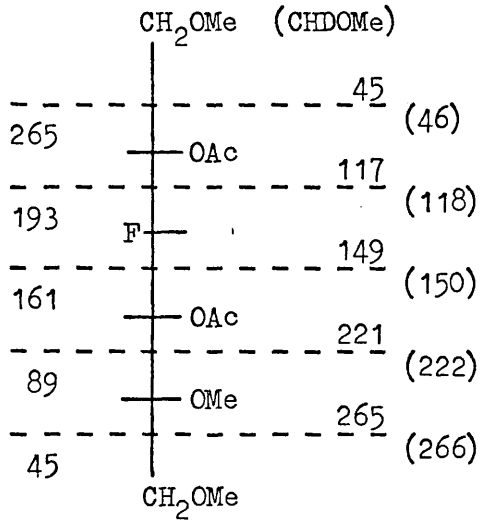


Fig. VI-11

Values in parentheses are m/e primary fragments of the C-1/^{2}H derivative. The base peak in both spectra is at m/e 89 arising from cleavage of the C-4/C-5 bond giving the primary fragment containing di-O-methyl groups. The secondary fragment formed from this by elimination of formaldehyde (see Fig. VI-6) is at m/e 59 in both spectra. All other observed primary fragments show an increase of one mass number in the spectrum of the C-1/^{2}H derivative.

The highest observed peak is at m/e 265 and 266(C-1/^{2}H). This arises from the primary fragment shown below (Fig. VI-12). Peaks at m/e 191 and 145 are secondary fragments formed by eliminations of methyl acetate and acetic acid from ion m/e 265.

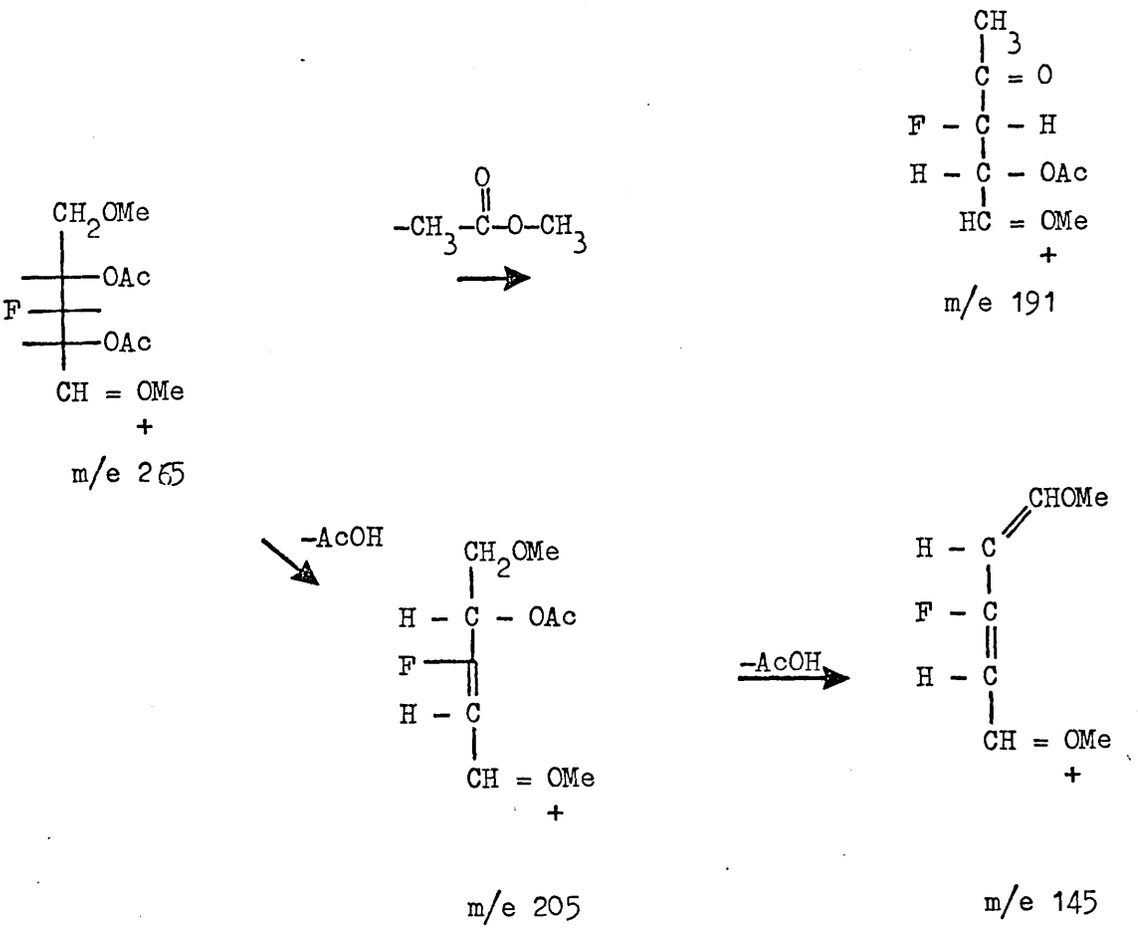


Fig. VI-12

The elimination of methyl acetate was confirmed by the appearance of a metastable peak at approximately m/e 137. The metastable ion position m is given by $m = d^2/p$ where d is the m/e value of the daughter ion and p is the m/e value of the parent ion.

The other primary ion showing an increase of one mass unit is at m/e 45 (m/e 46, C-1/^{2}H). This fragment is formed from cleavage of the C-1/C-2 bond of the alditol. There is an m/e 45 peak present in the spectrum of the C-1/^{2}H derivative however, this being formed from cleavage between C-5 and C-6 of the alditol chain.

The only other peak of note in the spectra is at m/e 129 (m/e 130, C-1/^{2}H). This may arise from the primary fragment with m/e 221 by elimination of acetic acid and methanol (Fig. VI-13).

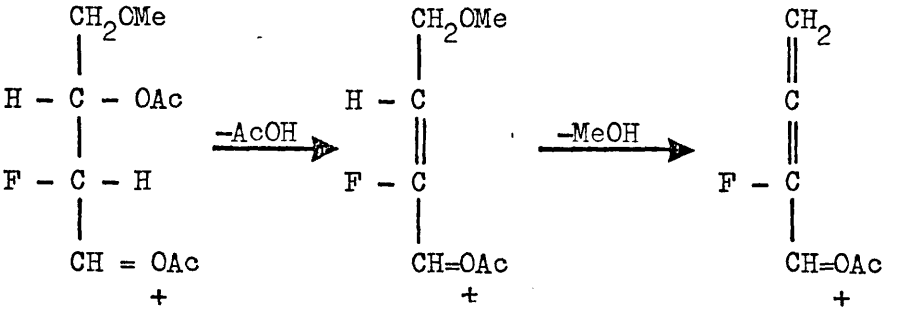


Fig. VI-13

(iii) Mass Spectrum of 4,5-Di-O-acetyl-6-deoxy-6-fluoro-1,2,3-tri-O-methyl-D-galactitol

The mass spectrum of the title compound is shown in Fig. VI-14. The possible primary fragmentation pattern is illustrated in Fig. VI-15.

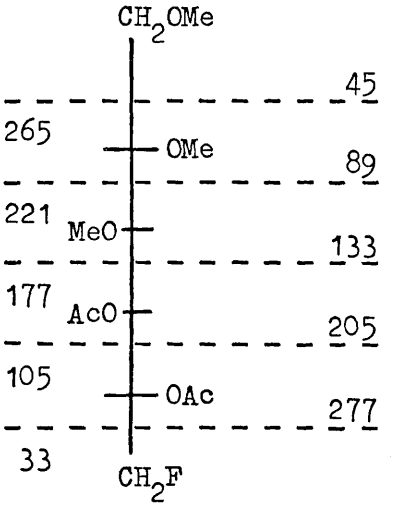


Fig. VI-15

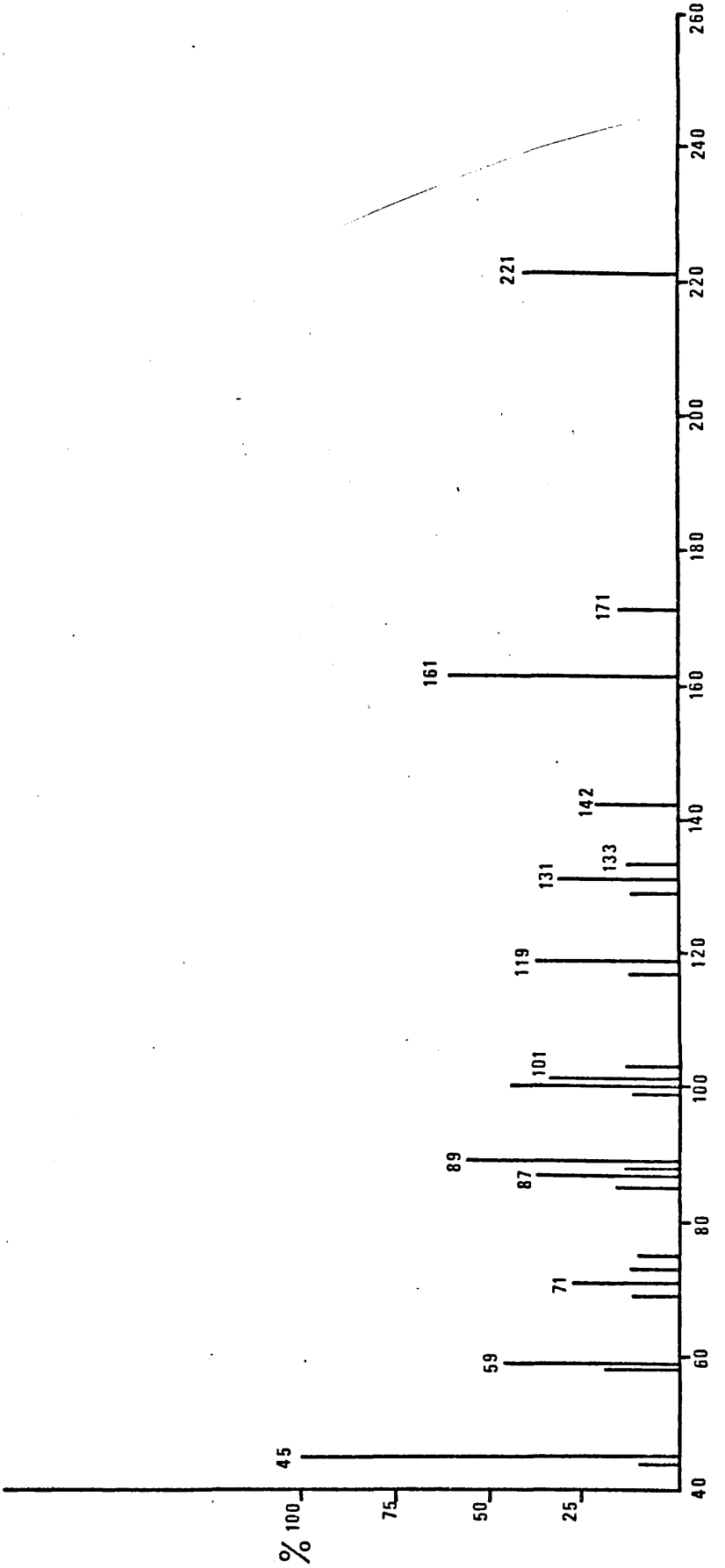


Fig. VI-14 Mass Spectrum of 4,5-Di-O-acetyl-6-deoxy-6-fluoro-1,2,3-tri-O-methyl-D-galactitol

The peak with highest m/e value is at 221 caused by cleavage between C-2 and C-3. It and the secondary fragments obtained from it by elimination of acetic acid and ketene are shown below (Fig. VI-16).

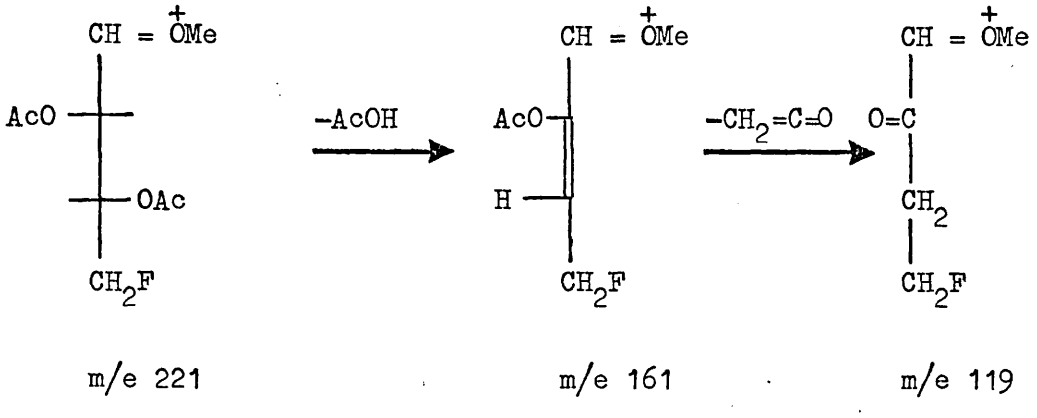


Fig. VI-16

The other primary fragments are at m/e 45 and 89 arising from mechanisms outlined earlier. The only other relevant primary fragment is at m/e 133 formed by cleavage of the C-3/C-4 bond of the alditol. The secondary fragment at m/e 101 is derived from it by elimination of methanol (Fig. VI-17).

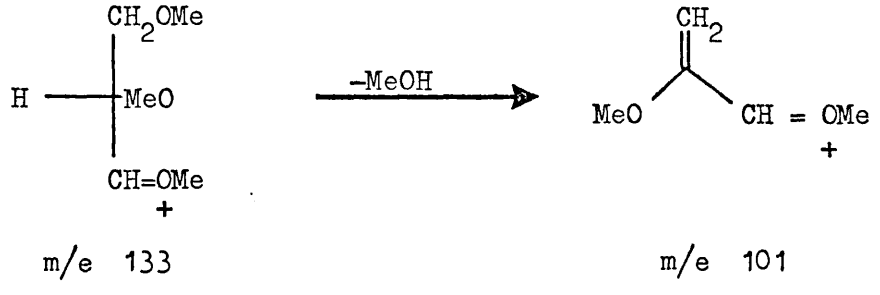


Fig. VI-17

VII Experimental

VII-A General Techniques and Materials

1. Nuclear Magnetic Resonance (n.m.r.)

The 60 MHz ^{1}H n.m.r. spectra were recorded on a Varian EM 360 spectrometer and were generally used as a means of quick analysis of reaction products. The 100 MHz ^{1}H spectra were recorded on a Varian HA 100 spectrometer. The 220 MHz ^{1}H spectra were recorded at the Physico Chemical Measurements Unit (P.C.M.U.) Harwell on a Varian HR 220 machine. The ^{13}C spectra were recorded on a Bruker HX 90E spectrometer operating at 22.63 MHz at P.C.M.U. The ^{19}F spectra were also recorded on the Bruker HX 90E machine at P.C.M.U. at 84.67 MHz. All spectra were run at ambient temperature. The reference for D_2O solutions was 3-(trimethylsilyl)-propanesulphonic acid sodium salt (T.S.P.) for ^{1}H and ^{13}C, for other solutions tetramethylsilane (T.M.S.) was used. The references for ^{19}F were trifluoroacetic acid or trichlorofluoromethane. All references were internal except trifluoroacetic acid.

2. Gas Liquid Chromatography

Gas liquid chromatography was performed on a Pye 104 gas chromatograph equipped with a flame ionization detector. Whenever peak areas were recorded a Hewlett Packard 3370B integrator was connected to the gas chromatograph. The carrier gas was nitrogen at a flow rate of 40 ml min^{-1} with hydrogen and air pressures at 25 p.s.i. and 15 p.s.i. respectively. The stationary phases were used as below:

(a) Apiezon-K (7.5%) and polyphenyl ether (10%) both on Chromasorb-W were used for trimethylsilyl ether derivatives of the acetals and polyols.

(b) OV-17 (7.5%) and OV-225 (3%) both on Chromasorb-W were used for methyl ethers, acetates and methylated, acetylated derivatives of the acetals and polyols. The OV-225 column was occasionally used for trimethylsilyl derivatives.

The derivatised samples for gas liquid chromatography were prepared as follows:

(a) Methylations were carried out in N,N-dimethylformamide (2 ml) using silver oxide (0.5 g), methyl iodide (0.5 ml) and the sample (25-50 mg). The reagents were added to a stirred solution of the sample and left stirring at room temperature for 24 hours. The reaction mixture was then filtered, the filtrate concentrated to a residue, then extracted with hot ethyl acetate. The ethyl acetate solution was tested by thin layer chromatography in solvent E to see if full methylation had occurred. If not, the sample was remethylated using an identical procedure. Products were not isolated crystalline, instead gas liquid chromatography or gas liquid chromatography /mass spectrometry was carried out on the syrupy product.

(b) Acetate derivatives were made by heating a dry pyridine solution (2 ml) of the sample (25-50 mg) with acetic anhydride (2 ml) in a stoppered test tube on a boiling water bath for 1 hour. Again the products were used without isolation for further work.

(c) Trimethylsilyl ethers were prepared according to Sweeley et al.[136] A solution of the sample (10-20 mg) in pyridine (1 ml) was treated with hexamethyldisilazane (0.2 ml) then trimethylsilyl chloride (0.1 ml) for about 3 minutes at 40°. The precipitate was

removed by centrifugation then the supernatant liquor used directly for injection onto the gas chromatograph.

3. Polarimetry

Optical rotation studies were carried out using a Perkin-Elmer 141 polarimeter operating at 589 nm (Na D Line). For $[\alpha]^t$ measurements of isolated compounds, a jacketed 10 cm glass cell of capacity 1 ml, was used. The solvents were methanol, water or chloroform. For monitoring reactions by polarimetry the cell was a jacketed 10 cm quartz cell of capacity 6 ml. Again the wavelength was 589 nm. The change in optical rotation of the reaction mixture with time was recorded until constant readings were obtained. The temperatures for all optical rotations studies were between 20-30°.

4. Thin Layer Chromatography

The thin layer chromatography plates were commercially available (Camlab, Cambridge). Dimensions were 5 x 20 cm precoated silica gel (Polygram Sil G) with a layer of 0.25 mm. The solvent systems were:

(a) Solvent A was butanone saturated with water.

(b) Solvent B was chloroform/methanol 99:1 v/v.

(c) Solvent C was ethyl acetate/pet. ether (40-60° boiling range) 3:1 v/v.

(d) Solvent D was benzene/ether 9:1 v/v.

(e) Solvent E was benzene/methanol 9:1 v/v.

The thin layer chromatography plates were developed by spraying with 95:5 v/v ethanol-sulphuric acid then heating at 120° for 30 minutes.

5. Mass Spectrometry

Mass spectra were recorded on a VG micromass 12F spectrometer with an ionization potential of 70 eV, operating in link up with a Pye 104 gas chromatograph for electron impact spectra. Some

chemical ionization (c.i.) spectra were recorded in order to ascertain molecular weights of samples. These samples were directly inserted into the spectrometer and not through the gas liquid chromatograph. The carrier gas for gas liquid chromatography/ mass spectrometry was helium at a flow rate of 30 ml min^{-1}. The working temperature of the spectrometer was about 200°.

6. Elemental Analysis

Micro elemental analysis was performed by Bernhardt's (Germany), School of Pharmacy (University of London) and Butterworth's Micro Analytical Consultancy (Teddington).

7. Melting Points

Melting points were recorded on a Gallenkamp or Thomas-Hoover melting point apparatus and are uncorrected.

8. Purification of Solvents

(a) N,N-Dimethylformamide was purified by distillation under reduced pressure from calcium hydride, then stored over calcium hydride.

(b) Pyridine was purified by distillation over potassium hydroxide followed by distillation from phosphor us pentoxide, then stored over potassium hydroxide pellets.

(c) Acetonitrile was dried by distillation from phosphor us pentoxide.

9. Preparation of Raney Nickel Catalyst [137]

Nickel/aluminium alloy (150 g) was carefully added to a stirred aqueous solution (750 ml) of sodium hydroxide (190 g) over a period of 2 hours. The reaction mixture was kept below 10° throughout the addition of the alloy. To prevent excessive foaming, n-octanol (5 ml) was added to the reaction. After addition of the alloy the mixture

was heated on a water bath until hydrogen evolution had ceased (2 hours). The volume was made up to 750 ml with distilled water, then this supernatant liquor decanted. The nickel residue was rinsed with 2.5 M-sodium hydroxide (250 ml) then the supernatant liquid decanted again. The nickel was washed with distilled water until neutral to litmus (30 x 500 ml) then transferred to a stoppered flask and stored over ethanol until required.

10. Periodate Oxidations and Related Estimations [42,43]

(a) Determination of Periodate Ion Uptake

Analar solutions of sodium metaperiodate and sodium iodate (both 0.015M) were prepared. An aliquot (1 ml) from each was diluted 250 times, then the absorbance of the resultant solutions were measured at 222.5 nm using a Unicam SP 500 spectrophotometer with distilled water as a blank. On the assumption that the periodate solution contained 100% IO_4^- ions and 0% IO_3^- ions and vice versa for the iodate solution, a calibration graph was obtained. The graph related absorbance with ion composition of the solution under investigation. An accurately weighed portion of the sample under scrutiny was dissolved in the bulk periodate solution (10 ml). Aliquots (1 ml) were withdrawn periodically and diluted by 250 then the absorbance of the resultant solution measured. This was repeated until two consecutive readings were identical. The molar uptake of periodate per mole of sample was obtained from the absorbance and the calibration graph. To test the accuracy of the method a standard of 2,5-O-methylene-D-mannitol was used at the same time.

(b) Formaldehyde Determination

Formaldehyde liberated due to the periodate oxidation was detected by its colour reaction with chromotropic acid reagent. After 24 h the periodate oxidation solution of the sample and the standard had a 1 ml aliquot diluted x 10. The standard also had aliquots (1 ml) diluted x 25 and x 50. An aliquot (1 ml) from each diluted solution was mixed with 20% sodium sulphite solution (0.1 ml) and the chromotropic acid reagent (8.4 ml), then heated for 1 hour on a boiling water bath. A blank of water was simil arly treated. The chromotropic acid reagent was prepared by adding 2:1 v/v sulphuric acid/water to an aqueous solution (50 ml) of chromotropic acid sodium salt (0.5 g) until the total volume was 250 ml. After heating, samples containing formaldehyde developed a violet colour. When cool 0.4% thiourea solution (0.5 ml) was added to each sample. The absorbance of each sample was read at 570 nm against the water blank. A calibration graph was prepared relating absorbance to formaldehyde concentration from the three absorbances taken for the standard 2,5-O-methylene-D-mannitol. Formaldehyde liberated by the test samples were obtained from this graph.

(c) Formic Acid Determination

When periodate oxidation was complete, an aliquot (2 ml) was removed from the solution and treated with several drops of ethylene glycol to destroy remaining periodate. This solution was then titrated against 0.01M-sodium hydroxide using methyl red as an indicator. A sample from the bulk periodate was similarly treated. The titre difference was used to calculate the formic acid liberated by the periodate oxidation.

11. Investigation of the Reactions between the Various Polyols and n-Butyraldehyde

Each reaction between a polyol and n-butyraldehyde was monitored by gas liquid chromatography and polarimetry. The general procedure is outlined below.

(a) Gas Liquid Chromatography

A solution (0.10M) of the polyol in 0.5M-hydrochloric acid (30 ml) was vigorously shaken with freshly distilled n-butyraldehyde (equimolar to polyol) for 1 minute then set aside in a water bath at 20-30°. At periodic time intervals an aliquot (usually 1 ml) was withdrawn from the reaction mixture and neutralised exactly with 0.5M-sodium hydroxide. The neutral solution was concentrated to a paste which was dried by addition of ethanol and re-evaporating. The residue was then converted to the trimethylsilyl ether derivatives of the organic components by the method previously described. The pyridine solution of the T.M.S. ethers was then injected onto the Pye 104 gas chromatograph. The output consisted of a series of peaks due to polyol and acetals with differing areas at differing reaction times. This was analysed and the plots of polyol uptake and acetal formation as a function of time were taken from this.

(b) Polarimetry

An aliquot (6 ml) of the above reaction mixture was taken immediately after mixing and transferred to a quartz polarimeter cell (path length 10 cm). The cell was placed in a Perkin-Elmer 141 polarimeter then the change in optical rotation with time was followed at 589 nm. The polarimeter cell was thermostated with a water jacket of temperature 20-30°.

The reactions were monitored by gas liquid chromatography and polarimetry until equilibrium was reached. The conditions used for each reaction were as tabulated below (Table VII-1)

Polyols	g.l.c. column	g.l.c. Oven temperature (°)	Reaction temperature (°)
2-Deoxy-D-arabino-hexitol	10% P.P.E.	163	30
2-Deoxy-D-lyxo-hexitol	7.5% A.P.K.	170	30
2-Deoxy-D-erythro-pentitol	10% P.P.E.	140	30
3-Deoxy-D-ribo-hexitol	7.5% A.P.K.	168	22.5
4-Deoxy-D-xylo-hexitol	3% OV-225	140	25
6-Deoxy-D-galactitol	3% OV-225	143	25
6-Deoxy-6-fluoro-D-galactitol	3% OV-225	142	25
3-Deoxy-3-fluoro-D-glucitol	7.5% A.P.K.	180	22.5

Table VII-1

VII-B Experiments

Experiment 1 2-Deoxy-D-arabino-hexitol

2-Deoxy-D-arabino-hexose (10 g) and sodium borohydride (1.5 g) were dissolved in water (300 ml), and kept at room temperature for 24 h. The solution was then shaken with Amberlite IR-120(H^+) resin (25 ml). The resin was filtered off and the filtrate evaporated to a syrup. Borate ions were removed as volatile methyl borate by repeated addition of methanol followed by evaporation. The resultant syrup was taken up in hot ethanol (40 ml) then left 2 days at 5° after which time crystalline 2-deoxy-D-arabino-hexitol had formed, yield 8.5 g (84%), m.p. 105-106°, lit.[138] m.p. 105-106°.

Experiment 2 C-1/^{2}H-2-Deoxy-D-arabino-hexitol

Sodium borodeuteride (0.04 g) was added to a solution of 2-deoxy-D-arabino-hexose (0.3 g) in distilled water (10 ml). The procedure was then as described for the non-deuterio polyol in experiment 1. C-1/^{2}H-2-Deoxy-D-arabino-hexitol was obtained as a white solid, yield 0.184 g, m.p. 104-105°.

Experiment 3 Reaction of 2-Deoxy-D-arabino-hexitol with n-Butyraldehyde

A solution of 2-deoxy-D-arabino-hexitol (9.15 g) in 0.5M-hydrochloric acid (550 ml) was shaken with n-butyraldehyde (3.97 g) then left at room temperature for 48 h. After such time the reaction mixture was neutralized using 4M-sodium hydroxide and the solution evaporated under vacuum to leave a paste. The organic fraction was extracted by shaking with absolute ethanol

then filtering. The filtrate was then rotary evaporated to a clear syrup.

Thin layer chromatography of the syrup in solvent A showed three spots, $\underline{R}_{F1}$ = 0.1 (2-deoxy-D-arabino-hexitol), $\underline{R}_{F2}$ = 0.54 (1,3-monoacetal), $\underline{R}_{F3}$ = 0.60 (4,6-monoacetal). The monoacetal fraction of the syrup was separated from unreacted polyol by passage down an alumina (active, neutral) column (1000 g) eluting with ethanol-water (9:1). Thin layer chromatography of the column fractions showed the two monoacetals had eluted together free from polyol.

The monoacetals were then fractionated using a Dowex 1-X8 (OH^-) resin column (300 ml slurry), eluting with carbon dioxide free deionised water. The fractions eluting from the column were tested by thin layer chromatography in solvent A. The 1,3-O-butylidene-2-deoxy-D-arabino-hexitol eluted first, yielding 0.2 g of chromatographically pure acetal ($\underline{R}_F$ = 0.54 in solvent A). The syrup slowly crystallized and was then recrystallized from ethyl acetate, m.p. 61.5 - 63.5°, lit.[6] m.p. 61.5 - 63.5°. The sample showed no depression of melting point upon admixture with an authentic specimen.

The 4,6-O-butylidene-2-deoxy-D-arabino-hexitol was eluted next. The fractions containing the acetal were combined and evaporated to a syrup, yield 0.66 g. The syrup was dissolved in hot ethyl acetate and when cool deposited crystals of 4,6-O-butylidene-2-deoxy-D-arabino-hexitol ($\underline{R}_F$ = 0.60 in solvent A), m.p. 89-91°, $[\alpha]_D^{25}$ = -12.5° (c, 0.79 in water). (Found: C, 54.50; H, 8.98. $C_{10}H_{20}O_5$ requires: C, 54.52; H, 9.15%).

Experiment 4 2-Deoxy-D-lyxo-hexitol

2-Deoxy-D-lyxo-hexose (1.75 g) and sodium borohydride (0.25 g) were dissolved in water (50 ml) and left at room temperature for 24 h. The reaction mixture was treated in a similar manner to that in experiment 1. 2-Deoxy-D-lyxo-hexitol was obtained and recrystallized from methanol, yield 1.52 g (86%), m.p. 110-110.5°, lit.[51] m.p. 112-113°.

Experiment 5 1,3-O-Butylidene-2-deoxy-D-lyxo-hexitol

A solution of 2-deoxy-D-lyxo-hexitol (3.23 g, 0.019 mol.) in 0.5M-hydrochloric acid (195 ml) was shaken with n-butyraldehyde (1.40 g, 0.019 mol.) and left at room temperature for thirty minutes. The reaction mixture was then neutralised using .4M-sodium hydroxide and the aqueous solution then concentrated under reduced pressure to a paste. The organic reaction mixture was removed by trituration with ethanol. The ethanolic extract was then concentrated until a syrupy residue was left. This residue slowly crystallized upon standing at room temperature. The crystalline residue was then extracted with hot chloroform (2 x 100 ml) and the hot chloroform solution filtered. The solvent was removed under reduced pressure leaving a syrup. Thin layer chromatography of the syrup in solvent A showed two spots, R_{F1} = 0.41, R_{F2} = 0.47. The syrup was fractionated using a Dowex 1-X8 (OH^-) column (100 ml wet slurry) eluting with carbon dioxide free deionised water. The major component of the syrup was eluted from the column first and fractions containing this were combined and the solvent removed by rotary evaporation. The resultant syrup slowly crystallized at room temperature and was then recrystallized from chloroform-petroleum ether (1:3) to give

needles of 1,3-O-butylidene-2-deoxy-D-lyxo-hexitol, yield 0.09 g, m.p. 60-61° (R_F = 0.47 in solvent A), $[\alpha]_D^{27.5}$ = -12.2° (c = 0.905 in MeOH) (Found: C, 54.63; H, 9.26. $C_{10}H_{20}O_5$ requires: C, 54.52; H, 9.15%).

Experiment 6 Reaction of 2-Deoxy-D-lyxo-hexitol with n-Butyraldehyde.

2-Deoxy-D-lyxo-hexitol (3.32 g, 0.02 mol.) was dissolved in 0.5M-hydrochloric acid (200 ml) then n-butyraldehyde (1.44 g, 0.02 mol.) was added. The mixture was shaken for 1 minute then left to stand at room temperature for two days. The reaction mixture was then neutralised using 4M-sodium hydroxide and the solvent removed using a rotary evaporator. The resultant paste was triturated with absolute ethanol then the ethanolic extract concentrated until a clear syrup was obtained.

Thin layer chromatography of the syrup in solvent A showed 3 spots, R_{F1}= 0.0 (polyol), R_{F2}= 0.41 (4,6-monoacetal), R_{F3}= 0.47 (mainly 4,5-monoacetal, slight 1,3-monoacetal). The monoacetal fraction was separated from the unreacted polyol using an alumina column and ethanol-water eluent as described in experiment 3. The syrup consisting of monoacetals was then fractionated using a Dowex 1-X8 (OH^-) resin column as previously described also in experiment 3.

The first monoacetal to elute from the Dowex 1-X8 (OH^-) column was gathered by concentrating the appropriate fractions to a syrup. The syrup crystallized upon standing at room temperature and was recrystallized from ethyl acetate to give 4,6-O-butylidene-2-deoxy-D-lyxo-hexitol, yield 0.12 g (R_F = 0.41 in solvent A), m.p. 90-91.5°, $[\alpha]_D^{20}$ = -7.3° (c, 0.78 in water) (Found: C, 54.2; H, 9.25. $C_{10}H_{20}O_5$ requires: C, 54.52; H, 9.15%).

The next monoacetal eluted from the Dowex 1-X8 column was similarly treated but recrystallized from chloroform to give crystalline 4,5-O-butylidene-2-deoxy-D-lyxo-hexitol, yield 0.2 g (R_F = 0.47 in solvent A), m.p. of stereoisomeric mixtures from three different preparations 75-77°, 78-79° and 86-87°, $[\alpha]_D^{20}$ = +80.5° (c, 0.8 in water) (Found: C, 54.25; H, 9.15. $C_{10}H_{20}O_5$ requires: C, 54.52; H, 9.15%).

Experiment 7 2-Deoxy-D-erythro-pentitol [53,139]

2-Deoxy-D-erythro-pentose (10 g) and sodium borohydride (1.5 g) were dissolved in water (250 ml) and left overnight at room temperature. The reaction mixture was worked up as in experiment 1. 2-Deoxy-D-erythro-pentitol was obtained as a syrup, yield 8.72 g (85.9%). Gas liquid chromatography of the polyol as its tetra-O-trimethylsilyl ether[140] showed the sample to be chromatographically homogeneous (retention time 705 seconds, 10% p.p.e. 140°).

Experiment 8 Reaction of 2-Deoxy-D-erythro-pentitol with n-Butyraldehyde

A solution of 2-deoxy-D-erythro-pentitol (18.25 g) in 0.5 M-hydrochloric acid (1325 ml) was shaken for 1 minute with n-butyraldehyde (9.5 g) then left to stand at room temperature for 48 h. The reaction mixture was then neutralised using 4 M-sodium hydroxide. The solvent was removed by rotary evaporation leaving a white paste as residue. The paste was shaken with ethanol then the mixture filtered. The filtrate was then concentrated under reduced pressure leaving a syrup.

The syrup was freed from unreacted polyol by passage down an alumina (active, neutral) column (1000 g). The monoacetal fraction

itself was also fractionated by passage down this column. The fractions eluting from the column were analysed by thin layer chromatography and the appropriate fractions concentrated to yield the monoacetals as syrups.

The first monoacetal to be eluted quickly crystallized and was recrystallized from ethyl acetate to give 3,5-O-butylidene-2-deoxy-D-erythro-pentitol, yield 4.7 g, m.p. 84-85° (R_F = 0.81 in solvent A), $[\alpha]_D^{20}$ = -57.6° (c, 0.84 in water) (Found: C, 56.98; H, 9.60. $C_9H_{18}O_4$ requires: C, 56.82; H, 9.54%).

The second monoacetal to be eluted was obtained as a chromatographically homogeneous syrup of 1,3-O-butylidene-2-deoxy-D-erythro-pentitol but could not be induced to crystallize, yield 2.73 g (R_F = 0.70 in solvent A), $[\alpha]_D^{27.5}$ = + 2.8°(c, 1.25 in MeOH) (Found: C, 54 .38; H, 9.27. $C_9H_{18}O_4$ requires: C, 56.82; H, 9.54%).

Experiment 9 1,3-O-Butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol

A solution of 1,3-O-butylidene-2-deoxy-D-erythro-pentitol (0.50 g) in pyridine (4 ml) was added to a solution of toluene-p-sulphonyl chloride (1.5 g) in pyridine (3.5 ml). The resultant solution was left at room temperature for 48 h. On pouring the reaction mixture onto ice-water (50 ml) an oil separated out. The oil was extracted into chloroform and the chloroform then evaporated off to yield a syrup which rapidly crystallized.

The product was recrystallized from ethanol giving 1,3-O-butylidene-2-deoxy-4,5-di-O-toluene-p-sulphonyl-D-erythro-pentitol, yield 0.84 g (65.1%), m.p. 120-121° (Found: C, 55.12; H, 6.09; S, 12.24. $C_{23}H_{30}O_8S_2$ requires: C, 55.40; H, 6.07; S, 12.86%).

Experiment 10 1,2:5,6-Di-O-isopropylidene-3-O-[(methylthio)-thiocarbonyl]-D-glucofuranose[141]

An excess of sodium pellets were added to a stirred solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (45 g) in ether (300 ml). The reaction mixture was stirred until hydrogen evolution had ceased, then refluxed for 6 h. After cooling, the supernatant liquid was decanted from unused sodium.

Carbon disulphide (60 ml) was added with stirring thereupon the reaction mixture solidified into a yellow mass. The solid was broken up then methyl iodide (50 ml) added. The reaction mixture was left stirring at room temperature for a further 20 h then filtered. The filtrate was concentrated under vacuo to a thick yellow syrup. This was the crude 1,2:5,6-di-O-isopropylidene-3-O-[(methylthio)$_{\lambda}^{thio}$carbonyl]-3-thio-D-glucofuranose. It was subsequently used without further purification.

Experiment 11 1,2:5,6-Di-O-isopropylidene-3-S-[(methylthio)-carbonyl]-3-thio-D-hexofuranose[141-143]

The crude product from the previous experiment was placed in a pressure equalized dropping funnel warmed by hot air. The syrup was then added dropwise into a pyrex tube (30 cm x 1 cm) which passed through a Griffin electric furnace (Type 17-90B). The crude xanthate ester was pyrolysed at 520° in a modified Chugaev reaction, the pyrolysate being drawn through the tube by means of a water pump vacuum system.

The pyrolysate was collected in a receiving vessel placed in a bath of ice-water. The collected solid was crushed and rinsed with a little chilled methanol to remove tarry by-products. Recrystallization from methanol afforded 1,2:5,6-di-O-isopropylidene-3-S-

[(methylthio) carbonyl]-3-thio-D-hexofuranose, yield 21.44 g, m.p. 143-145°, lit.[143] m.p. 143-144°.

Experiment 12 3-Deoxy-1,2:5,6-di-O-isopropylidene-D-ribo-hexofuranose[143]

A solution of 1,2:5,6-di-O-isopropylidene-3-S-[(methylthio)-carbonyl]-3-thio-D-hexofuranose (26.9 g) in 9:1 v/v ethanol-water (1250 ml) was refluxed for 3 h., in the presence of Raney nickel (450 ml of wet slurry). Filtration followed by evaporation yielded a residue which was distilled to give 3-deoxy-1,2:5,6-di-O-isopropylidene-D-ribo-hexofuranose, yield 10.3 g, as a colourless oil, b.p. 80°/0.2 torr (external bath temperature), lit.[143] b.p. 74-78°/0.3 torr.

Experiment 13 3-Deoxy-D-ribo-hexose

3-Deoxy-1,2:5,6-di-O-isopropylidene-D-ribo-hexofuranose (14.35 g) was dissolved in ethanol-water 4:1 v/v (750 ml) then Amberlite IR-120(H^+) resin (150 ml) added. The mixture was stirred and heated for 8 h at 70° then left to cool. When cool the resin was filtered off and the filtrate concentrated under reduced pressure to a syrup, yield 9.3 g. Thin layer chromatography in solvent A showed 2 spots, the main component having practically no mobility, the minor component was of higher R_F (approximately 0.5).

The syrup was fractionated on an alumina column (active, neutral grade, 500 g) eluting with ethanol-water (9:1). The high R_F component of the syrup eluted first to give what was presumed to be the bicyclic 1,6-anhydro-3-deoxy-β-D-ribo-hexopyranose.[144] The second component to be eluted from the column gave a positive Fehling's test and was assumed to be 3-deoxy-D-ribo-hexose. The compound was

isolated as a syrup which could not be induced to crystallize and was used without further purification.

Experiment 14 3-Deoxy-D-ribo-hexitol [145]

3-Deoxy-D-ribo-hexose (3.55 g) and sodium borohydride (0.5 g) were dissolved in water (100 ml) then left at room temperature for 24 h. The reaction mixture was worked up as in experiment 1 to give syrupy 3-deoxy-D-ribo-hexitol (3.17 g). Gas liquid chromatography of the syrup as its penta-O-trimethylsilyl ether [140] showed the product to be chromatographically homogeneous (retention time 1174 seconds, 7.5% A.P.K., 168°).

Experiment 15 C-1/^{2}H-3-Deoxy-D-ribo-hexitol

Sodium borodeuteride (0.19 g) was added to a solution of 3-deoxy-D-ribo-hexose (1.06 g) in water (30 ml). The mixture was left 24 h at room temperature then worked up in the usual manner. C-1/^{2}H-3-Deoxy-D-ribo-hexitol was obtained as a syrup, yield 0.86 g. Gas liquid chromatography of the syrup as its penta-O-trimethylsilyl ether showed it to be chromatographically pure.

Experiment 16 Reaction of 3-Deoxy-D-ribo-hexitol with n-Butyraldehyde

3-Deoxy-D-ribo-hexitol (1.80 g, 0.011 mol.) was dissolved in 0.5M-hydrochloric acid (110 ml) then n-butyraldehyde (0.78 g, 0.011 mol.) added. The mixture was shaken for 1 minute then left at room temperature for 48 h. The reaction mixture was then neutralised using 4M-sodium hydroxide. The neutral solution was concentrated under reduced pressure to a solid residue which was triturated with hot dry pyridine. The pyridine solution was concentrated to a syrup which crystallized upon standing overnight at room temperature.

Thin layer chromatography of the product in solvent A showed 2 main components, R_{F1}=0.0 (polyol), R_{F2} = 0.41 (2,4-monoacetal). The monoacetal was separated from the polyol by passage through an alumina column (300 g) using ethanol-water (9:1) as eluent. The fractions containing the monoacetal were combined and concentrated to a syrup which quickly crystallized at room temperature, yield 1.5 g. The compound was recrystallized from methyl acetate to give needle like crystals of 2,4-O-butylidene-3-deoxy-D-ribo-hexitol (R_F = 0.41 in solvent A), m.p. 112-112.5°, $[\alpha]_D^{27}$ = -4.7° (c, 1.15 in methanol) (Found: C, 54.53; H, 9.15. $C_{10}H_{20}O_5$ requires: C, 54.52; H, 9.15%).

Experiment 17 2,4-O-Butylidene-3-deoxy-1,5,6-tri-O-toluene-p-sulphonyl-D-ribo-hexitol

A solution of 2,4-O-butylidene-3-deoxy-D-ribo-hexitol (0.1 g) in dry pyridine (1.5 ml) was added to a solution of toluene-p-sulphonyl chloride (1.1 g) in dry pyridine (0.5 ml). The resultant solution was left at room temperature for 48 h then poured onto ice-water (25 ml). The mixture was extracted with chloroform and the chloroform layer concentrated to a syrup. The syrup was dissolved in hot ethanol (5 ml) and stored at 5°. After several days crystalline 2,4-O-butylidene-3-deoxy-1,5,6-tri-O-toluene-p-sulphonyl-D-ribo-hexitol formed, yield 0.22 g, m.p. 85-87° (Found: C, 54.51; H, 5.64; S, 14.17. $C_{31}H_{38}O_{11}S_3$ requires: C, 54.53; H, 5.61; S, 14.10%).

Experiment 18 Methyl α-D-galactopyranoside monohydrate[146]

Anhydrous D-galactose (50 g) was refluxed in methanolic hydrogen chloride (400 ml) for twelve hours. The solution was allowed to cool then shaken with lead carbonate until it was neutral.

When neutral, the inorganic salts were removed by filtration through celite. The filtrate was concentrated using a rotary evaporator at 50° to an amber syrup. The warm syrup was mixed with water (15 ml) and scratched. When cool, white crystals of methyl α-D-galactopyranoside monohydrate were deposited. The mixture was left for 1 day at room temperature then 1 day at 5° to complete the crystallization. The crystals were filtered and rinsed with chilled ethanol (2 x 10 ml), yield 17.9 g, m.p. 100-102°, lit.[145] m.p. 102-103°.

Experiment 19 Methyl 2,3,6-Tri-O-benzoyl-α-D-galactopyranoside[147,148]

The procedure followed was that of Williams and Richardson.[148] Methyl α-D-galactopyranoside monohydrate (74.2 g) was dissolved in dry pyridine (2250 ml) followed by dropwise addition of benzoyl chloride (170 ml) at -30°. The reaction mixture was then kept for two hours at -20° then allowed to warm up to room temperature overnight. The pyridine was removed under reduced pressure on a rotary evaporator at 40°. The residue was dissolved in chloroform (1000 ml) then successively washed with M-hydrochloric acid (800 ml), 5% sodium bicarbonate (800 ml), and water (800 ml). The chloroform layer was then dried over magnesium sulphate, filtered and concentrated to a solid. The solid was twice recrystallized from ethanol to give methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside, yield 109 g, m.p. 137-139°, lit.[148] m.p. 139-140° (Found: C, 66.30; H, 5.19. $C_{28}H_{26}O_9$ calc. : C, 66.40; H, 5.18%).

Experiment 20 Methyl 2,3,6-Tri-O-benzoyl-4-O-methanesulphonyl-α-D-galactoside[148]

Methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside (109 g) was dissolved in dry pyridine (1150 ml) then the solution was cooled in an ice bath. Methanesulphonyl chloride (18.2 ml) was added dropwise with stirring, the temperature being kept at 0°. When addition was complete the reaction mixture was allowed to reach room temperature and left two days. After such time, water (100 drops) was added to decompose any remaining methanesulphonyl chloride. The reaction mixture was then poured onto ice-water (4000 ml). The solid product was collected then dissolved in chloroform (1000 ml). The chloroform solution was successively washed with M-hydrochloric acid (1000 ml), 5% sodium bicarbonate (1000 ml), and water (1000 ml). The chloroform layer was then dried over magnesium sulphate and concentrated to a syrup. The syrup was dissolved in hot ethanol (1000 ml) then left to cool. The deposited crystals were recrystallized from ethanol giving methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-galactoside, yield 105 g, m.p. 141-142°, lit.[148] m.p. 143-144° (Found: C, 59.39; H, 4.75; S, 5.54. $C_{29}H_{28}O_{11}S$ calc.: C, 59.58; H, 4.85; S, 5.48%).

Experiment 21 Methyl 2,3,6-Tri-O-benzoyl-4-deoxy-4-thiocyano-α-D-glucoside [149]

Methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-galactoside (51.65 g) was dissolved in dry N,N-dimethylformamide (450 ml), then potassium thiocyanate (67 g) was added. The mixture was stirred at 140° for two days. After cooling, the mixture was poured onto ice-water (4500 ml) whereupon a brown solid separated out. The

solid was purified by passage down a silica-gel (Merck 7734) column (2000 g) eluting with chloroform. The eluting fractions were tested by thin layer chromatography in chloroform. The appropriate fractions were combined and the solvent removed on a rotary evaporator. The residual solid was recrystallized from ethanol-chloroform (9:1) to give methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-thiocyano-α-D-glucoside, yield 33.2 g (R_F = 0.64 in chloroform), m.p. 189-191°, lit.[149] m.p. 194-194.5°. (Found: C, 63.59; H, 4.77; N, 2.41; S, 5.68. $C_{29}H_{25}NO_8S$ calc.: C, 63.61; H, 4.6; N, 2.56; S, 5.86%).

Experiment 22 Methyl 2,3,6-Tri-O-benzoyl-4-Deoxy-α-D-xylo-hexoside

Methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-thiocyano-α-D-glucoside (32.16 g) was added to a suspension of freshly prepared Raney nickel (75 g) in ethanol (750 ml). The mixture was refluxed for six hours then filtered (celite), the residual nickel was leached with a further portion of ethanol (500 ml) then this also filtered. The combined filtrate was concentrated at reduced pressure to a residual solid. The solid was recrystallized from methanol giving methyl 2,3,6-tri-O-benzoyl-4-deoxy-α-D-xylo-hexoside, yield 15.0 g, m.p. 112-113° (Found: C, 68.31; H, 5.58; $C_{28}H_{26}O_8$ requires: C, 68.56; H, 5.34%).

Experiment 23 Methyl 4-deoxy-α-D-xylo-hexoside [143]

To a stirred solution of methyl 2,3,6-tri-O-benzoyl-4-deoxy-α-D-xylo-hexoside (5.12 g) in methanol (100 ml) and chloroform (25 ml) was added methanolic sodium methoxide (3 ml, 0.5M). After four hours thin layer chromatography in solvent B showed no trace of the starting material (R_F = 0.64). Only one component was present and it had no mobility in solvent B. The reaction mixture

was neutralised using 0.1M-hydrochloric acid then the solvent mixture removed at reduced pressure on a rotary evaporator. The residue was partitioned between a chloroform and water mixture. The aqueous layer was concentrated to yield a syrup which was dissolved in hot ethyl acetate. When cool, crystalline methyl 4-deoxy-α-D-xylo-hexoside formed, yield 1.33 g, m.p. 91-92°, lit.[143] m.p. 90°.

Experiment 24 4-Deoxy-D-xylo-hexose[143]

A solution of methyl 4-deoxy-α-D-xylo-hexoside (1.33 g) in M-sulphuric acid (20 ml) was boiled for six hours. The solution was neutralised using saturated barium hydroxide solution then the mixture was filtered. The filtrate was concentrated to a syrup which could not be induced to crystallize, yield 1.19 g. Gas liquid chromatography of the syrup as its t.m.s. derivative on the Pye-104 instrument (7 ft A.P.K. column, 164°) showed two peaks with retention times 1042 and 1557 seconds. The two peaks were attributed to the α- and β-anomers of the sugar. Also, a Fehling's test on the syrup was positive thus it was accorded the structure 4-deoxy-D-xylo-hexose.

Experiment 25 4-Deoxy-D-xylo-hexitol

A solution of 4-deoxy-D-xylo-hexose (1.0 g) in water (40 ml) was mixed with sodium borohydride (0.2 g) and left at room temperature for 2 days. The reaction was worked up as in experiment 1. The syrupy product crystallized overnight at room temperature and was recrystallized from ethanol. A Fehling's test on the product was negative showing the absence of any reducing sugar. The productwas assigned the structure 4-deoxy-D-xylo-hexitol,

yield 0.75 g, m.p. 93-94°, lit.[150] m.p. 90-93° (L-isomer) (Found: C, 43.35; H, 8.1. $C_6H_{14}O_5$ calc.: C, 43.36; H, 8.4%).

Experiment 26 C-1/^{2}H-4-Deoxy-D-xylo-hexitol

Sodium borodeuteride (0.1 g) was added to a solution of 4-deoxy-D-xylo-hexose (0.30 g) in water. After 24 h at room temperature the usual work-up was applied resulting in C-1/^{2}H-4-deoxy-D-xylo-hexitol, yield 0.14 g, m.p. 90-92°.

Experiment 27 Reaction of 4-Deoxy-D-xylo-hexitol with n-Butyraldehyde

A solution of 4-deoxy-D-xylo-hexitol (2.38 g, 0.014 mol.) and n-butyraldehyde (1.01 g, 0.014 mol.) in 0.5M-hydrochloric acid was left at room temperature for 2 days. The solution was then neutralised using 4M-sodium hydroxide. The neutral solution was concentrated under reduced pressure to a solid residue. The residue was triturated with hot absolute ethanol. The ethanolic solution was concentrated under reduced pressure to a syrup. Thin layer chromatography of the syrup in solvent A showed 3 components, R_{F1} = 0.0 (polyol), R_{F2} = 0.41 (1,3-monoacetal), R_{F3} = 0.49 (2,3-monoacetal).

The monoacetals were separated from unreacted polyol by passage through an alumina column (250 g) eluting with ethanol-water (9:1). The monoacetal fraction was itself fractionated using a Dowex 1-X8 (OH^-) resin column eluting with carbon dioxide free deionized water. The 1,3-monoacetal was eluted first. Collection, then concentration of the appropriate fractions gave a syrup which rapidly crystallized, yield 0.9 g. Recrystallization from ethyl acetate gave 1,3-O-butylidene-4-deoxy-D-xylo-hexitol, m.p. 107-108°

(R_F = 0.41 in solvent A), $[\alpha]_D^{26.5}$ = -14.7° (c, 1.25 in methanol) (Found: C, 54.87; H, 9.22. $C_{10}H_{20}O_5$ requires: C, 54.53; H, 9.15%).

The 2,3-monoacetal eluted next from the column. Similar treatment gave a syrup which again quickly crystallized, yield 0.29 g. Recrystallization from ethyl acetate gave 2,3-O-butylidene-4-deoxy-D-xylo-hexitol, m.p. 79-80° (R_F = 0.49 in solvent A), $[\alpha]_D^{26.5}$ = -55.7° (c, 0.85 in methanol) (Found: C, 54.48; H, 8.83. $C_{10}H_{20}O_5$ requires: C, 54.53; H, 9.15%).

Experiment 28 Tetra-n-butylammonium Fluoride[151]

A 40% aqueous solution of tetra-n-butylammonium hydroxide (300 ml) was titrated against a 40% aqueous solution of hydrogen fluoride in a large necked plastic bottle using indicator paper. The neutral solution was concentrated to remove as much water as possible under reduced pressure at 25°. The resultant syrup was stored over phosphor us pentoxide at 0.5 torr with daily replenishment of the drying agent until the syrup was a constant weight. Initially the syrup formed a crystalline dodecahydrate which then formed a further syrup upon prolonged drying, yield 112.9 g.

Experiment 29 1,2:5,6-Di-O-isopropylidene-α-D-allofuranose[152]

A solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (13 g) in dimethyl sulphoxide (150 ml) was mixed with acetic anhydride (100 ml). The mixture was left for 24 hours at room temperature then concentrated to a syrup by means of vacuum distillation (40°/0.05 torr). The syrup of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose was dissolved in ethanol-

water (7:3, 500 ml) and sodium borohydride added (13 g). The mixture was left for thirty minutes then poured onto water (700 ml). The reaction products were extracted into ethyl acetate (8 x 500 ml), the ethyl acetate solution dried over anhydrous sodium sulphate, then filtered. The filtrate was then concentrated to a syrup under reduced pressure. Thin layer chromatography of the syrup in solvent C showed two spots, $\underline{R}_{F1}$ = 0.35 (diacetone allose), $\underline{R}_{F2}$ = 0.41 (diacetone glucose).

The two isomers were separated using a silicic acid column (500 g, Sigma SIL-R-100-300 mesh), eluting with solvent C. The appropriate fractions were collected and concentrated to give 1,2:5,6-di-O-isopropylidene-α-D-allofuranose, yield 9.25 g. The product was recrystallized from benzene-ether (9:1), m.p. 76-77°, lit.[152] m.p. 77-78° (Found: C, 55.49; H, 7.68. $C_{12}H_{20}O_6$ calc.: C, 55.37; H, 7.75%).

Experiment 30 1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose[153]

A solution of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (8.66 g) in dry pyridine (70 ml) was mixed with a solution of toluene-p-sulphonyl chloride (11.0 g) in dry pyridine (50 ml) and the resultant solution left at room temperature for 2 days. The mixture was poured onto ice-water (1500 ml), the white solid deposited was filtered off and recrystallized from ethanol giving 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose, yield 12.57 g, m.p. 119-120°, lit.[153] m.p. 121° (Found: C, 55.17; H, 6.16; S, 7.68. $C_{19}H_{26}O_8S$ calc.: C, 55.1; H, 6.3; S, 7.7%).

Experiment 31 3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose [151]

1,2:5,6-Di-O-isopropylidene-3-O-toluene-p-sulphonyl-α-D-allofuranose (18.54 g) was added to a solution of tetra-n-butyl-ammonium fluoride (106 g) in dry acetonitrile (100 ml). The mixture was stirred and heated for 3 days at 70-80°. The reaction as followed by thin layer chromatography in solvent D showed two main spots, R_{F1} = 0.17 (decreased with time), R_{F2} = 0.23 (increased with time). After 3 days the reaction mixture was poured onto ether (250 ml). The ether layer was washed with water (2 x 100 ml), dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure at 40°C to give a syrup. The syrup was purified by column chromatography on silica gel (180 g, Merck 7734, 70-230 mesh), eluting with solvent D. The column eluent was tested by thin layer chromatography and the early fractions concentrated to give a pale yellow syrup of 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, yield 8.37 g.

Experiment 32 3-Deoxy-3-fluoro-D-glucose [151]

A solution of 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (7.1 g) in ethanol (70 ml) was mixed with water (350 ml) and Amberlite IR-120(H^+) resin (100 ml). The mixture was stirred and heated at 70° for four hours. Thin layer chromatography in ethyl acetate showed the hydrolysis to be complete. The mixture was filtered, the filtrate concentrated to a syrup and the syrup seeded. The deposited crystals were recrystallized from 1:1 v/v ethanol-ethyl acetate to give 3-deoxy-3-fluoro-D-glucose, yield 3.17 g, m.p. 114-115°, lit.[151] m.p. 114-115°.

Experiment 33 3-Deoxy-3-fluoro-D-glucitol [135]

3-Deoxy-3-fluoro-D-glucose (0.77 g) in water (22 ml) was mixed with sodium borohydride (0.1 g). After 20 hours the solution was non-reducing to Fehling's reagent, excess borohydride was destroyed by addition of a few drops of glacial acetic acid. The solution was then shaken with Amberlite IR-120(H^+) resin (20 ml) filtered and the filtrate concentrated to a syrup. The syrup quickly crystallized and was recrystallized from 2:1 v/v methanol-ethyl acetate to give 3-deoxy-3-fluoro-D-glucitol, yield 0.58 g, m.p. 120-122°, lit.[135] m.p. 128-133° (Found: C, 39.16; H, 6.87; F, 10.09. $C_6H_{13}FO_5$ calc.: C, 39.13; H, 7.12; F, 10.32%).

Experiment 34 C-1/^{2}H-3-Deoxy-3-fluoro-D-glucitol [135]

Sodium borodeuteride (0.06 g) was added to a solution of 3-deoxy-3-fluoro-D-glucose (0.33 g) in distilled water (10 ml). The experiment was continued in identical fashion as that for the non deuterio fluoro polyol. C-1/^{2}H-3-Deoxy-3-fluoro-D-glucitol was obtained crystalline, yield 0.259 g (79%), m.p. 119-120°, lit.[135] m.p. 117-120°.

Experiment 35 Reaction of 3-Deoxy-3-fluoro-D-glucitol with n-Butyraldehyde

A mixture of 3-deoxy-3-fluoro-D-glucitol (3.28 g, 0.017 mol.), n-butyraldehyde (1.22 g, 0.017 mol.) and 0.5M-hydrochloric acid (180 ml) was left at room temperature for 3 days. The mixture was then neutralised with 4M-sodium hydroxide and the neutral solution concentrated under reduced pressure to a residue. The residue was triturated with hot dry pyridine then the pyridine solution concentrated to a syrup which slowly crystallized. Thin layer

chromatography of the crystals in solvent A showed three components,

$\underline{R}_{F1} = 0.22$ (polyol), $\underline{R}_{F2} = 0.53$ (2,4-monoacetal), $\underline{R}_{F3} = 0.59$ (4,6-monoacetal).

The monoacetal fraction was separated from the polyol in the usual manner with an alumina column. The monoacetal fraction was collected then tested by thin layer chromatography and gas liquid chromatography. Both techniques showed the presence of two monoacetals. An attempt was made to separate the two monoacetals from each other using a Dowex 1-X8 column eluting with carbon dioxide free deionised water. However, the only monoacetal to be eluted from the column was 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol, yield 1.18 g. The monoacetal was recrystallized from ethyl acetate as needles m.p. 130-131° ($\underline{R}_F = 0.53$ in solvent A) $[\alpha]_D^{27°} = +9.1°$ (c, 1.06 in methanol) (Found: C, 50.50; H, 8.20; F, 7.86. $C_{10}H_{19}FO_5$ requires: C, 50.41; H, 8.04; F, 7.98%). The Dowex column was continually eluted but no trace of another monoacetal or fluoro polyol was found.

Experiment 36 1,5,6-Tri-O-acetyl-2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol

A solution of 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol (0.049 g) in dry pyridine (2 ml) was mixed with acetic anhydride (0.2 ml) and left at room temperature for 2 days. The mixture was then poured onto ice-water (75 ml) and the resultant crystals of 1,5,6-tri-O-acetyl-2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol collected by vacuum filtration, yield 0.039 g, m.p. 84-85°

(Found: C, 52.69; H, 6.95; F, 5.08. $C_{16}H_{25}FO_8$ requires: C, 52.74; H, 6.92; F, 5.21%).

Experiment 37 Acetylated Methylated 3-Deoxy-3-fluoro-D-glucitols

A portion (0.35 g) of the polyol free mixed monoacetals of 3-deoxy-3-fluoro-D-glucitol obtained from the alumina column was dissolved in ethyl acetate (10 ml). The solution was seeded with 2,4-O-butylidene-3-deoxy-3-fluoro-D-glucitol and stored at 5° for 24 h. The deposited crystals were filtered off, leaving a mother liquor enriched with the previously unisolatable monoacetal. The mother liquor was then concentrated to a syrup, yield 0.23 g. A portion (0.09 g) of the syrup was methylated by the procedure described in general techniques. Thin layer chromatography of the syrupy mixed methylated acetals showed one spot, R_F = 0.59 in solvent E.

The syrup of methylated acetals was dissolved in ethanol-0.5M-hydrochloric acid (10 ml, 1:1) then heated for 2 h on a boiling water bath. Thin layer chromatography in solvent E showed acetal hydrolysis to be complete. The solution was neutralised with M-sodium hydroxide, concentrated under reduced pressure to a residue then triturated with hot ethyl acetate. The ethyl acetate solution was concentrated to give a syrupy mixture of 3-deoxy-3-fluoro-tri-O-methyl-D-glucitol's, yield 0.064 g. Thin layer chromatography showed two main components, R_{F1} = 0.17 (3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol) R_{F2} = 0.14 (3-deoxy-3-fluoro-1,2,5-tri-O-methyl-D-glucitol). The partially methylated polyol mixture (0.03 g) was then acetylated using the method outlined in general techniques. This resulted in a solution containing two different di-O-acetyl-3-deoxy-3-fluoro-tri-O-methyl-D-glucitols

derived from the two different monoacetals. This solution was then subjected to a gas liquid chromatography/mass spectrometry analysis.

Experiment 38 2,4-Di-O-acetyl-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol

2,4-O-Butylidene-3-deoxy-3-fluoro-D-glucitol (0.045 g) was methylated to give syrupy 2,4-O-butylidene-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol. Thin layer chromatography in solvent E showed one component (R_F = 0.59). The acetal ring was hydrolysed to give syrupy 3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol (R_F = 0.16 in solvent E), yield 0.034 g. The methylated polyol was acetylated leaving a solution of 2,4-di-O-acetyl-3-deoxy-3-fluoro-1,5,6-tri-O-methyl-D-glucitol which was further investigated by gas liquid chromatography/mass spectrometry. The methylation, hydrolysis and acetylation were carried out as in general techniques and experiment 37.

Experiment 39 Deuterium Labelled Acetylated Methylated 3-Deoxy-3-fluoro-D-glucitols

The acetal synthesis was carried out as described in experiment 35 up to the point of obtaining the mixed monoacetals free from polyol off an alumina column. The synthesis was scaled down starting with 3-deoxy-3-fluoro-D-glucitol (0.284 g). Also the starting material was monodeuterated at carbon 1. The deuterium labelled monoacetal fraction was treated in identical fashion as that in experiment 37. The resultant solution containing deuterated, methylated alditol acetates was then analysed by gas liquid chromatography/mass spectrometry.

Experiment 40 6-Deoxy-D-galactitol (D-fucitol)

Sodium borohydride (0.15 g) was added to an aqueous solution (30 ml) of α-D-fucose (1 g) then left at room temperature for 2 days. The reaction was neutralised using Amberlite IR-120(H^+) resin then filtered. The filtrate was concentrated to a syrup which was then taken up in methanol. The methanol was then removed under reduced pressure. This was repeated six times (6 x 50 ml). The residue was a white solid which was recrystallized from methanol to give D-fucitol, yield 0.63 g, m.p. 152-153°, lit.[154] m.p. 153-154°.

Experiment 41 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose[155]

To a suspension of anhydrous D-galactose (200 g) in acetone (2500 ml) was added powdered zinc chloride (240 g), then concentrated sulphuric acid (8 ml). The mixture was stirred for four hours at room temperature then treated with hydrated sodium carbonate (400 g) in water (700 ml). After further stirring for 30 minutes the mixture was filtered, the collected salts rinsed with acetone and the filtrates combined. The acetone was removed under reduced pressure leaving a mixture consisting of two liquid phases. The mixture was shaken with ether (1000 ml), then the ether layer collected, washed with water (1000 ml), dried over magnesium sulphate and filtered. The filtrate was concentrated to a syrup of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, yield 203 g.

Experiment 42 1,2:3,4-Di-O-isopropylidene-6-O-methanesulphonyl-α-D-galactopyranose[156]

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (200 g) in dry pyridine (1200 ml) was cooled in a bath of ice-water. Methanesulphonyl chloride (80 ml) was added dropwise to the cooled, stirred solution. The resultant solution was kept at 0° for three hours then

allowed to attain room temperature overnight. When poured onto ice-water (800 ml), a white solid was deposited. The solid was collected and recrystallized from methanol to give 1,2:3,4-di-O-isopropylidene-6-O-methanesulphonyl-α-D-galactopyranose, yield 189 g, m.p. 120-121.5°, lit.[156] m.p. 122°.

Experiment 43 6-Deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose[157]

A mixture of 1,2:3,4-di-O-isopropylidene-6-O-methanesulphonyl-α-D-galactopyranose (75 g) and anhydrous potassium fluoride (75 g) was gently refluxed for seventy five minutes in dry ethanediol (600 ml). When cool, the mixture was poured onto water (2500 ml) and the resultant mixture ether extracted (2 x 1000 ml). The ether layer was dried over anhydrous sodium sulphate, filtered and concentrated to give the crude product as a syrup Thin layer chromatography of the syrup in 9:1 v/v toluene-ether showed two main spots, R_{F1} = 0.12 (starting material), R_{F2} = 0.35 (fluorinated product). The crude syrup was purified by column chromatography with silica gel (1250 g, Merck 7734,70-230 mesh) using 9:1 v/v toluene-ether as eluent. The fast moving fraction was collected, giving syrupy 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, yield 32.34 g (Found: C, 54.31; H, 7.34; F, 7.05. $C_{12}H_{19}FO_5$ calc.: C, 54.95; H, 7.30; F, 7.24%).

Experiment 44 6-Deoxy-6-fluoro-α-D-galactopyranose[157]

A solution of 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (19.70 g) in methanol (300 ml) was mixed with 0.02M-sulphuric acid (500 ml). The reaction mixture was then

boiled for four hours on a water bath. When cool, the solution was neutralised using 0.1M-barium hydroxide. The mixture was filtered and the filtrate concentrated under reduced pressure to a solid residue, yield 12.26 g. The solid was recrystallized from methanol giving 6-deoxy-6-fluoro-α-D-galactopyranose, m.p. 160-161°, lit.[157] m.p. 160°.

Experiment 45 6-Deoxy-6-fluoro-D-galactitol[158]

A solution of 6-deoxy-6-fluoro-α-D-galactopyranose (0.52 g) in water (15 ml) was mixed with sodium borohydride (0.1 g), then the mixture left at room temperature for 48 hours. The work-up procedure was then as in experiment 1. The solid obtained was recrystallized from methanol to give 6-deoxy-6-fluoro-D-galactitol, yield 0.37 g, m.p. 175-176°, lit.[158] m.p. 173-174° (Found: C, 39.24; H, 7.32; F, 10.09. $C_6H_{13}FO_5$ calc.: C, 39.13; H, 7.12; F, 10.32%).

Experiment 46 Reaction of 6-Deoxy-6-fluoro-D-galactitol with n-Butyraldehyde

A solution of 6-deoxy-6-fluoro-D-galactitol (6.3 g, 0.034 mol.), n-butyraldehyde (2.45 g, 0.034 mol.) and 0.5M-hydrochloric acid (345 ml) was left two days at room temperature. It was then neutralised using 4M-sodium hydroxide and the neutral solution concentrated to a residue under reduced pressure. The residue was triturated with hot dry pyridine then the pyridine solution concentrated under reduced pressure. Thin layer chromatography in solvent A showed the presence of unreacted polyol and several monoacetals.

The monoacetal fraction was separated from the polyol using an alumina column. Thin layer chromatography and gas liquid chromatography revealed the monoacetal components to be unchanged after passage through the alumina column. The monoacetals were then passed through a Dowex 1-X8 (OH^-) column for an attempted fractionation.

The first material to be eluted from the Dowex 1-X8 (OH^-) column was a mixture consisting of 2,5-anhydro-1,3-O-butylidene-L-altritol and 2,6-anhydro-1,3-O-butylidene-D-galactitol, composite yield 1.26 g. The latter compound was isolated pure by fractional crystallisation using an ethyl acetate/pet. ether solvent mixture with addition of pet. ether until slight turbidity then leaving at room temperature, m.p. 109-110° (R_F = 0.43 in solvent A), $[\alpha]_D^{26°}$ = -67.2° (c, 1.08 in methanol) (Found: C, 54.71; H, 8.20. $C_{10}H_{18}O_5$ requires: C, 55.03; H, 8.31%).

The next component to be eluted from the Dowex 1-X8(OH^-) column was 4,5-O-butylidene-6-deoxy-6-fluoro-D-galactitol which quickly crystallized and was recrystallized from ethyl acetate, yield 0.29 g, m.p. 83-84° (R_F = 0.58 in solvent A), $[\alpha]_D^{26°}$ = +22.6° (c, 1.01 in methanol) (Found: C, 50.55; H, 8.17; F, 7.85. $C_{10}H_{19}FO_5$ requires: C, 50.41; H, 8.04; F, 7.98%).

The final component to be eluted from the Dowex 1-X8(OH^-) column was 2,3-O-butylidene-D-galactitol obtained as a syrup which quickly crystallized and was recrystallized from ethyl acetate, yield 0.19 g, m.p. 84-85° (R_F = 0.42 in solvent A, lit.[45] R_F = 0.38 in solvent A), $[\alpha]_D^{26°}$ = -30.2° (c, 0.94 in methanol) (Found: C, 50.48; H, 8.43. $C_{10}H_{20}O_6$ calc.: C, 50.83; H, 8.53%).

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