CONFORMATIONAL STUDIES OF FURANOSYL FLUORIDES BY PROTON AND FLUORINE NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

by

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ABSTRACT

Proton and fluorine nuclear magnetic resonance spectroscopy was used to investigate the favoured forms of several furanosyl fluorides. The low energy barrier to pseudo-rotation in these systems precludes the assignment of only one favoured conformation for each molecule. A systematic study of five membered ring sugar conformations was undertaken by examining three types of systems, varying from a relatively rigid molecule involving three fused rings, to more flexible molecules involving a "free" furanosyl fluoride ring. The spectral assignment was greatly facilitated by heteronuclear fluorine decoupling and computer analysis.

5-fluoro-3,6-anhydro-α-L-idofuranose was synthesized in good yield from several precursors and the molecule's furanose ring conformation of $_2T^3$ was assigned on the basis of vicinal ^1H-^1H coupling constants. Using the values for vicinal ^1H-^{19}F couplings obtained from this molecule, together with data from other workers, a partial Karplus type curve was constructed relating vicinal ^1H-^{19}F couplings to dihedral angles. This curve - which was found to be more asymmetric than the Karplus relationshp for vicinal ^1H-^1H couplings - was then used, together with the known

Karplus curve for vicinal ^{1}H-^{1}H couplings, to determine the conformations of the triester furanosyl fluorides of ribose, arabinose and xylose. Assuming pure sp^3 hybridization and maximum ring puckering, the conformations for most of the sugars studied were found to involve the displacement of C_2 and/or C_3 positions out of the plane of the ring formed by the other atoms. The conformation for α-fluoro-ribofuranosyl triester ($_3T^4$) was found to be different than that of the β-fluoro-ribofuranosyl triester ($^1T_2$). A significant and apparently stereospecific long-range $^4J_{H_4,F}$ coupling through oxygen of ca. 6.5 Hz. is observed when H_4 and F are in a trans arrangement, while a much smaller coupling for $^4J_{H_4,F}$ of ca. 1.0 Hz. is observed when these two nuclei are in a cis or approximately "planar M" arrangement. On the other hand, $^4J_{H_3,F}$ couplings were found to have a value of ca. 2.2 Hz. in the cis or "planar M" geometry, while in the trans geometry, $^4J_{H_3,F}$ is ca. 0.5 Hz.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF FLOW SHEETS

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Special thanks are extended to Dr. C. Pedersen for providing several compounds which added significantly to the scope of this study.

INTRODUCTION

In the past two decades organic chemists have become increasingly interested in the field of conformational analysis. Such interest arises from the seemingly close relationship between molecular conformation and the chemical and thermodynamical properties of a molecule. This present study was undertaken with the object of determining the favoured conformation of various furanose sugars by utilizing proton (^{1}H) and fluorine (^{19}F) nuclear magnetic resonance spectroscopy.

The elucidation of the conformation of pyranose carbohydrates and other saturated six membered rings by proton magnetic resonance (^{1}H n.m.r.) has in recent years demonstrated the strength of this spectroscopic tool (1,2). Most of these studies have been based on the use of vicinal coupling constants, however, the observations of chemical shift between axial and equatorial protons (Δ_{ae}) is also important. Initially, it was concluded that the proton of an equatorially oriented hydrogen resonates at lower field by ca. 0.5 p.p.m. than that of a chemically similar but axially oriented hydrogen (17). However, more recent studies have shown several cases where this trend is reversed (18).

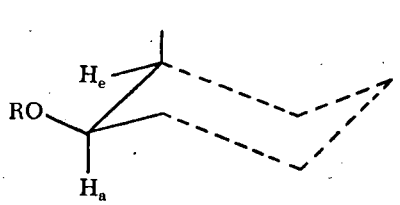
In 1959 Karplus determined the now famous

semi-theoretical relationship between vicinal proton coupling constants and dihedral angles for ethane type molecules (3). The generalized Karplus equation has the form

$$J = J_o \cos^2\phi + K$$

where J is the vicinal coupling constant due to the interaction between two hydrogen atoms bound to adjacent carbon atoms and separated by a dihedral angle of ϕ. J_o and K are coefficients which have a value of K = -0.28 and J_o = 8.5 for $0^\circ < \phi < 90^\circ$ and J_o = 9.5 for $90^\circ < \phi < 180^\circ$. A plot of vicinal coupling constant against dihedral angle (Figure 1) gives an unsymmetrical curve about the negative coupling at $\phi = 90^\circ$. This relationship has been applied to other molecular systems by slightly modifying the parameters J_o and K (4,5,6).

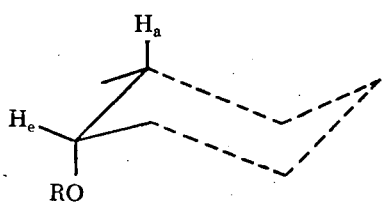
Recently Williams and Bhacca (7), when investigating a series of steroidal alcohols, observed a configurational dependence (as shown in A and B) for vicinal coupling constants where electronegative substituents are involved. This dependence



A

R = H or Ac

$J_{a,e} = 5.5 \pm 1.0$ Hz.



B

R = H or Ac

$J_{e,a} = 2.5$—3.2 Hz.

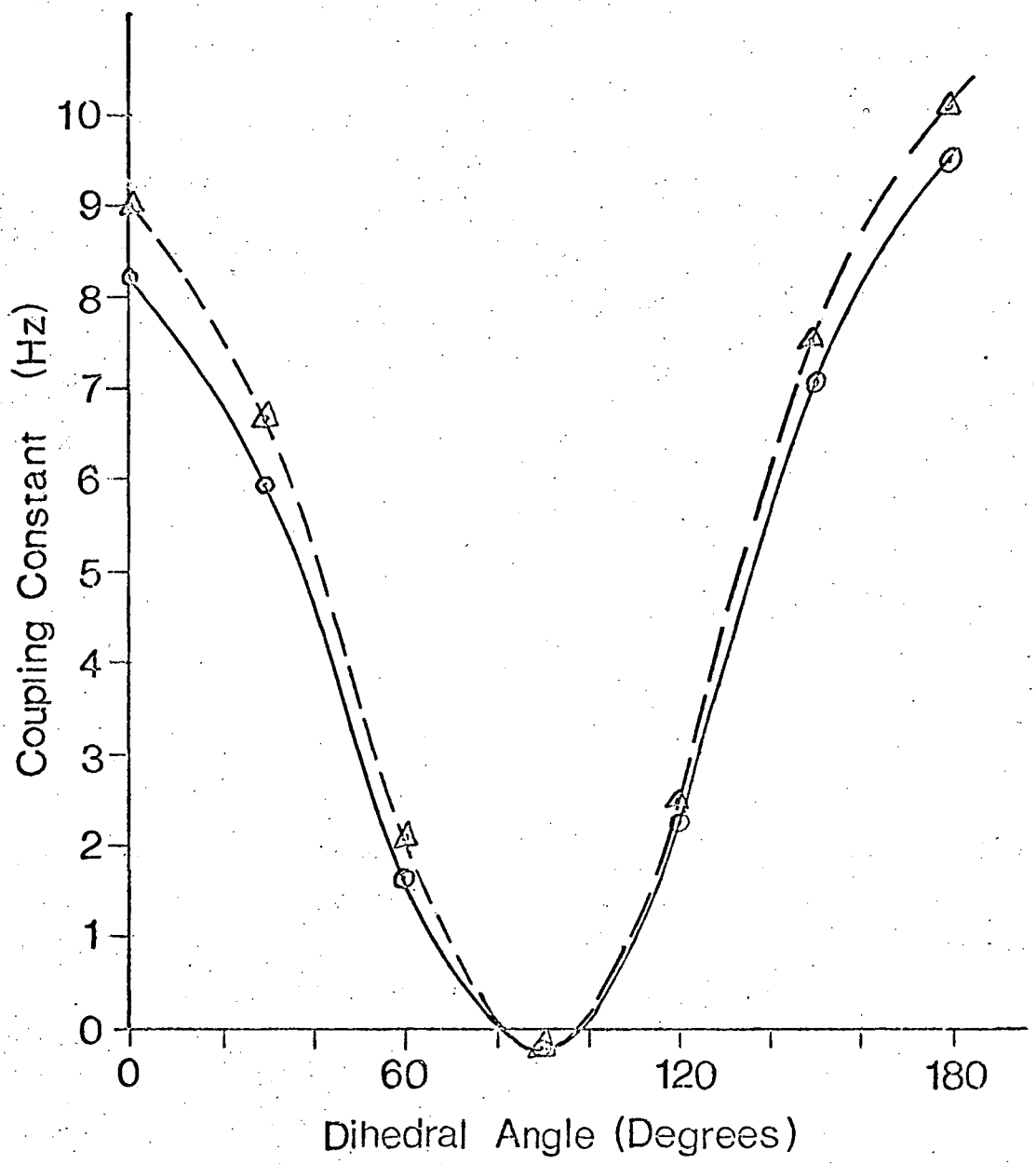


FIG. 1 The Karplus curve for $J = J_o\cos^2\phi + K$; ___ the relationship for ethane with $K = -0.28$ and $J_o = 8.5$ for $0^\circ < \phi < 90^\circ$ and $J_o = 9.5$ for $90^\circ < \phi < 180^\circ$. --- the modified relationship for carbohydrates (See Reference 1) with $K = -0.28$ and $J_o = 9.5$ for $0^\circ < \phi < 90^\circ$ and $J_o = 10.5$ for $90^\circ < \phi < 180^\circ$.

also has been reported in pyranose sugars (8,9). This configurational dependence appears to be maximal when the electronegative substituent is co-planar with one of the protons involved in the vicinal coupling (10) as in B. Indeed several authors have suggested that a linear relationship exists between vicinal coupling constants and the electronegativity of substituents on these centres (19). However, by using a larger range of electronegative substituents, this relationship now appears to be exponential, that is, as the electronegativity of the substituent increases, the J's decrease sharply (20).

Although most conformational studies have been based on ^{1}H n.m.r. spectroscopy, such spin $^{1}/_{2}$ nuclei as ^{19}F, ^{13}C and ^{31}P also have been utilized for conformational studies (11). In a recent communication (9) Hall and Manville have shown that fluorine can be used as a probe to determine the conformations of glycosyl fluorides. This concept now has been applied to other specifically fluorinated carbohydrates (12). Introduction of a fluorine substituent provides increased sensitivity since the order of magnitude of vicinal fluorine-hydrogen coupling constants are three to four times greater than the vicinal proton-proton J's (21).

Roberts has shown from his investigation of 1,1 difluorocyclohexanes that a large chemical shift difference of 15 to 20 p.p.m. exists between the axial and equatorial fluorines. Similar observations have been reported for pyranose sugars (9). This chemical shift difference is almost forty times that observed for hydrogen.

Studies to determine the precise dihedral angle dependence of vicinal J_{HF} have involved several groups (9,23). Recently Williamson (24) reported the angular dependence of J_{HF} using a series of compounds with "minimized substituent effects". From several bicyclic compounds which are assumed to have fixed dihedral angles, Williamson found the vicinal J_{HF} to dihedral angle dependence to have the same shape curve as that for vicinal J_{HH}, with a maximum at 0° of 31 Hz., a minimum at 90° (ca. 0 Hz.) and a maximum of 44 Hz. at 180°. However, as pointed out in the author's discussion, these coupling constants seem to be extremely dependent on bond angle and since one is dealing chiefly with strained systems, the assumption of sp^3 hybridization and interpolation of dihedral angle from X-ray data may not be valid in many of these cases.

The primary concern of this study was a conformational investigation of specifically fluorinated furanoses.

The conformations of five membered rings are of general interest since, next to six membered rings they comprise the second most abundant ring form in organic compounds. For example: ring D of steroids, nucleotides and many heterocyclic compounds all contain five membered rings. Indeed the presence of furanose forms of ribose and 2-deoxy-ribose in RNA and DNA respectively - two very important molecules in the life process - has initiated many of the conformational investigations of the five membered ring forms (25).

In the case of cyclopentane, Pitzer (26) has shown by thermodynamical calculations that the repulsion of the neighbouring hydrogen atoms will favour a puckering of the ring at the expense of deviating from the normal tetrahedral angles. In effect, this puckering is not fixed but rotates around the ring by an up and down motion often referred to as "pseudorotation".

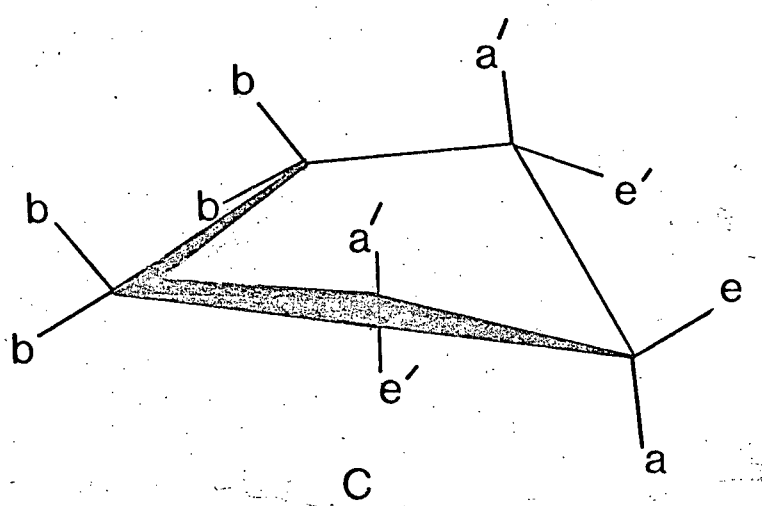
Hendrickson (27), using a computer program which essentially ignored symmetry restrictions, calculated the preferred conformation of cyclopentane by minimization of the total energy with respects to bond angle strain, torsional strain, non-bonding repulsions and non-bonding attractions. His results confirmed Pitzer's pseudorotation concept.

Hence in contrast to the two stable chair forms

of cyclohexane where both angle and torsional strain are minimum, cyclopentane has numerous possible conformations with similar energies and low energy barrier separations. If only the two symmetric forms - envelope and twist - are used*, twenty conformations are possible.

In order to facilitate a meaningful discussion of furanose conformations - one which allows a workable concept of five membered ring forms - the envelope and twist conformations will only be considered here. Such a restriction has been applied successfully by other workers (28).

In cyclopentane the conformations can be described in the following manner: the envelope form (C) has one carbon above or below the plane of the ring defined by the other four



carbon atoms. Five types of bonds are present in this conformer:

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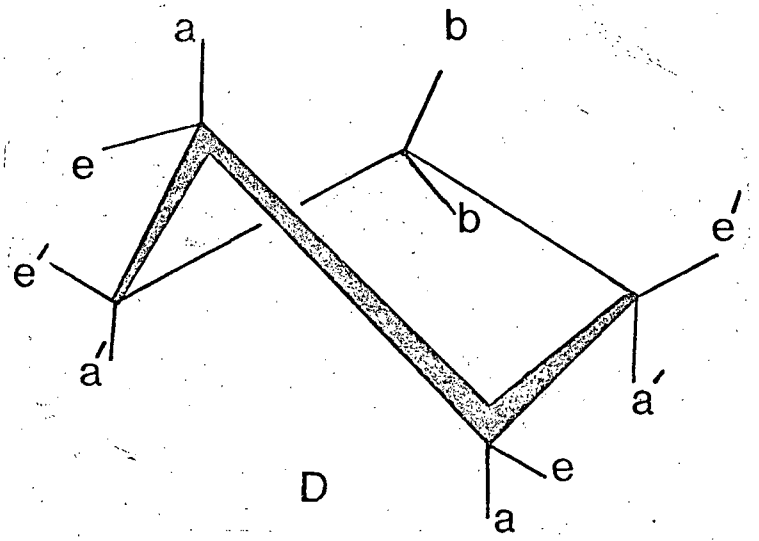
*Alternate designations of C_s for envelope and C_2 for twist arise from the presence of a plane of symmetry and a two fold axis for these respective forms in cyclopentane.

axial (a), equatorial (e), quasi-axial (a'), quasi-equatorial (e') and bisectional (b), the latter which assumes a position between the axial and equatorial bonds. The twist form (D) has one carbon above and an adjacent carbon below the plane



of the ring defined by the other carbon atoms. This form contains the same bonds as present in the envelope structure.

In order to apply the apparent advantages of fluorine magnetic resonance (^{19}F n.m.r.) for conformational analysis of furanoses it was desirable to learn more about the relationship between ^{19}F and ^{1}H n.m.r. with respect to angular dependences. To accomplish this aim a project was undertaken to synthesize rigid, specifically fluorinated furanose sugars using ^{1}H n.m.r. to define their conformations and then to relate the vicinal H-F couplings obtained from such conformations to dihedral angle.

It was thought that this constructed "Karplus curve" for J_{HF} might later be applied to the examinations of furanosyl fluorides which are expected to adopt more flexible conformations.

Primary sugar fluorides are synthesized readily from nucleophilic displacements of suitable derivatives by metal fluorides (13). Secondary carbohydrate fluorides have been synthesized from the opening of suitable sugar epoxides with hydrogen fluoride (14) or potassium fluoride (15). Recently Foster and co-workers have used tetra-n-butylammonium fluoride in acetonitrile to synthesize 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose via nucleophilic displacement of a tosyloxy group. Pedersen has made extensive use of hydrogen fluoride to replace anomeric acetates or benzoates with fluorine (29) and this area has been reviewed by Micheel and Klemer (30).

The concept of applying ^{19}F and ^{1}H n.m.r. together for structural elucidation of ring systems has been shown to be successful for pyranosyl fluorides (31). In the case of furanosyl fluorides a similar approach can be applied but the problem is inherently more difficult due to the abundance of possible conformations having almost identical energy minima. This thesis shows that systematic treatment of n.m.r. data makes it possible to arrive at reasonably definitive conclusions about the conformation of furanosyl fluorides in solution.

RESULTS AND DISCUSSION

The low energy barrier to pseudorotation in five membered rings has made a definitive study of these ring forms difficult (28b,32,33,34). In attempting a conformational study of the favoured forms of furanosyl fluorides we undertook to examine first, the relatively rigid molecules and then to proceed to the more flexible forms*. Each of the three furanose systems studied will be discussed separately in Sections A, B and C, proceeding from a conformational elucidation of high confidence (i.e. rigid structures) to one which is more speculative (i.e. flexible structures). General factors involved in all the compounds studied will be discussed in the latter portion of Section C.

SECTION A: 5-FLUORO-3,6-ANHYDRO-1,2-O-ISOPROPYLIDENE-α-L-IDOFURANOSE; THREE FUSED FIVE MEMBERED RINGS.

In studying a molecule with three connected five membered rings some rigidity is introduced into the molecular system. Each ring shares two mutual centres with the other,

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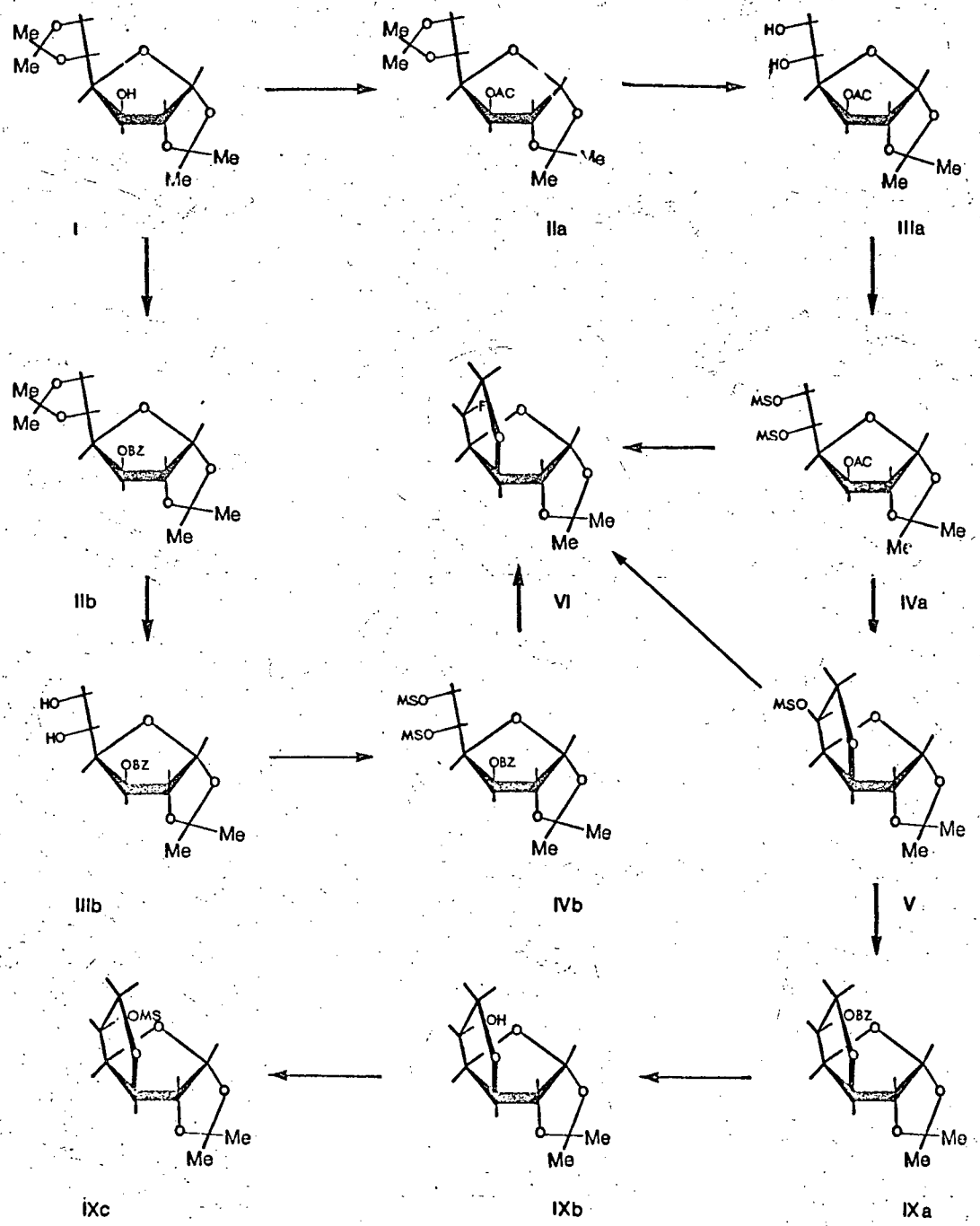
*In this thesis the terms "rigid" or "non-flexible" designate a molecule which can have a series of possible conformations of similar minimum energy, but exist as one specific conformation due to a high energy barrier to mobility and/or a large population of that molecule being maintained in the one specific conformation. Non-flexible forms include molecules with fused rings which introduce rigidity into the system. On the other hand, the term "flexible" will designate molecules whose representative form cannot be described by a single conformer, but instead reside in a restricted portion of the pseudorotation cycle. Here, this latter term applies to the free furanose rings described in Section C of the discussion.


Me
Me
OH
Me
Me
I
OAC
IIa
HO
HO
IIIa
OBZ
IIb
F
VI
MSO
MSO
IVa
HO
HO
IIIb
MSO
MSO
IVb
V
OMS
IXc
IXb
IXa

FLOW SHEET 1

thus restricting the pseudorotation cycle. In essence the presence of more than one five membered ring in the molecule provides the possibility of overdefining the system. Since several coupling constants are interrelated to mutually fused rings, one can in effect, observe deformations in two rings by looking at one coupling constant (a common bond exists between two rings).

The 3,6-anhydro-1,2-O-isopropylidene furanose system was chosen as the conformationally rigid model for several reasons. Firstly, the synthesis of these compounds is well known and can easily be accomplished (5). Secondly, the stability of the 3,6-anhydro ring allows one to apply various harsh reagents, such as potassium fluoride, in the fluorination procedure which would degrade most sugars (35). Indeed, once the 3,6-anhydro bond is formed under moderately alkaline conditions, it will remain resistant to both base and acid. The 3,6-anhydro portion of the ring forms a cyclic ether and in this regard is more stable than the furanose sugar ring (36). Thirdly and most importantly, the n.m.r. spectra of these derivatives are usually first order* (5). The ^{1}H n.m.r. spectrum of 5-O-tosyl-3,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose has been extensively studied by Abraham,

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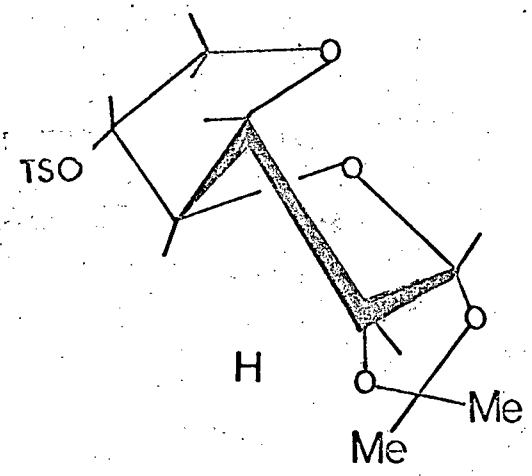
*The term "first order analysis" indicates that the chemical shifts and coupling constants are taken directly from the spectral splittings.

Hall and co-workers (5). Detailed examination of the vicinal coupling constants provided these workers with enough information to make definitive statements about the conformation of this molecule.

By using the Karplus equation and the concept that "symmetry in ring buckling is reflected in the equality of certain coupling constants", they rationalized the conformation of this molecule (H). The very small value of $J_{2,3}$ is conclusive that the dihedral angle between these two hydrogen bonds is near 90° (Table I). The approximately equal



value of $J_{1,2}$ and $J_{3,4}$ suggests a symmetrical deformation of the furanose ring. This can occur when the ring is in the twist form with the puckering of C_2 and C_3 centres respectively below and above the ring plane. The twist arrangement of the main sugar ring implies that the

isopropylidene group is non-planar due to the axial and quasi-equatorial ring linkages. However, no specific conformation is assigned to the isopropylidene moiety. The conformation of the 3,6-anhydro portion of the molecule was suggested from the observation that $J_{3,4}$ and $J_{4,5}$ are approximately equal and different from $J_{5,6_1}$ and $J_{5,6_2}$. This situation occurs only in the envelope form in which C_4 is displaced below the plane of the other four ring atoms.

By treating the 5-O-mesyl or 5-O-tosyl-3,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (V and X respectively) with sodium benzoate, the C_5 centre is readily inverted to obtain 5-O-benzoyl-3,6-anhydro-1,2-isopropylidene-α-L-idofuranose (IXa). The n.m.r. data (Table I) indicates that the coupling constants $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ are similar to the gluco isomer previously discussed, but the other couplings have now changed due to the inversion of the C_5 centre. 5-O-mesyl-3,6-anhydro-1,2-isopropylidene-α-L-idofuranose (IXc) exhibits similar ^{1}H n.m.r. data. The small value of $J_{4,5}$ and $J_{5,6_2}$ in these L-ido derivatives suggests an angle approaching 90°. This is still in agreement with an envelope conformation where C_4 is bent down out of the plane formed by the four atoms of the 3,6-anhydro ring. Hence, altering

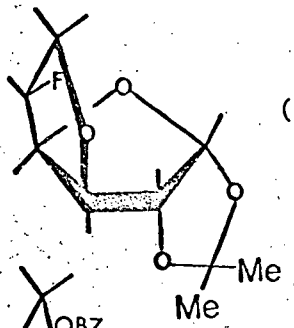
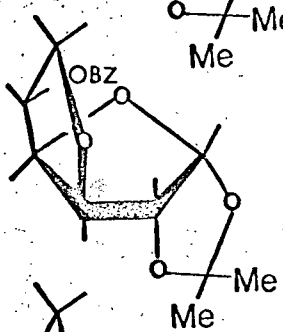
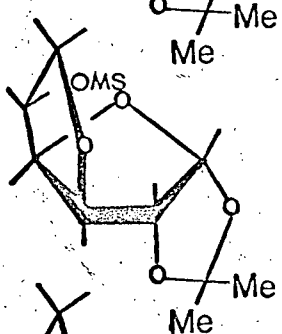
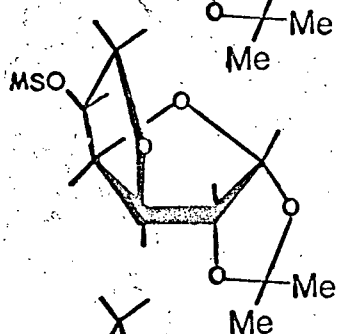
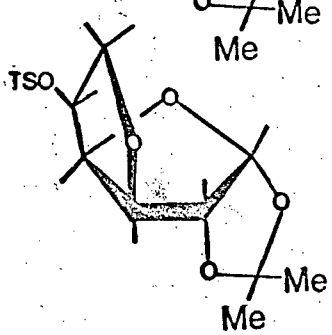
the C_5 epimer, does not change the conformation of the 3,6-anhydro furanose system.

With the high degree of confidence in the conformations of these multi-ring compounds there is now the question of introducing fluorine into this model system. Fortuitously, the specific fluorination of the 3,6-anhydro ring was achieved to give good yields of 5-fluoro-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (VI) from three glucofuranose derivatives. All these reactions involved refluxing the glucofuranose derivative in ethylene glycol for 1.5 hours. Indeed, at high enough temperatures, the crystalline product will sublime out of the reaction mixture and onto the condenser walls.

The use of potassium fluoride as a fluorinating agent has been known for some time. Primary deoxy-fluoro sugars such as, 6-fluoro-6-deoxy-D-galactose (37) and 6-fluoro-6-deoxy glucose (38) have been synthesized by the direct displacement of the terminal O-mesyl or O-tosyl group using potassium fluoride. Reactions of halo sugars with this reagent has been reported to give anomalous results, with an oxide being the usual isolated material (39). Synthesis of secondary sugar fluorides with potassium fluoride has usually occured by the opening of epoxides, however, low yields and much degradation result (13a).

TABLE I

First Order Coupling Constants for Three Fused Ring Systems. (Hz)

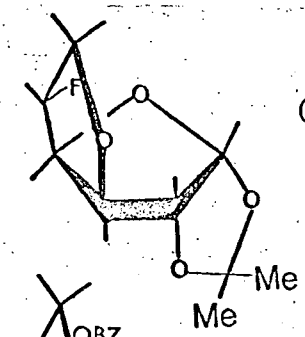
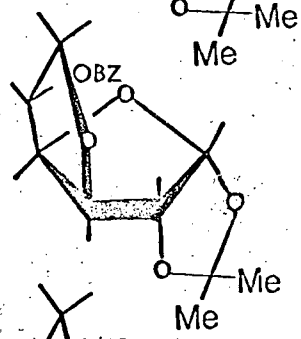
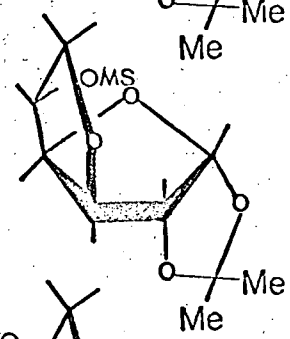
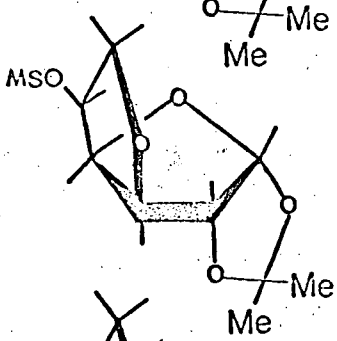
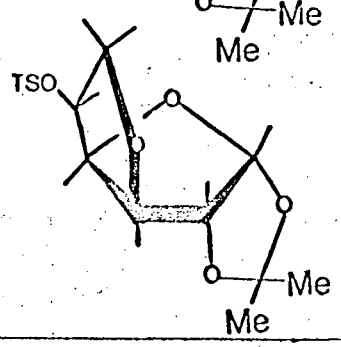
COMPOUND	H_1H_2	H_2H_3	H_3H_4	H_4H_5	$H_5H_{6_1}$	$H_5H_{6_2}$	$H_{6_1}H_{6_2}$
 (b) VI	3.5	<0.5	3.2	<0.5	0.8	2.8	-11.1
	H_1F	H_2F	H_3F	H_4F	H_5F	$H_{6_1}F$	$H_{6_2}F$
	1.5	<0.5	1.5	7.5	50.4	26.1	38.3
 (c) IXa	3.6	<0.5	3.2	0.8	3.6	1.1	-10.4
 (a) IXc	3.5	<0.5	3.4	0.8	2.4	1.4	-10.6
 (c) V	3.7	0.5	3.5	4.4	6.7	7.4	-8.2
 (c) X	3.3	<0.5	3.6	3.8	6.3	8.2	-8.8
(a)*	3.5	<0.5	3.7	4.1	6.5	8.1	-8.8

The compounds above are measured in (a) acetone-d_6, (b) benzene-d_6, and (c) chloroform-d.

*60 MHz. data from Reference 5.

TABLE II

First Order Chemical Shifts (τ and ϕ) for Three Fused Ring-Systems

COMPOUND	F	H_1	H_2	H_3	H_4	H_5	H_{6_1}	H_{6_2}	R
 (b) VI	189.7	4.41	5.68	5.41	5.29	5.30	6.25	6.41	–
 (c) IXa	–	4.10	5.34	5.29	5.09	4.53	5.79	6.01	1.9-2.9 (OBZ)
 (a) IXc	–	4.12	5.41	5.38	5.12	4.92	5.90	5.96	6.97 (OMS)
 (c) V	–	4.02	5.38	5.43	5.03	4.95	5.92	6.20	6.92 (OMS)
 (c) X	–	4.12	5.48	5.56	5.33	5.18	6.08	6.31	7.57 (OTS_{CH_3})
(a)*	–	4.06	5.45	5.54	5.27	4.98	6.37	6.90	7.51

The compounds above are measured in (a) acetone-d_6, (b) benzene-d_6, and (c) chloroform-d.

*60 MHz. data from Reference 5.

The probable mechanism for the reaction of potassium fluoride with 5,6-di-O-mesyl-3-O-acetyl-1,2-O-isopropylidene-^{x}-D-glucofuranose (IVa) involves the displacement of the acetyl group by base (potassium fluoride) and the backside attack of this formed O_3 anion onto C_6, displacing the mesyloxy group and forming a 3,6-anhydro ring. The driving force behind this reaction appears to be the formation of this new five membered ring which decreases the energy of the molecular system*. The newly formed 5-O-mesyl-3,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (V) now undergoes a SN_2 displacement reaction of mesyloxy by F^- to give the desired product. The yield of this reaction can be increased from 48% to 75% by initially reacting V with potassium fluoride. That this latter reaction proceeds readily, seems added proof to the above stated mechanism. It might also be noted that the attack of F^- ion to give the 5-fluoro-L-ido anomer has little steric hinderance, since the anion attacks from the outer-side of the molecule. However, in the case of synthesizing the 5-fluoro-D-gluco anomer from the 5-O-mesyl-L-ido starting material, much more steric hinderance is present, since the anion must now attack from the inner

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*Lee and Sawi (See Reference 13a) found that on treating methyl-6-O-tosyl-α-D-glucoside with KF, the only product formed was methyl-3,6-anhydro-α-D-glucoside. They rationalized this situation by saying, "In alkaline medium ionization of the hydroxyl group is favoured and this will tend to stabilize the form showing the widest charge separation. Attack by fluoride ion is strongly hindered in this form; oxide formation is strongly favoured."

"V" portion of the molecule. This can easily be seen by constructing a simple "framework" model.

The third derivative used for the preparation of VI was 5,6-di-O-mesyl-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (IVb) Indeed, it was initially thought that the benzyl ether would be resistant to base*, but the 45% yield of VI on reaction with potassium fluoride, indicated such not to be the case. A communication published after the above observation indicated a similar cyclization in the case of methyl-2,3-di-O-benzyl-6-O-mesyl-α-D-galacto-pyranoside** (40).

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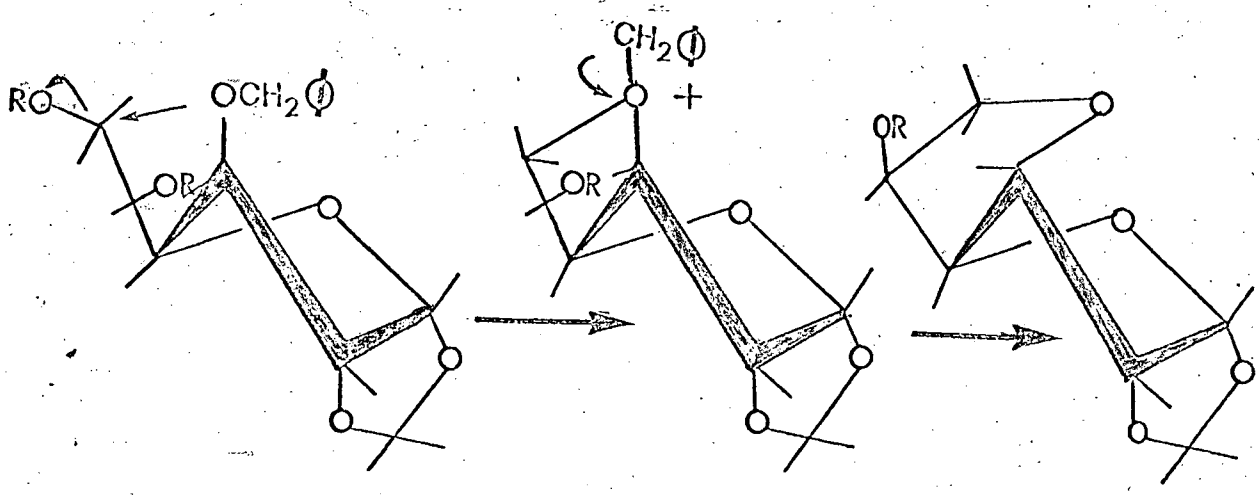
*Benzyl ethers have been used extensively as protecting groups and only recently have been shown to provide anichimeric assistance in the solvolysis of 2,3,4 tri-O-benzyl-1,5-di-O-toluene-p-sulphonylpentitols (G.R. Gray, F.E. Hartman and R. Baker, J. Org. Chem. 30, 2020 (1965)).

**Following the completion of this study, Brimacombe (See Reference 41) published a paper proposing the following mechanism for the cyclization involving benzyl group participation in compound IVb.



The n.m.r. spectra of VI is shown in Figure 2a. Analysis was assigned in the following manner: the anomeric hydrogen is observed as a doublet at lowest field (τ 4.41), since it is attached to a carbon centre bonded to two oxygen atoms. Irradiation of the H_1 doublet collapses the doublet at τ 5.58, thus identifying the H_2 resonance. H_5 is assigned from the expected large geminal hydrogen-fluorine coupling constant* which is present in the multiplet at τ 5.30. The assignment of H_3 and H_4 can be rationalized on the basis that H_3 should at most be a broad doublet, since $J_{2,3} = 0$ and thus any splittings should be from H_4 and minor long-range couplings. On the otherhand H_4 is expected to be at least a quartet with possible couplings from H_3, H_5 and F. Thus H_4 is assigned to the quartet at τ 5.29 and H_3 to the broad doublet at τ 5.41. The two H_6 protons can now be assigned by first finding the geminal coupling constant which is repeated eight times. The assignment is complicated, however, by the overlap of two H_6 resonances due to the large vicinal hydrogen-fluorine coupling. In Figure 3 an expanded sweep width of the H_6 region shows these two protons in more detail. The initial assignment was based on first order analysis**; however, due to the large coupling constants and the small chemical shifts in the H_6 region, this portion of the spectra

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*This coupling has been observed to be of the order of 50 Hz. at the anomeric centre of pyranose sugars and 60 Hz. at furanose anomeric centres, while primary fluorides have geminal coupling constants of 50 Hz.

**See footnote Page 14.

is truly an AB of an ABMY spectra. The computer program TWØSUM (See Appendix A) was used to perform iterative-fit calculations of this region to give the true chemical shifts and coupling constants. These values are compared with the first order values in Table III.

TABLE III. Comparison of Computer Analysis to First Order Analysis for Coupling Constants and Chemical Shift Involving the H_6 Protons of Compound VI.

	First Order Values	TWØSUM Values
$J_{5,6_1}$	2.9 Hz.	2.8 Hz.
$J_{5,6_2}$	1.1 Hz.	0.8 Hz.
$J_{6_1,6_2}$	-11.3 Hz.	-11.1 Hz.
$J_{5,F}$	50.1 Hz.	50.4 Hz.
$J_{6_1,F}$	26.5 Hz.	26.1 Hz.
$J_{6_2,F}$	37.6 Hz.	38.3 Hz.
ϕ H_5	τ 5.30	τ 5.30
ϕ H_{6_1}	τ 6.22	τ 6.25
ϕ H_{6_2}	τ 6.48	τ 6.41

A histogram plot of these iterative values (Figure 3) gives a perfect fit with the experimental spectra.

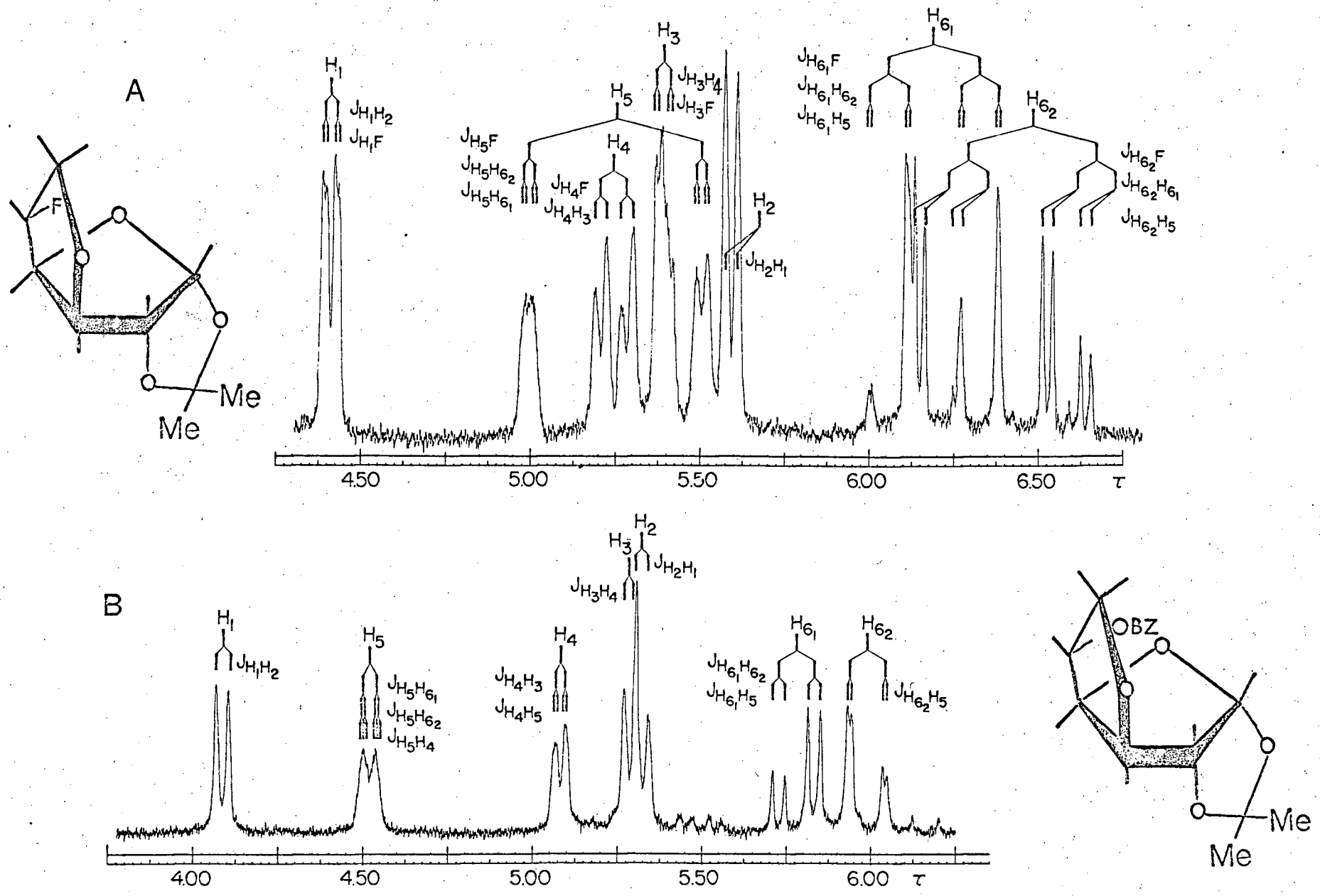

FIG. 2 100 MHz. proton magnetic resonance spectra of (A) 5-fluoro-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (VI) in benzene-d_6 solution and (B) 5-O-benzoyl-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (IXa)

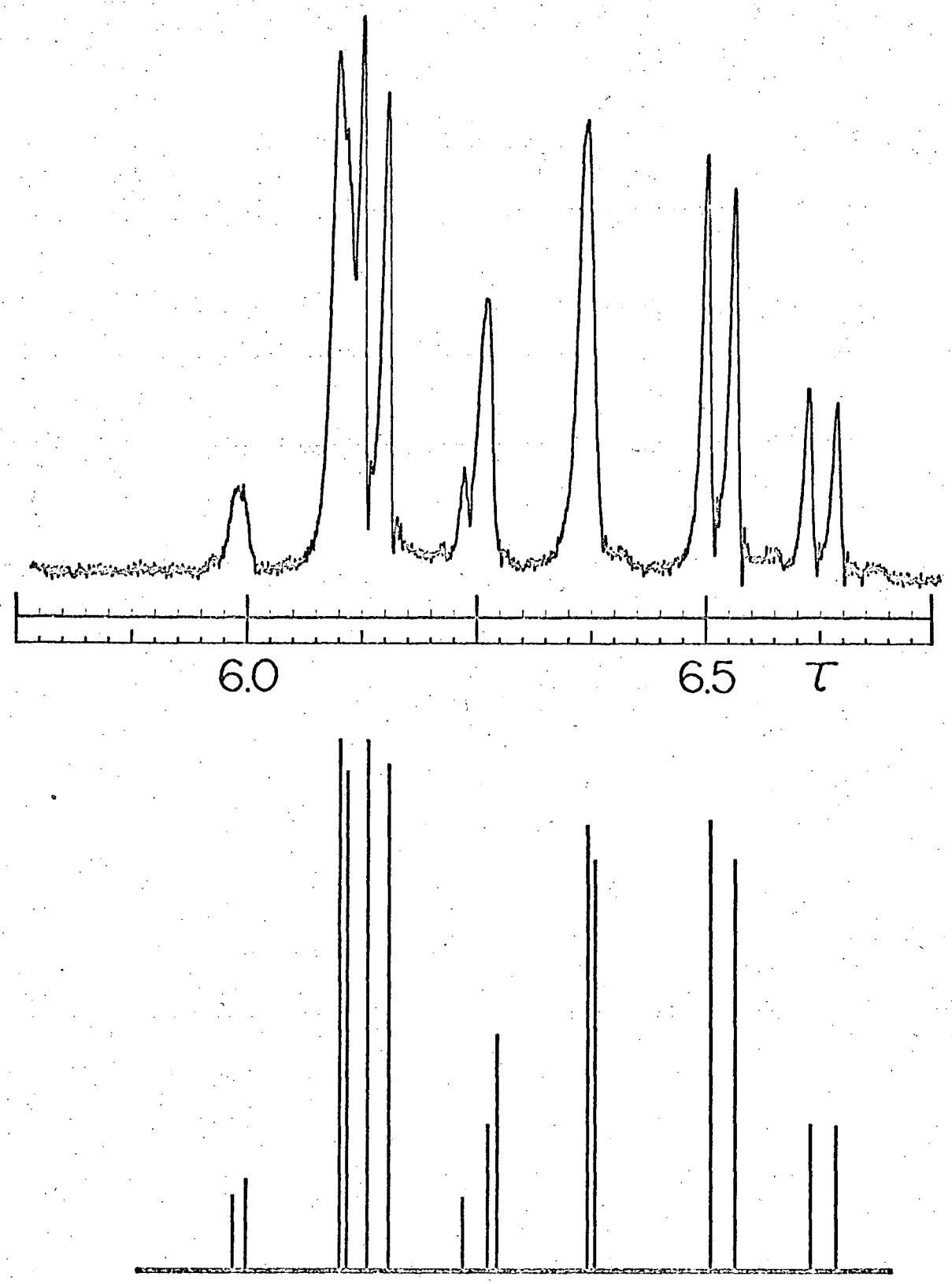

FIG. 3 Spectra of the H_6 protons for compound VI in benzene-d_6 solution (100 MHz.) with a matching histogram of this region simulated using mode C of TWØSUM (See Appendix A).

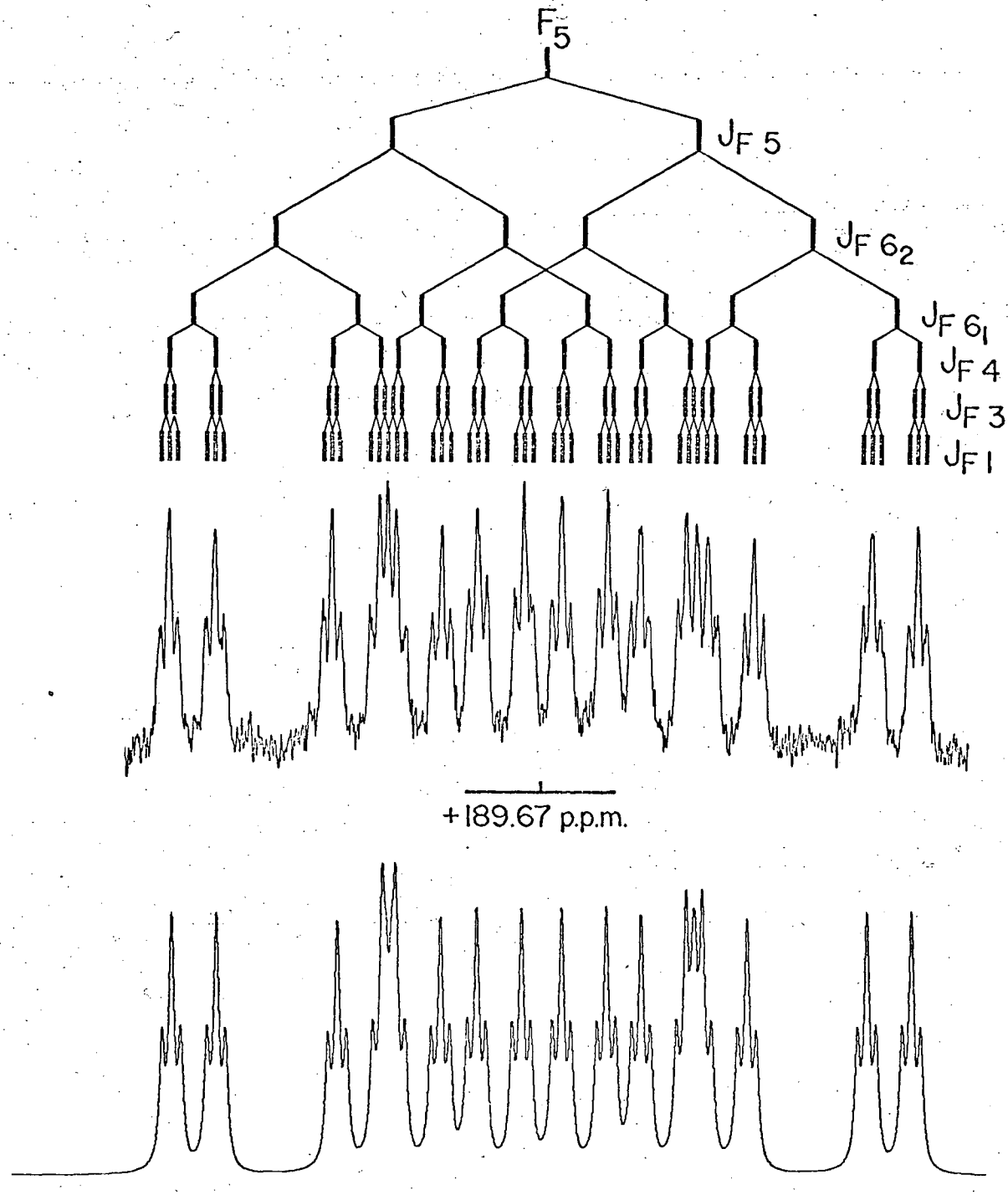

FIG. 4 The ^{19}F n.m.r. spectra of VI in benzene-d_6 (top spectra) resulting from the interactions of one fluorine atom with all protons except H_2. A simulated spectra (bottom) was computed using[2] LACØØN III. The discrepancy between the left hand quintet of the observed and computed spectra arises from second order effects in the proton spectra (See Text).

As can be seen from Table III, the first order couplings and chemical shifts for VI are within 5% of those values obtained by detailed analysis. Hence, even when dealing with spectra exhibiting some second order effects, the coupling constants obtained from the routine first order analysis are close enough to be used in conformational elucidations*. Organic chemists find this approximation to the first order case useful, since without spending much of their time on n.m.r. analysis, they can be confident of obtaining values which are close to the real values. Most of the furanosyl fluorides studied here were analyzed on a first order basis. However, all the obtained coupling constants and chemical shifts were checked by computer techniques and the values considered real only if the computed and experimental spectra matched.

It is interesting to note the similarities of the fluoride derivative (Figure 2a) with that of the O-benzoyl derivative (Figure 2b). The only differences are due to extra splittings from fluorine in all but H_2 of the fluoride derivative VI. These similarities further support the concept that changing from a benzoate to a fluorine substituent at C_5 does not drastically alter the conformation of the 3,6-anhydro monoacetone furanoses.

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*Since the Karplus curve is calculated formally for ethane, the accuracy in applying this relationship to other systems is likely to be at most, within ±5% of the true angle or coupling constant. (See Reference 1 page 75)

This approximation will not hold for highly coupled systems; that is, one that can be described as an ABCD or AA'BB'.

The fluorine spectrum of VI (Figure 4) consists of 46 lines which can readily be assigned on a first order basis from the coupling constants determined in the proton spectrum. A spectrum simulated by using a plotting program SMASH* in conjunction with LACØØN III* is shown at the bottom of Figure 4. Indeed, the spectrum is symmetrical except for the region of the two quintets. This apparent abnormality has been observed in other systems (42) and can be rationalized in the following manner: In the ^{1}H n.m.r. spectra the H_6 region has two large vicinal ^{1}H-^{19}F couplings (Figure 3). This region can be analyzed as two subspectra corresponding to the orientation of the fluorine spin in the α or β spin states. Assuming that the signs of all vicinal ^{1}H-^{19}F coupling constants are the same**, one can arbitrarily set α fluorine spin states to the first half of each H_6

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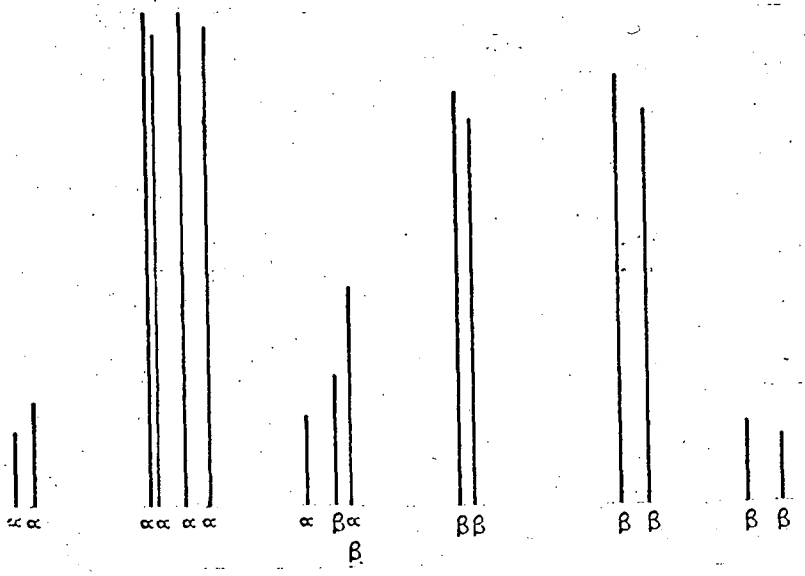
*See Appendix A.

**The signs of vicinal ^{1}H-^{19}F coupling are positive as in the case of vicinal ^{1}H-^{1}H couplings, while geminal ^{1}H-^{19}F couplings are also positive in contrast to the negative sign of geminal ^{1}H-^{1}H coupling (See Reference 43).

and H_{6_2} multiplet. Correspondingly, the latter half of the two H_6 multiplets is assigned the β fluorine spin state. Hence, the H_6 line assignments for fluorine spin states are:



and the overlap of α and β states makes the effective chemical shifts of H_{6_1} and H_{6_2} almost equal in one part of the subspectra, while different in another. This overlap gives rise to large second order effects - often referred to as "virtual coupling" (44) - which are reflected in the fluorine spectrum. The lines of the fluorine spectra will be affected to different degrees depending on which transition the line is associated with (i.e. different spin state transitions associated with overlapping lines in the H_6 proton region will show more second order effects). The computer simulated ^{19}F spectrum (Figure 4), matches well with the observed spectrum, except in the region

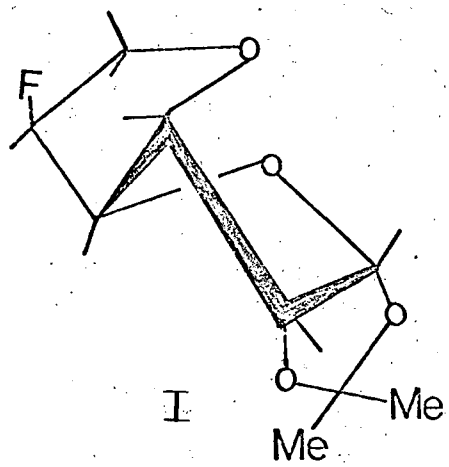
of the left-hand-side quintet. In the observed spectra, the two triplets forming this quintet are shifted further apart than in the computed spectra where the two lines of each triplet overlap to give a quartet. The fluorine spectrum is very sensitive to second order effects and the discrepancy in the observed and computed spectra arises from the slight errors (±0.005 p.p.m.) in assigning one of the proton shifts. This difference probably arises from the small errors involved in matching observed frequencies to line assignments in the computer analysis.

An interesting aspect of the spectrum of 5-fluoro-3,6-anhydro-mono-acetone idose is the presence of a multitude of long-range ^{1}H-^{19}F couplings. Indeed, as the number of lines in the ^{19}F spectra indicates, fluorine is coupled significantly to every proton except H_2. As subsequently will be seen, these long-range couplings were observed in all sugars studied here and their magnitude appears to be dependent on the configuration and/or conformation of the molecule (45).

It is important to note the large values of 38 Hz. and 26 Hz. for the $^{1}H_6$-^{19}F couplings in VI. One has difficulty rationalizing these two large values on the basis of what is presently known of the Karplus relationship of "vicinal" ^{1}H-^{19}F couplings. In other words, these couplings should be

due to a dihedral angle of θ and 120° + θ, if we assume tetrahedral symmetry at the carbon centre. Since the dihedral angles are somewhat defined from the proton couplings, these angles should be approximately 150°-170° and 30°-50°. This would make the curve relating dihedral angle to vicinal $^{1}H-^{19}F$ constant much more asymmetric than presently thought (46). This point will be considered further in Section C.

From an examination of the coupling constant data for the 3,6-anhydro-1,2-O-isopropylidene derivatives studied (Table I), it is evident that the replacement of the C_5 substituent from fluorine to benzoate to mesyl does not significantly change the conformation of the furanose or anhydro ring. On the basis of vicinal $^{1}H-^{1}H$ couplings the conformation of VI is shown in I. The changes in $J_{5,6_1}$ and $J_{5,6_2}$ going



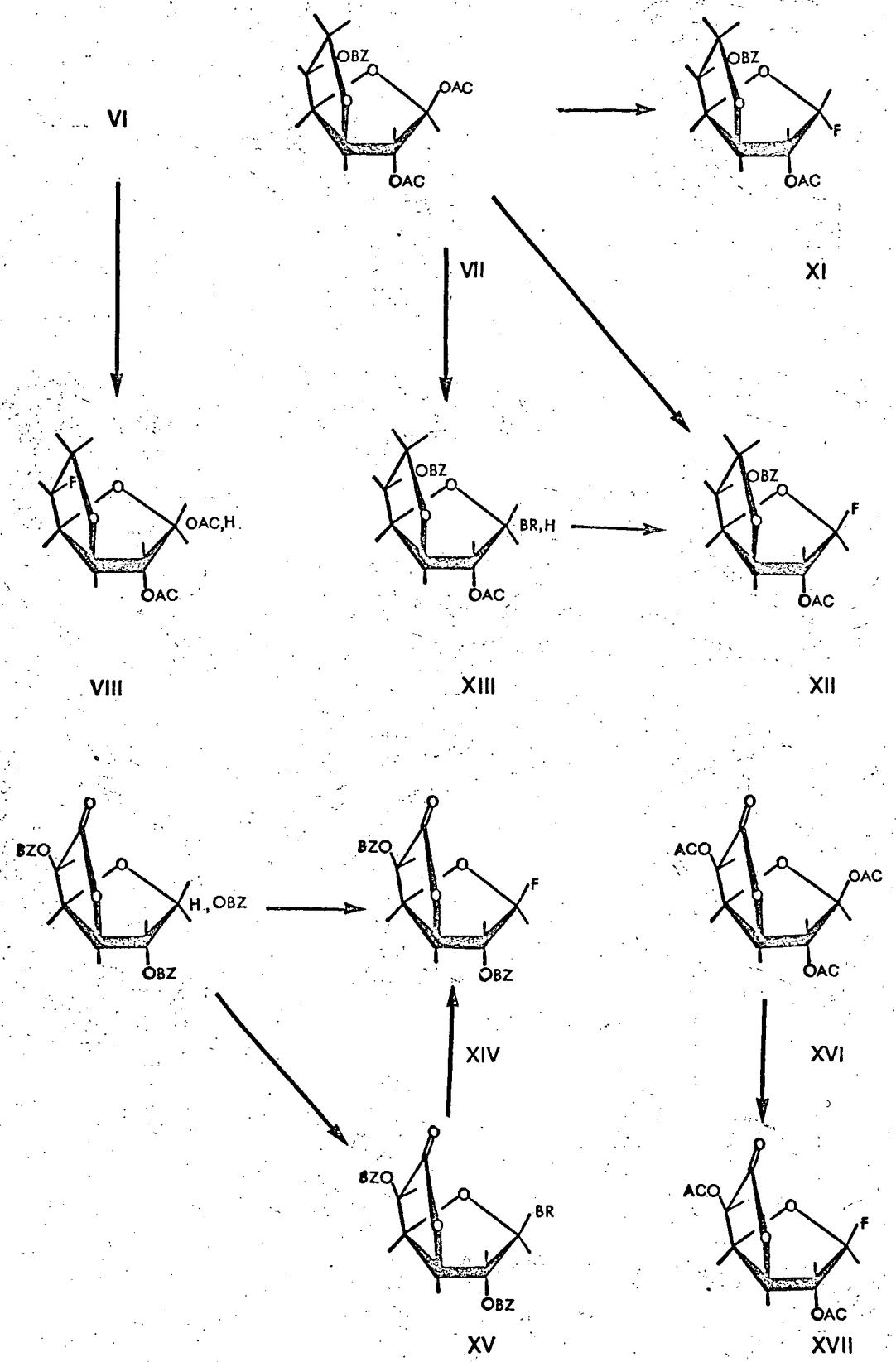
I

from fluoro to other C_5 derivatives, is attributed to the differences in electronegativity of these substituents. As was previously shown, the inversion of the C_5 substituent also does not alter the conformation of the molecule. These two observations further support the contention of rigidity in this molecular system.

SECTION B: FURANOSYL FLUORIDES CONTAINING TWO FUSED RINGS.

A series of compounds having less rigid five membered rings were investigated by synthesizing fluorinated derivatives of furanose sugars involving two fused rings. Furanosyl fluorides XII, XIV and XVII were prepared by reacting a tri-O-benzoyl or tri-O-acetyl precursor with anhydrous hydrogen fluoride. The β fluoride anomer was the major product, however, in the case of XII, during a reaction which was quenched in half the usual time, the α anomer was observed by ^{19}F n.m.r., but could not be isolated. The α anomer consisted of two doublets with couplings of 61 Hz. and 18 Hz. at + 139 p.p.m. from freon 11, while the β anomer was two sextets separated by 60 Hz. with a chemical shift of + 120 p.p.m. upfield from freon 11. As will be subsequently seen in Section C, the chemical shifts of the α fluorides appear to be 10-15 p.p.m. higher than those of the β anomer in furanose sugars.

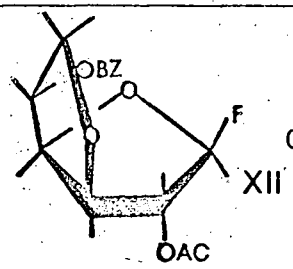
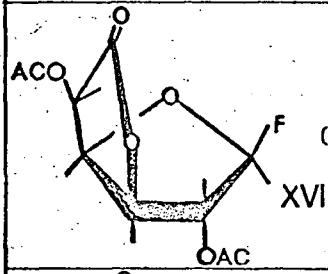
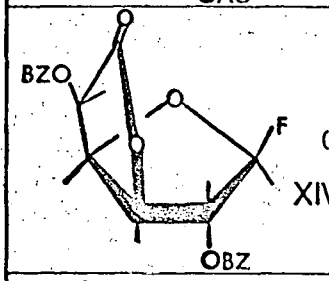
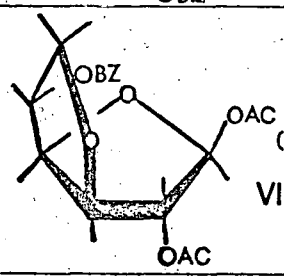
The n.m.r. data for XII, XIV and XVII is shown in Tables IV and V. First, it should be noted that in all cases, the proton coupling constant $J_{1,2}$ and $J_{2,3}$ are ca. 0. This is characteristic of dihedral angle approaching 90°


VI
OBZ
OAC
OAC
F
XI
VII
OAC,H
BR,H
VIII
XIII
XII
BZO
H, OBZ
OBZ
F
XIV
ACO
XVI
BR
XV
XVII

FLOW SHEET 2

TABLE IV

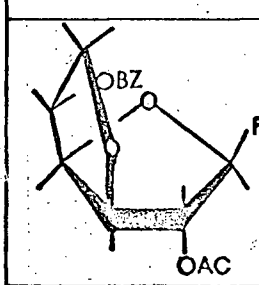
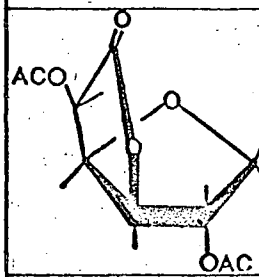
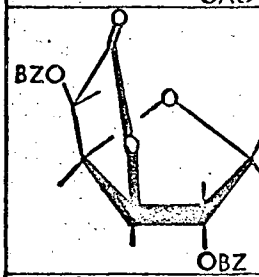
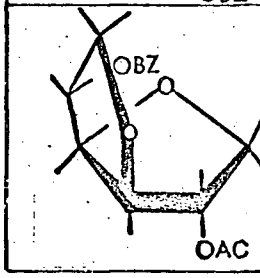
First Order Coupling Constants for Two Fused Ring Systems. (Hz)

COMPOUND	H_1F	H_1H_2	H_2F	H_2H_3	H_3F	H_3H_4	H_4F	H_4H_5	H_5F	$H_5H_{6_1}$	$H_5H_{6_2}$	$H_{6_1}H_{6_2}$
 (a) XII	62.3	0.8	5.8	<0.5	<0.5	4.8	4.8	<1.0	-	4.0	1.5 $H_{6_2}F$ 1.5	-10.6
 (a) XVII	60.1	0.6	4.5	<0.5	<0.5	4.6 H_3H_5 <0.5	4.4	6.3	<0.5	-	-	-
 (a) XIV	60.1	<0.5	4.0	<0.5	0.5	4.6 H_3H_5 <0.5	4.6	6.3	0.3	-	-	-
 (c) VII	-	<0.5	-	<0.5	-	4.5	-	<0.5	-	4.1	1.0	-10.6

The compounds above are measured in (a) acetone-d_6 and (c) chloroform-d.

TABLE V

First Order Chemical Shifts (τ and ϕ) for Two Fused Ring Systems

COMPOUND	F	H_1	H_2	H_3	H_4	H_5	H_{6_1}	H_{6_2}	OAC	OBZ
 (a) XII	119.8	4.28	4.72	4.94	5.28	4.44	5.58	5.94	7.93	1.9-2.8
 (a) XVII	118.3	4.09	4.65	4.77	4.64	4.37	-	-	7.14	-
 (a) XIV	118.5	3.80	4.30	4.44	4.29	4.02	-	-	-	1.8-2.7
 (c) VII	-	3.79	4.76	5.00	5.23	4.48	5.29	5.95	7.98 8.04	1.9-2.8

The compounds above are measured in (a) acetone-d_6 and (c) chloroform-d. The shifts of the CH_3 groups were all in the range 8.5-8.7τ.

which can readily be accomplished by depressing the C_2 centre downward out of the plane defined by the other carbon centres. $J_{3,4}$ is generally larger in these moleculesthan in compound VI, suggesting the possibility the C_3 has less puckering - a concept recently labelled "pseudoliberation" (47) - than in the case of the three fused ring molecules. On this basis one could suggest an envelope conformation for the furanose portion of the 3,6-anhydro molecule*. The ^1H-^1H couplings in the 3,6-anhydro ring are almost identical for the two and three fused ring systems, suggesting that the envelope conformation is retained in this portion of the molecule.

Hence, the conformation of these 3,6-anhydro derivatives are similar to that of the three fused ring molecules with the possibility that the furanose ring may be favouring the envelope form in the former case, rather than a twist form as the latter**.

Recently, Pedersen and co-workers have examined the intermediates and products arising from the reaction of

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*Alternatively, the increase of $J_{3,4}$ may be due to the reduction of ring strain resulting from the removal of the isopropylidene group. In this case the twist form could still be the dominant conformation.

**As will be discussed subsequently (Section C), the n.m.r. technique is not sufficiently sensitive to differentiate a twist form involving C_2 and C_3 from an envelope form involving C_2 or C_3.

ribofuranose and arabinofuranose sugar esters with hydrogen fluoride (48). They found brief treatment of acetylated or benzoylated D-ribofuranoses with hydrogen fluoride gave exclusively β fluoro tri-esters of ribofuranose, while similar treatment of the esterified D-arabinofuranose gave the α fluoro tri-ester of arabinofuranose. These observations were consistent with their proposed mechanism involving the formation of a 1,2 oxonium ion (observed by n.m.r.).

In this present investigation the reaction of precursors with hydrogen fluoride gave almost exclusively the "trans product"*. Only in one instance (Xb), involving a reaction quenched in half the usual time, was the formation of the α anomer ("cis product"*) observed. However, upon repeating the fluorination for the normal reaction time, only the β anomer was observed. Pedersen found that prolonged treatment of the ribofuranose and arabinofuranose derivatives led to the formation of a 2,3 oxonium ion which resulted in a mixture of α and β fluorides on work up.

To rationalize the formation of the α fluoride from Xb,

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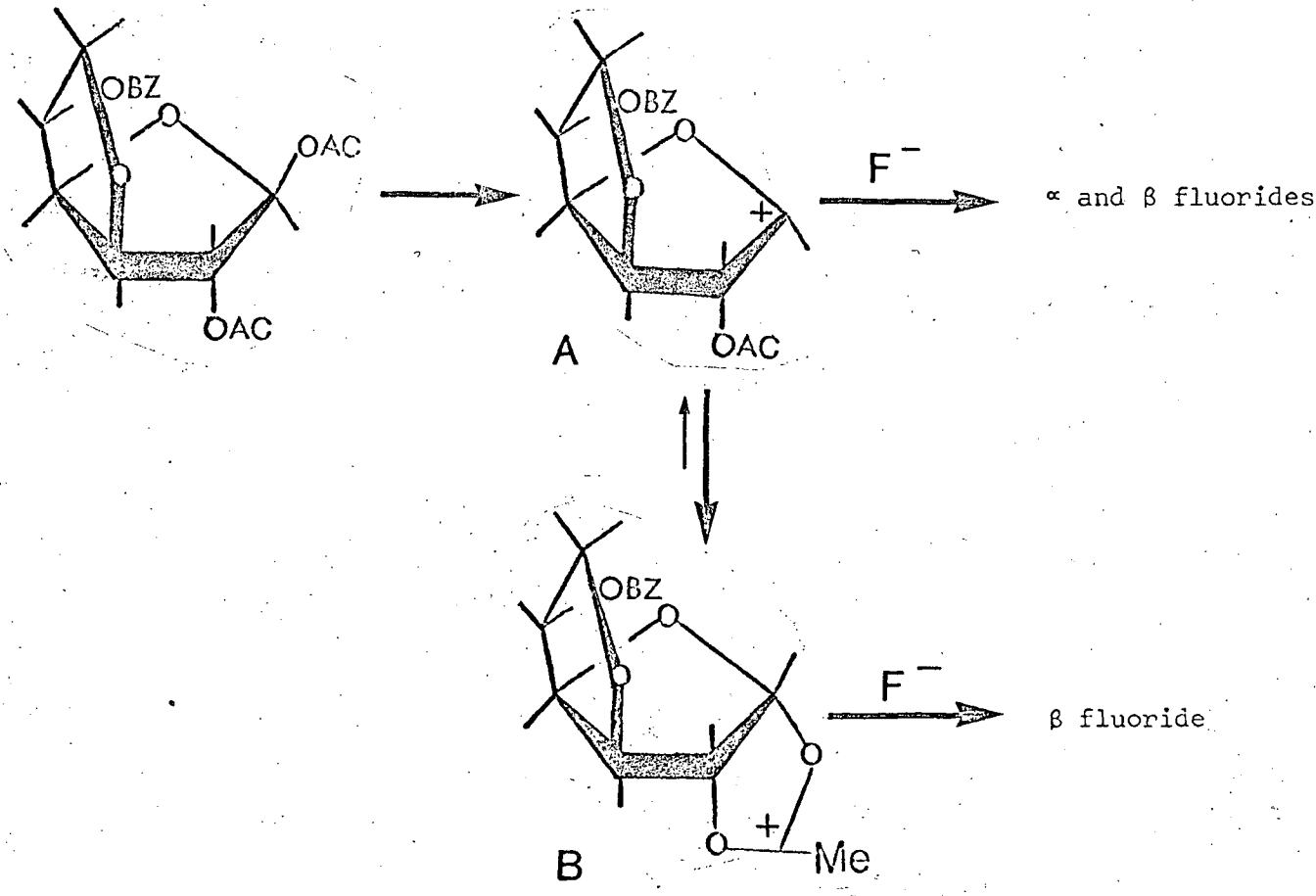
*In this context the term "trans product" is used to indicate a molecule where the fluorine at C_1 is trans to the substituent at C_2; similarly, the term "cis product" will be used to designate a molecule where the fluorine at C_1 is cis to a substituent at C_2.

one could suggest the following equilibrium:



The initial formation of the carbonium ion A, followed by the possible SN_1 attack of fluoride ion, seems reasonable when one considers that the reaction of some esterfied pyranose sugars with hydrogen fluoride gives a mixture of anomeric fluorides*. Presumably, the steric influences of the 3,6-anhydro system

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*D-ribopyranose tetraacetate and D-altropyranose pentaacetate are reported to give a mixture of ∝ and β fluorides upon reaction with HF for ca. 20 min. (Ph.D. thesis of J.F. Manville (U.B.C.,1967)).

causes the non-cyclic carbonium ion (See A) to be initially formed. With longer reaction times the equilibrium shifts to the more stable cyclic carbonium ion B, giving the β anomer exclusively.

An interesting ^{1}H n.m.r. spectrum which demonstrates the application of heteronuclear decoupling* occurs in the case of XIV (Figure 5a). This molecule shows a highly coupled system, since all five protons have chemical shifts within a 100 Hz. sweep range. H_1 is readily identified from the large geminal ^{1}H-^{19}F coupling. The resonance of the other nuclei are complicated, however, by the presence of the couplings from fluorine. Initially, the spectra could not be analyzed by computer techniques, since good first order approximations could not be obtained. Selective ^{1}H-^{1}H decoupling proved somewhat inconclusive because of the highly coupled nature of the system. The spectrum was finally analyzed by application of heteronuclear fluorine decoupling (Appendix B) in combination with selective proton decoupling. The multi-transition spectrum is greatly simplified by irradiation of fluorine (Figure 5b). The doublet at τ 4.44 and τ 4.02 remain unperturbed and hence cannot be H_2 or H_4, since the former should have a fluorine coupling and the latter should be at least a quartet (due to coupling form H_3 and H_5).

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*See Appendix B.

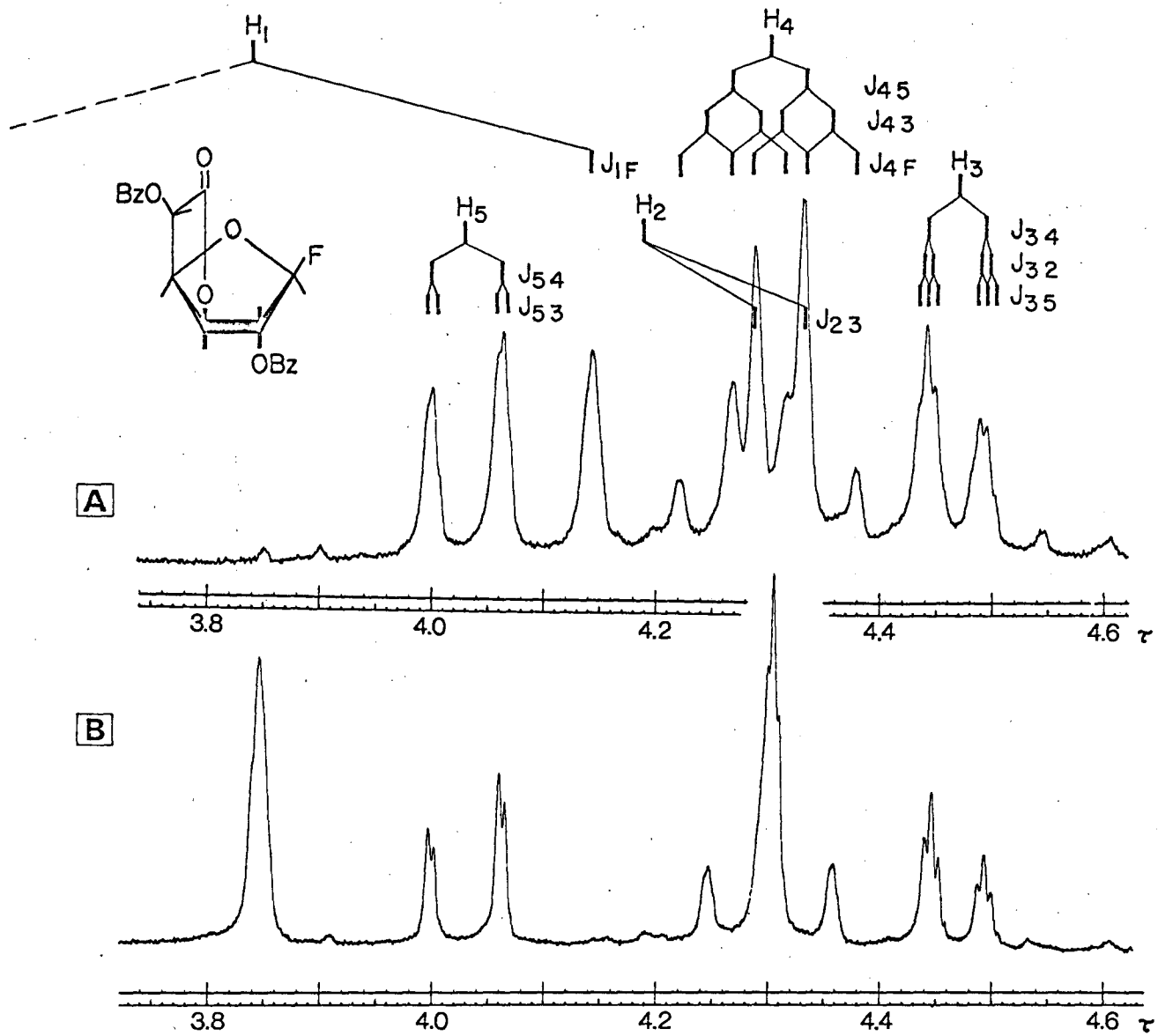

FIG. 5 100 MHz. proton spectra of 2,5-di-O-benzoyl-β-fluoro-D-glucuronolactone (XIV) in acetone-d_6. (A) normal spectra (B) ^{19}F decoupled spectra.

From the presence of a carbonyl and O-benzoyl group near H_5, one expects this proton to be deshielded. Initial assignment of the doublet at τ 4.02 to H_5, followed by irradiation of this doublet collapsed a multiplet at τ 4.29 which was assigned to H_4. From the intensity build up, the doublet at τ 4.30 in the undecoupled spectra was thus assigned to H_2. (This resonance was observed to collapse to a singlet in the ^{19}F decoupled spectrum. Irradiation of the highest field doublet was found to collapse H_4; thus this doublet at τ 4.44 was assigned to H_3.

First order values obtained from the ^{19}F decoupled spectra of XIV were now entered into TWØSUM and a spectrum simulated which matched both the experimental fluorine and proton spectra. This further verified the above assignment.

It should be noted for this series of compounds that a significant long-range coupling is present for $^4J_{F,4}$ (4.8-6.3 Hz.) while $^4J_{F,3}$ is very small (ca. 0.5 Hz.). This important observation will be discussed in greater detail in Section C.

SECTION C: FLEXIBLE FURANOSYL FLUORIDES

A series of flexible furanosyl fluorides* (XVIII-XXIV) were now extensively examined by ^{1}H and ^{19}F n.m.r. (Tables VI & VII). Their synthesis was initially attempted in our laboratory, however this proved somewhat unsuccessful**. Fortuitously, a number of the desired sugar fluorides were made available to us by Dr. C. Pedersen, allowing this study to proceed more rapidly to the ultimate aim. Subsequently, some of the other desired fluoro sugars were synthesized in our laboratory by applying the hydrogen fluoride reaction.

Much of the pertinent information in this series arises from the two anomeric tri-O-benzoyl-D-ribofuranosyl fluorides XVIII and XIX (Table VI). The spectrum of the β anomer (XVIII) is shown in Figure 6A together with its fluorine decoupled spectrum (Figure 6B). H_1 was readily assigned from the characteristic 60 Hz. coupling with fluorine and its low field chemical shift. The H_4 and two H_5 protons, as expected, are to highest field, while H_2 and H_3 are highly coupled at τ 4.04 and τ 3.96 respectively. The H_3 resonance was identified by spin decoupling both fluorine and H_4, while observing that the

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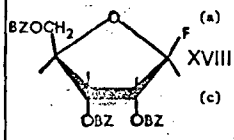
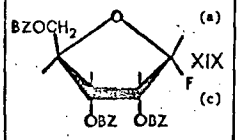
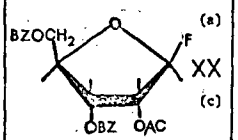
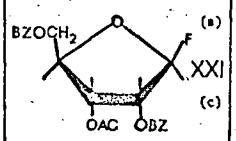
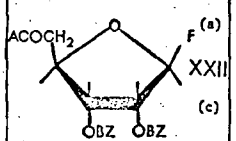
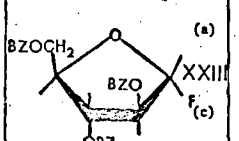
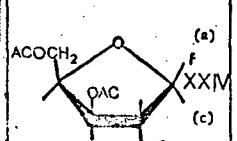
*See footnote on page 12.

**Difficulties were encountered because methods employed to synthesize these furanosyl fluorides involved the preparation of a furanosyl bromide or choride from the O-acetyl or O-benzoyl derivative and then replacing this halide by fluorine using silver fluoride. However, the intermediate halides were found to be highly labile and often hydrolyzed before the exchange could take place.

TABLE VI

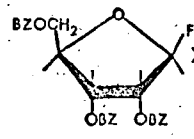
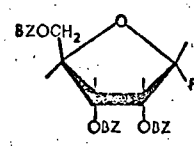
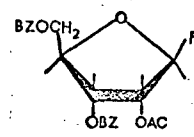
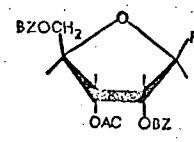
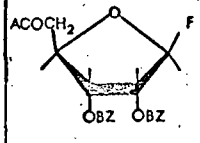
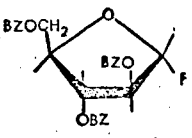
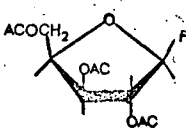
First Order Coupling Constants for Furanosyl Fluorides (Hz)

COMPOUND		H_1F	H_1H_2	H_2F	H_2H_3	H_3F	H_3H_4	H_4F	$H_4H_{5_1}$	$H_4H_{5_2}$	$H_{5_1}H_{5_2}$
 XVIII	(a)	61.5	<0.5	4.8	4.8	2.2	5.6	6.6	3.9	5.2	-12.2
	(c)	61.2	<0.5	4.9	4.9	2.2	6.2	7.3	3.9	5.2	-11.9
 XIX	(a)	64.4	3.2	20.6	6.9	≈0	2.3	1.0	3.1	3.5	-12.1
	(c)	63.6	3.5	20.6	6.9	≈0	2.5	1.8	3.2	3.8	-12.3
 XX	(a)	60.9	<0.5	4.7	4.7	2.4	6.9	6.7	3.5	4.6	-11.9
	(c)	61.4	<0.5	4.8	4.7	1.9	6.7	6.8	3.8	5.6	-12.5
 XXI	(a)	61.6	<0.5	4.5	5.0	1.7	5.0	7.9	4.5	5.4	-12.4
	(c)	61.1	-	-	-	-	-	-		-	-
 XXII	(a)	61.3	<0.5	4.9	4.9	2.1	4.9	7.2	3.6	5.3	-12.1
	(c)	61.4	<0.5	-	-	-	-	-	3.8	5.3	-12.2
 XXIII	(a)	58.4	0.9	6.4	<0.5	<0.7	4.4	1.5	3.3	5.8	-12.1
	(c)	58.1	<0.5	6.1	1.0	0.5	3.5	1.0	3.0	6.5	-12.1
 XXIV	(a)	-	-	-	-	-	-	-	-	-	-
	(c)	60.5	1.0	5.2	<0.5	<0.5	5.5	5.2	5.3	7.1	-11.4

The compounds above are measured in (a) acetone-d_6 and (c) chloroform-d solutions.

TABLE VII

First Order Chemical Shifts (τ and ϕ) for Furanosyl Fluorides

COMPOUND		F	H_1	H_2	H_3	H_4	H_{5_1}	H_{5_2}	OBZ	OAC
 XVIII	(a)	115.9	3.82	4.04	3.98	4.89	5.11	5.31	1.9-2.8	-
	(c)	116.1	4.04	4.54	4.43	5.10	5.26	5.43	1.9-2.8	-
 XIX	(a)	133.3	3.70	4.49	4.14	5.07	5.24	5.39	1.9-2.8	-
	(c)	133.6	3.86	4.53	4.16	5.10	5.23	5.41	1.9-2.8	-
 XX	(a)	115.8	4.20	4.45	4.26	5.21	5.32	5.49	1.9-2.7	7.85
	(c)	116.0	4.21	4.24	4.38	5.23	5.29	5.48	1.9-2.7	7.95
 XXI	(a)	115.5	4.05	4.30	4.38	5.26	5.32	5.58	1.9-2.7	6.98
	(c)	115.7	-	-	-	-	-	-	-	-
 XXII	(a)	115.7	3.96	4.19	4.25	5.18	5.39	5.75	2.0-2.8	7.95
	(c)	-	4.09	-	-	5.32	5.38	5.75	2.0-2.8	7.90
 XXIII	(a)	123.8	3.83	4.26	4.25	5.05	5.12	5.27	1.9-2.8	-
	(c)	124.7	4.01	4.35	4.43	5.15	5.20	5.31	1.8-2.8	-
 XXIV	(a)	-	-	-	-	-	-	-	-	-
	(c)	113.2	4.37	4.82	4.66	5.30	5.71	5.80	-	7.95 7.98

The compounds above are measured in (a) acetone-d_6 and (c) chloroform-d.

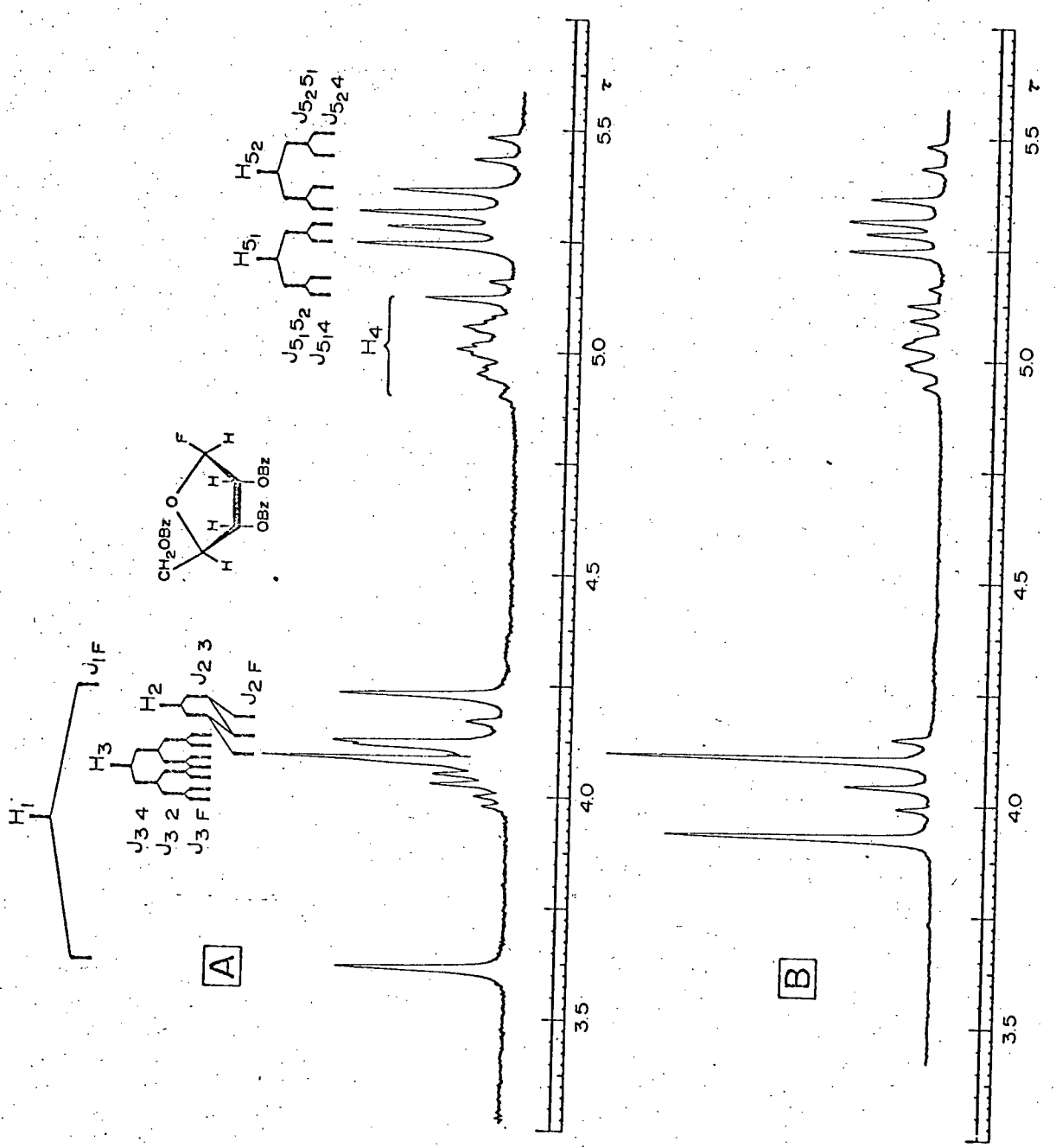


FIG. 6 100 MHz. proton spectra of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl fluoride (XVIII) in acetone-d_6. (A) normal spectra (B) ^{19}F decoupled spectra. (See Text for details)

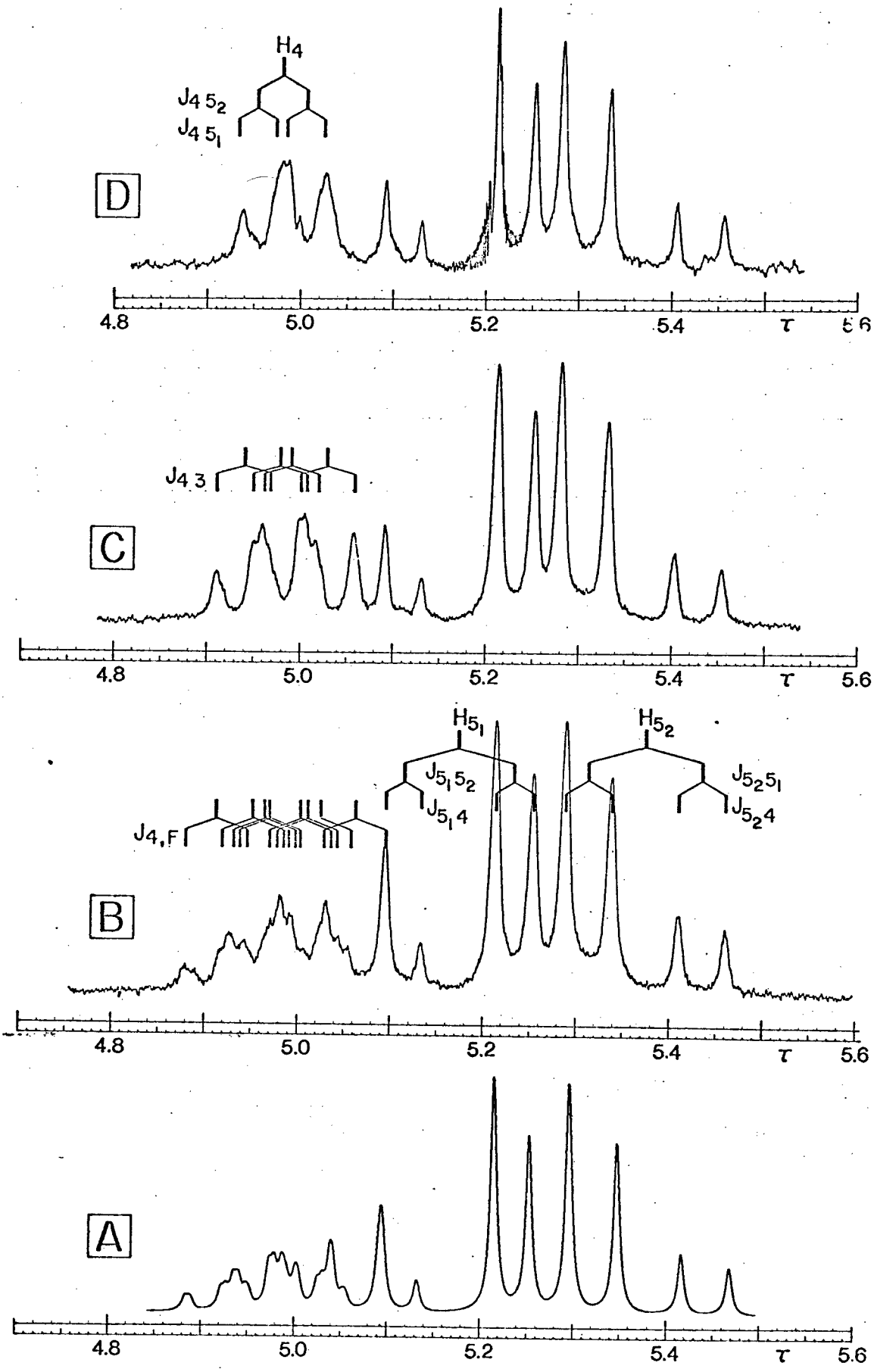


FIG. 7 Partial 100 MHz. spectra of H_4 and H_5 region of XVIII in acetone-d_6 with (A) computer simulated spectra using LACØØN, (B) normal spectra, (C) ^{19}F decoupled spectra and (D) ^{19}F and H_3 decoupled spectra. The beat pattern in the top spectra is due to a noise beat arising from the proton decoupler.

heptet at τ 3.96 collapses to a doublet. It should be noted here that $J_{1,2} \simeq 0$ and $J_{2,F} = 4.8$ Hz; both coupling constants are indicative of the β anomer of all ribofuranosyl fluoride derivatives studied here. At this stage a comment should be made concerning the fluorine decoupled spectrum of this compound. An ambiguity appears to be present in the H_2 and H_3 region of the decoupled spectrum (Figure 6B). H_3 should collapse to a quartet and H_2 to a doublet when fluorine is decoupled. Instead, one sees a multiplet which cannot be analyzed by simple first order analysis and arises from an effective decrease in the chemical shift difference between H_2 and H_3*. This change in chemical shifts comes from an increase in the temperature of the sample due to the power of the heteronuclear decoupling field. Such temperature shifts were observed in all ^{19}F decoupling experiments and are reproducible. Furthermore, the complication arising from these temperature shifts could be readily simulated by TWØSUM.

Returning now to compound XVIII, the most informative portion of the proton spectrum is the H_4 region. Figure 7B shows the H_4 and H_5 protons at expanded sweep width. Upon irradiation of fluorine the H_4 multiplet collapses with the band width at half height decreasing by 6.6 Hz. (Figure 7C). By simultaneously irradiating H_3 and ^{19}F (Figure 7D), H_4

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*An alternate designation of this region as part of a "deceptively simple" ABX spectrum (See Reference 72), is precluded on the basis that a similar derivative, XX, in which H_2 and H_3 are shifted well apart, exhibits the same first order coupling constants as this compound.

further collapses into a broad quartet whose splitting arises from the coupling to the two H_5 protons. The broadening of these transitions can be attributed to both long-range ^1H-^1H coupling and second order effects arising from the small J/Δ ratio for the two H_5 protons. Thus, it becomes apparent from these irradiation experiments that a suprisingly large coupling of 6.6 Hz. exists for a four bond coupling through oxygen between fluorine and H_4. This coupling was readily observed in the ^{19}F spectrum. Computer analysis of XVIII was used to check the first order values given in Table VI. A computer simulation of the upfield region of the β anomer (Figure 7A) shows a perfect fit with the experimental observations.

The normal and ^{19}F decoupled spectra of tri-O-benzoyl-α-D-ribofuranosyl fluoride (XIX), are shown in Figure 8A & 8B. Again note the temperature shifts of H_2 and H_3 in the fluorine decoupled spectrum. The assignment of H_1, H_2 and H_3 are straightforward. Values of 3.2 Hz. and 20.6 Hz. for $J_{1,2}$ and $J_{2,F}$ respectively (checked by computer analysis), are significantly different than those of the β anomer. Hence $J_{1,2}$ and $J_{2,F}$ may be taken as characteristic for differentiating between the α and β anomers in furanosyl fluorides. Further differentiation arises from the observation that the chemical shift of fluorine is over 17 p.p.m. greater in the case of the

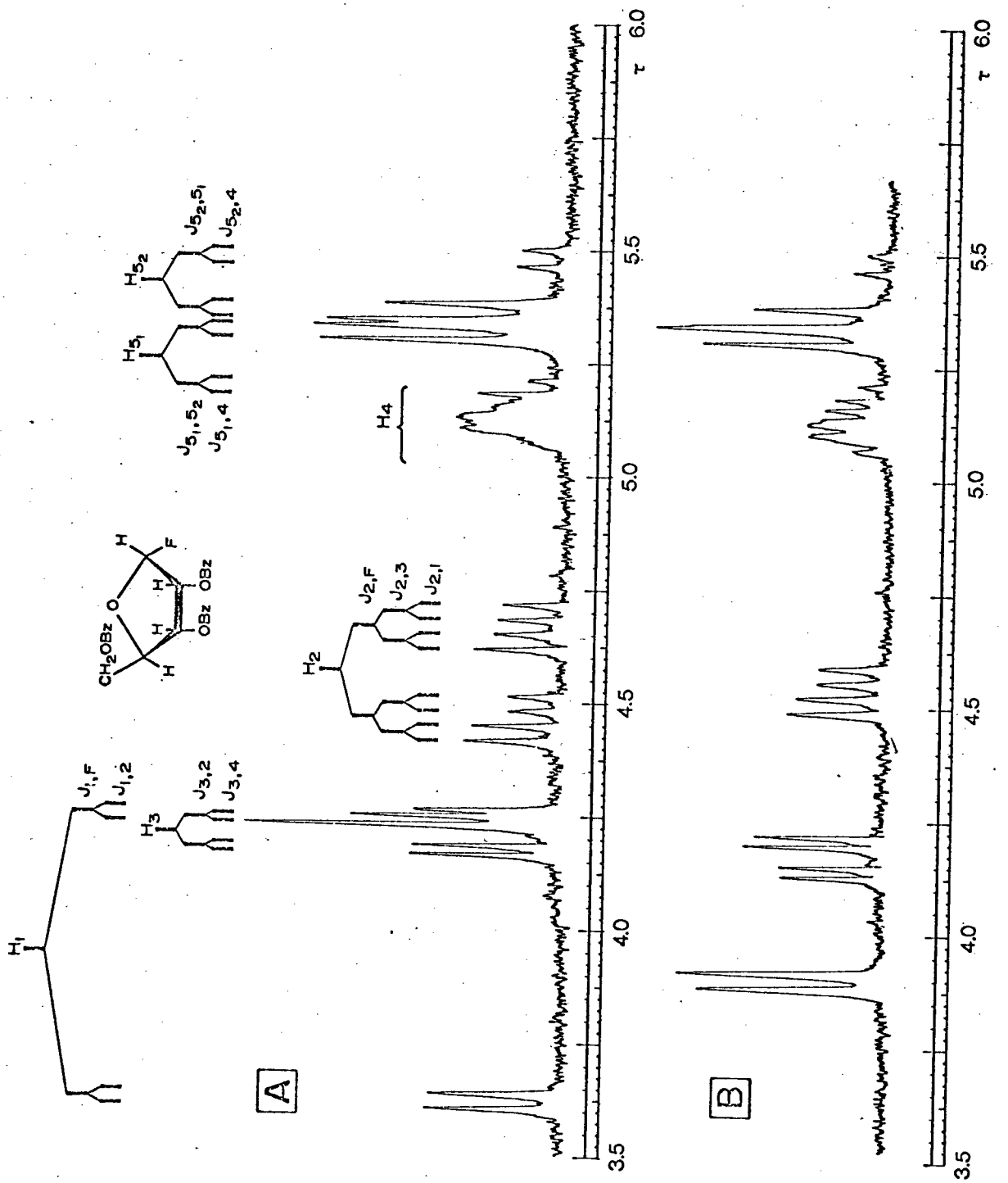

FIG. 8 100 MHz. proton spectra of 2,3,5-tri-O-benzoyl-α-D-ribofuranosyl fluoride (XIX) in chloroform-d. (A) normal spectra, (B) ^{19}F decoupled spectra. (See Text for details)

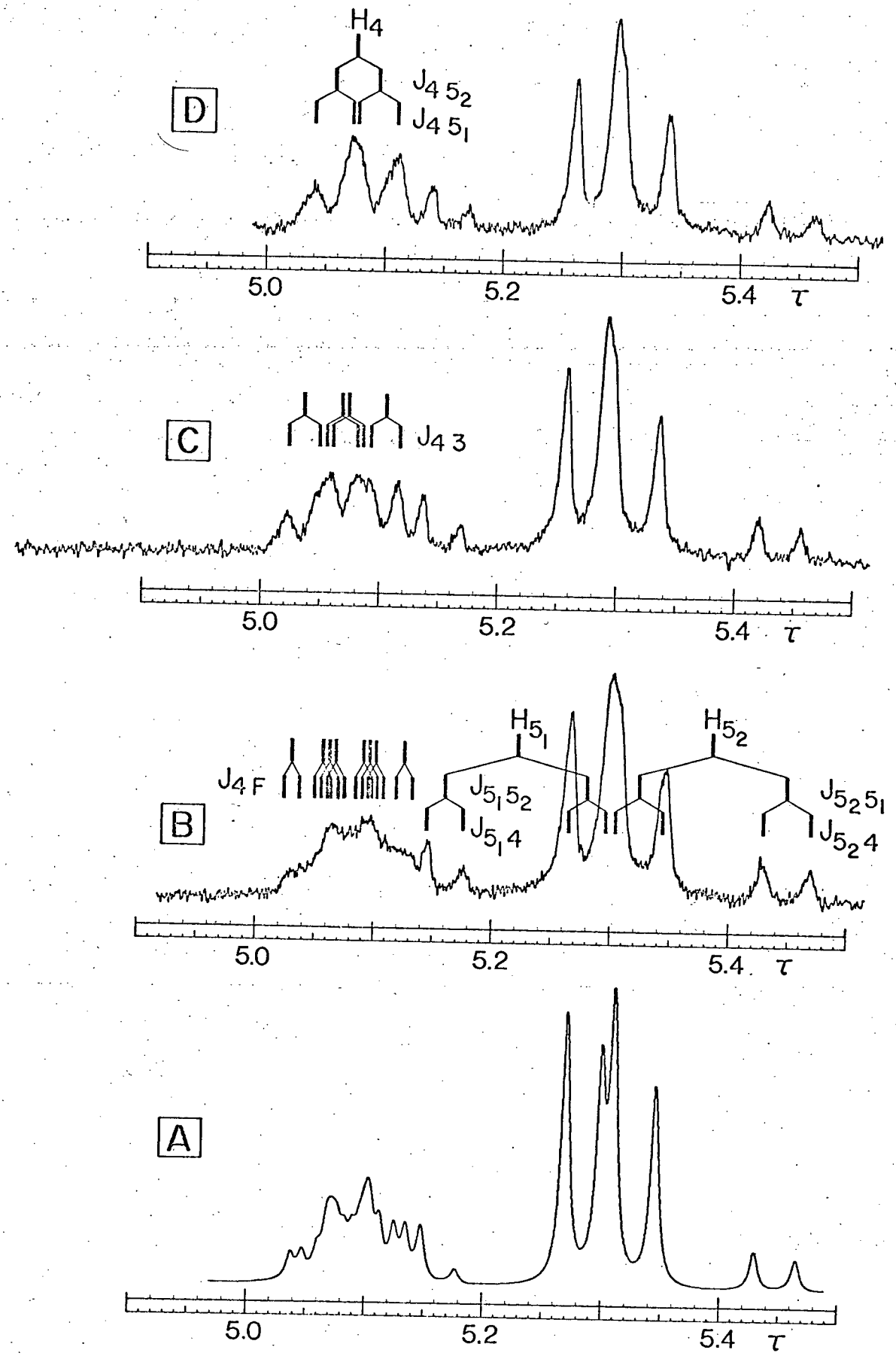

FIG. 9 Partial 100 MHz. spectra of H_4 and H_5 region of compound XIX in chloroform-d with (A) computer simulated spectra using LACØØN, (B) normal spectra, (C) ^{19}F decoupled spectra and (D) ^{19}F and H_3 decoupled spectra.

α anomer compared to that of the β anomer. This difference in chemical shift seems to be a characteristic of anomeric configuration in all the pairs of anomeric furanosyl fluorides examined in this investigation. The upfield region of XIX is shown on expanded sweep width in Figure 9B. Fluorine decoupling (Figure 9C) decreases the band width of H_4, however this decrease is significantly smaller than that observed in the fluorine irradiation of the β anomer. This coupling is ca. 1.0 Hz. The assignment of couplings in H_4 can be further verified by the similtaneous irradiation of fluorine and H_3 (Figure 9D) which leaves H_4 essentially as a broad quartet, the couplings of which arise from the two H_5 protons. The line broadening observed here probably arises from incomplete ^{19}F decoupling due to the larger band width of the fluorine spectrum (See Appendix B). Long-range coupling could also account for some of the line width. Finally, using the values derived from first order analysis, a simulated spectrum could be computed which fit the experimental H_4 and H_5 region (Figure 9A).

By comparing the data obtained for the two anomeric fluorides XVIII and XIX (Table VI), it becomes evident that not only do the couplings involving the nuclei at C_1 and C_2 differ, but those couplings involving H_3 and H_4 are also significantly changed. Notably, on inverting fluorine from the β

to the α position, the coupling $J_{3,4}$ changes from 5.8 Hz. to 2.3 Hz. This is indicative of an alteration in the dihedral angle between H_3 and H_4 arising from the anomerization of the sugar and signifies a conformational change in the molecule. The nature of this conformational change will be subsequently discussed.

Several other β-ribofuranosyl fluoride derivatives (compounds XX, XXI and XXII) were studied and these results are given in Tables VI & VII. Essentially, the coupling constants and chemical shifts are very similar to the tri-O-benzoyl-β-D-ribofuranosyl fluoride discussed previously. Any minor changes in coupling constants is attributed to the electronegativity effect of the acetate group in the ring and not to any conformational changes. These derivatives also show the large long-range $^4J_{H_4,F}$ of ca. 7 Hz.

In most cases these flexible furanosyl fluorides were dissolved in acetone-d_6 for n.m.r. studies. This solvent produced chemical shifts which reduced the second order effects in many spectra. Several derivatives were examined in more than one solvent to determine if specific solvation could alter the conformation of the molecule. However, in no case was there any evidence of solvent effects changing conformation.

Other furanose sugars, such as, tri-O-benzoyl-α-D-arabinofuranosyl fluoride (XXIII) and tri-O-acetyl-β-D-xylofuranosyl fluoride (XXIV) also were studied in order to observe the effects of inverting C_2 and C_3 in the furanose ring on the conformation and ^{1}H-^{19}F coupling constants. Considering the C_3 and C_4 positions of XXIII, the configuration around these two centres is the same as in XIX, however, the respective coupling $J_{3,4}$ of 4.4 Hz. and 2.3 Hz. are considerably different. Similarly, the long-range coupling $J_{3,F}$ is different in both these molecules. This is indicative of a conformational change between compounds XXIII and XIX. In the case of XXIV, the C_1 and C_2 centres have the same configuration as that of XVIII and the related J's are similar, indicating at most, a minor alteration in the conformation. It should be noted here that the $^{4}J_{4,F}$ is smaller in the xylo case than in that of the ribo sugar. This may be due either to the slight conformational change or to the effect of the 3-acetoxy group which is trans to H_4 in the xylofuranose sugar.

As mentioned previously, the concept of pseudorotation is prevalent in any study of furanose conformation. Restricting our discussion only to the envelope and twist conformations, allows twenty different forms which are represented in the

pseudorotation circle in Figure 10*. The energy barrier between each equilibrating form is the same order of magnitude as that of the rotational barrier in ethane (50) and will essentially depend on the substituents present in the ring. Due to the highly substituted nature of furanoses used in this study, it was expected that the energetically favoured forms would be restricted to a small portion of the pseudorotation cycle. It should be noted here that the assignment of conformations to a molecule by ^{1}H and ^{19}F n.m.r. will be limited at best to part of the pseudorotation cycle (usually three equilibrating forms). For instance, due to the limitations of the Karplus curve, n.m.r. could not differentiate between a specific conformation in the restricted cycle $V_2 \rightleftarrows {}_2T^3 \rightleftarrows V^3$. The limiting of conformation to only part of the pseudorotation cycle, instead of one distinct form, should not greatly hinder this study. It appears likely that the molecule will exist to some degree in all forms of the restricted cycle, since the energy differences between these forms are expected to be very low, even in highly substituted rings.

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*Using the system proposed by L.D. Hall (See Reference 49), the envelope and twist form will be designated by V and T respectively with subscripts and superscripts used to indicate respective displacements below or above the reference plane. For example, in the D series a twist conformation with C_2 below and C_3 above the reference plane is designated ${}_2T^3$, while an envelope form with C_3 below the plane of the ring, will have the notation V_3.

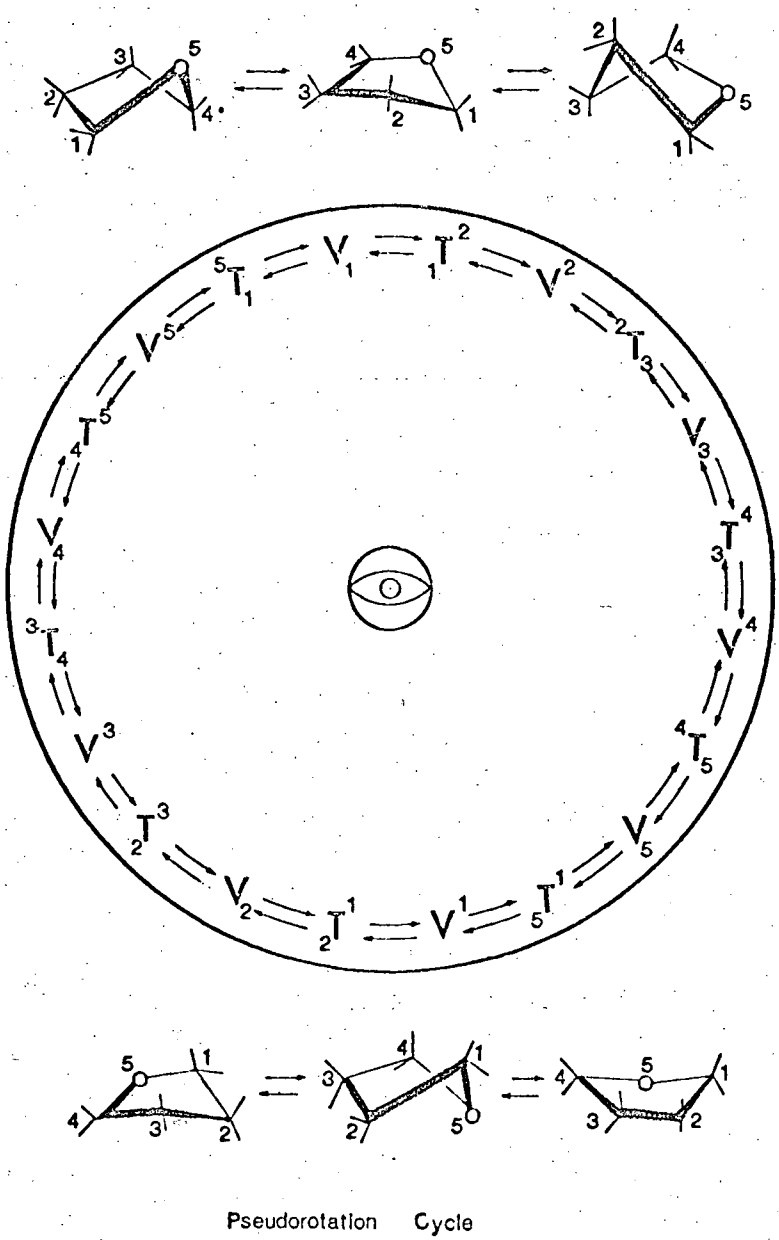

FIG. 10 Cycle of the Pseudorotation Scheme (CYCLOPS) for furanose sugars with T and V respectively, designating twist and envelope conformations. Restricted pseudorotation cycles are represented at the top and bottom of the circle.

It is proposed to make the following assumptions before proceeding to apply the n.m.r. data obtained in this study to the conformational analysis of furanose sugars:

(a) The arrangement around the carbon centres can be described as approximately tetrahedral, even though slight deviations from an angle of 109° 28' will occur for the molecule to be non-planar. (The dihedral angles were measured using framework models.)

(b) Only the envelope and twist conformations are considered.*

(c) The conformations are defined with maximum puckering, such that the bonds can be described as either equatorial (e), axial (a), quasi-equatorial (e'), quasi-axial (a') and bisectional (b). These latter three bonds are defined in the following manner:

quasi-axial	-	10° less than axial
quasi-equatorial	-	± 10° from equatorial
bisectional	-	± 30° from axial or equatorial (i.e. bisects 60° angle between vicinal axial and equatorial bonds).

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*The definition of envelope and twist was based on the presence of C_s and C_2 symmetry respectively in cyclopentanes. The furanoses however, have an oxygen ring atom and a substituent at each carbon centre, making it impossible for these pentose sugars to exist in a conformation with two-fold rotation symmetry.

Assumption (a) is essential - both (b) and (c) are dependent on it - since a deviation in the internal angle from tetrahedral hybridization can significantly alter both the geminal and vicinal coupling constants of a molecule (24). Notably, the Karplus curve is based on sp^3 hybridization only.

Previous investigations of the relationship between dihedral angle and vicinal ^1H-^{19}F couplings have attempted to use molecules of known conformation and have applied the experimental values thus obtained to produce a Karplus type curve (21,23,24). However, electronegativity or distortion effects have often been ignored. Indeed, many of the dihedral angles have been taken from X-ray data(24) and some of the coupling constants have been taken from low temperature studies, using techniques which are now under dispute (20,55).

This study attempts to arrive at conformations for furanosyl fluorides by using a combination of the Karplus curve for vicinal ^1H-^1H couplings, together with a vicinal ^1H-^{19}F Karplus type curve constructed from values obtained in studies of carbohydrates. From the data available (11a,31,51) and realizing the above limitations, a Karplus type comparison was plotted for vicinal ^1H-^{19}F couplings (Figure 11) in which trends could be observed. As can be seen, the absence of values for certain regions of the curve does not allow one to draw a

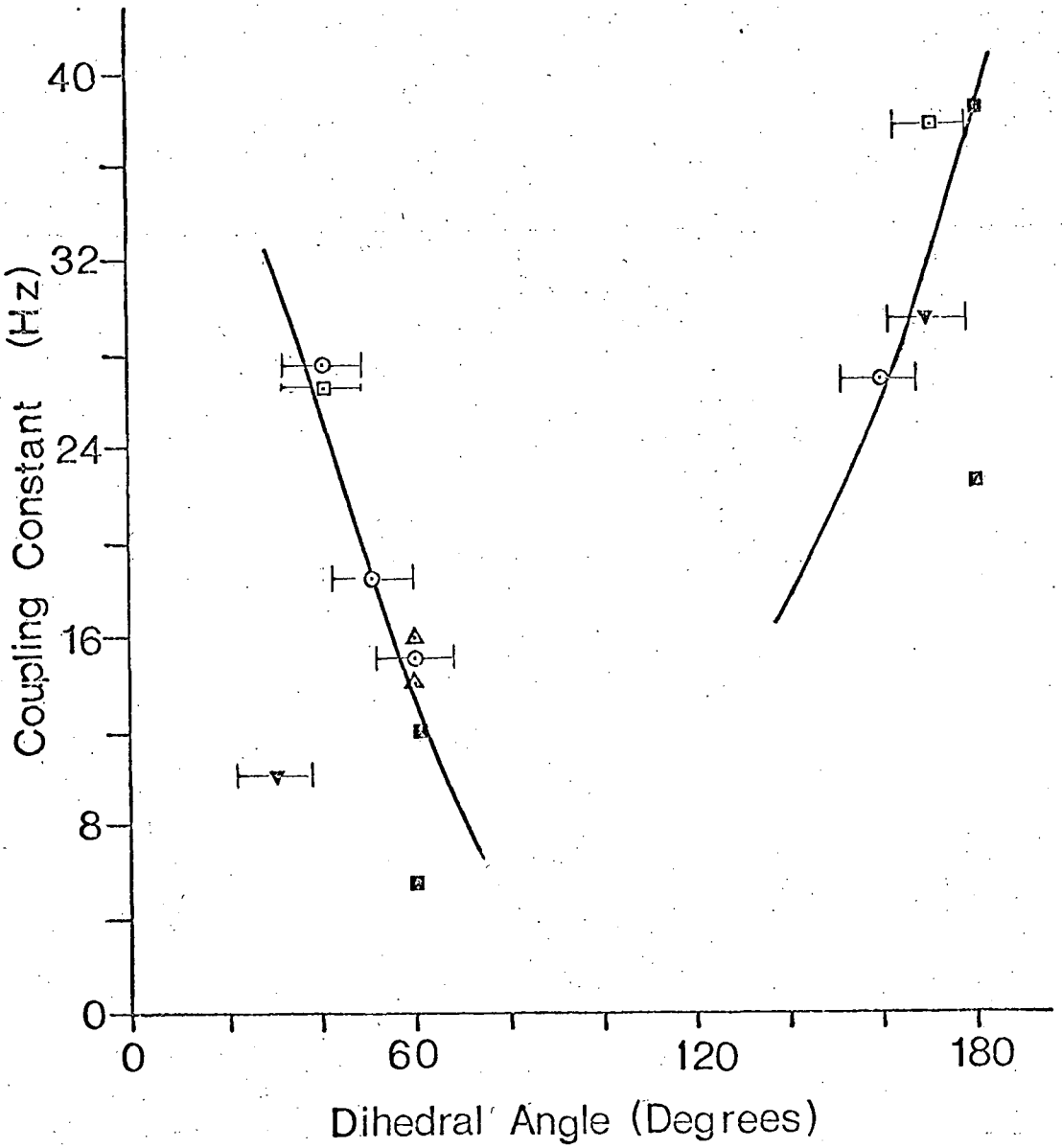

FIG. 11 The relationship between vicinal ^{1}H-^{19}F coupling constants and dihedral angles, using values taken from studies involving fluorinated carbohydrates:

- ⊙ - Ref. 11a - 2 and 3 fluoro furanoses.
- ▲ - Ref. 51 - 3 fluoro pyranoses.
- ▼ - Ref. 51 - 3 fluoro furanoses.
- ◘ - Ref. 31 - pyranosyl fluorides.
- ⊡ - compound VI - present work.

continuous line through the points. Notably, this plot appears to be more asymmetrical than that of the Karplus curve for vicinal ^{1}H-^{1}H couplings. The vicinal $J_{H,F}$ couplings obtained from the fluorinated derivative VI (whose conformation was based on vicinal ^{1}H-^{1}H couplings) fits reasonably well on this curve. Actually, the relationship is probably not a single curve, but a family of curves best represented by a band, which depends on the environment of the fluorine atom. This band effect does not alter the use of this curve for conformational determinations, since the restricted pseudo-rotation cycle consists of a family of conformations whose accuracy in dihedral angle determinations will generally be of the same magnitude as the band present in our ^{1}H-^{19}F Karplus curve.

The dihedral angles for compounds XVIII-XXIV were calculated for all possible twenty conformations using "framework models" and the above stated assumptions. From the Karplus relation for ^{1}H-^{1}H couplings, a dihedral angle range (ca. 20°) was assigned to each of the coupling constants used for determining the ring shape. The ^{1}H-^{19}F couplings were also assigned a dihedral angle range using the rough curve determined from the data available (Figure 11). Conformations were chosen which best fit the observed couplings*. By a process of

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*No account was taken of electronegativity effects on coupling constants except in the case where a substituent was co-planar with one of the nuclei involved in the vicinal coupling. In this latter case the coupling was arbitrarily considered to be ca. one-half of the normal coupling.

elimination, only two or three likely conformations remained.

For example, Table VIII shows the characteristic data for compound XVIII. A "X" in the last column, indicates the elimination of that conformer from consideration, while a darkened circle beside one of the corresponding dihedral angles of that conformer, gives the angle involving largest deviation, which led to the elimination of this conformer. The most characteristic dihedral angle in this procedure is 90° (0 Hz. coupling), while any large couplings can be attributed to an angle of 0° or 180°. As seen from this example (Table VIII), V^1, $^1T_2$ and V_2 are clearly the most favoured conformations for XVIII*. Table IX shows the favoured conformations for the other flexible furanosyl fluorides studies here.

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*The presence of oxygen in the furanose ring skeleton makes it highly probable that this heteroatom will remain in the plane of the ring. The absence of substituents on oxygen removes any strain due to eclipsing with groups on adjacent carbons, making it very likely that C_5, O and C_1 will be in the planar portion of the favoured conformation, while C_2 and C_3 are displaced out of the plane. Hence, all conformations involving a displacement of oxygen out of the ring plane, will be considered thermodynamically unfavoured.

TABLE VIII

Data for the Evaluation of the Favoured Conformations of Compound XVIII.

J	Observed Couplings (Hz.)	Dihedral Angle Ranges
H_1 H_2	<0.5	80°-100°
H_2 F	4.8	30°-50°; 140°-150°
H_2 H_3	4.8	30°-50°; 130°-150°
H_3 H_4	6.0	20°-40°; 140°-160°

Conformation	Dihedral Angle (degrees)				Evaluation
	H_1H_2	H_2F	H_2H_3	H_3H_4	
V_1	170 ⊙	50	30	120	X
${}_1T^2$	180 ⊙	60	50	100	X
V^2	170 ⊙	50	50	90 ⊙	X
${}^2T_3$	170 ⊙	50	60	90 ⊙	X
V_3	150 ⊙	20	50	70	X
${}_3T^4$	140 ⊙	20	50	60	X
V^4	120	0 ⊙	30	70	X
${}^4T_5$	100	20	20	50	X*
V_5	90	20	0 ⊙	90 ⊙	X
${}_5T^1$	70	50	20	100 ⊙	X
V^1	70	50	30	120	
${}^1T_2$	60	60	50	140	
V_2	70	50	50	150	
${}_2T^3$	70	50	60	170 ⊙	X
V^3	90	20	50	170 ⊙	X
${}^3T_4$	100	20	50	180 ⊙	X
V_4	120	0 ⊙	30	170 ⊙	X
${}_4T^5$	140 ⊙	20	20	170 ⊙	X
V^5	150 ⊙	20	0	150	X
${}^5T_1$	170 ⊙	50	30	150	X

*See Footnote Page 60.

TABLE IX

COMPOUND	FAVOURED FORMS
XVIII	V^1, $^1T_2$, V_2
XIX	V_3, $_3T^4$, V^1, $^1T_2$
XXIII	V_1, V_3, $_3T^4$
XXIV	V_2, $_2T^3$, V^3
XII,XIV	$^1T_2$, V_2, $_2T^3$

In most cases the favoured forms involve ring puckering at C_2 and/or C_3. X-ray diffraction studies of the furanose rings in nucleic acids (52) conclude that the sugar ring involves only the puckering of C_2 and C_3. Although this is in agreement with the present study, it appears questionable, because of the low barrier to pseudorotation, whether one can relate the conformational results obtained for solids to the conformation in solution.

A recent paper by Stevens and Fletcher (28b) examined a series of pentofuranose derivatives. Using ^1H n.m.r. and a correction factor for $J_{1,2}$ - to take in account that C_1 is attached to two oxygen atoms, while the other carbon atoms of the ring bear only one oxygen - they arrived at conformations for furanose derivatives of ribose, arabinose and xylose, which differed from the furanosyl fluorides discussed here. To evaluate the relationship between this present study and that of Stevens and Fletcher, the data obtained from these worker's investigation was applied to conformational studies using the methods adopted in this thesis. The results are shown in Table X.

TABLE X

COMPOUND (tetraester)	CONFORMATION	
	Stevens & Fletcher*	Present Study
α-Ribofuranose	${}_1T^2$, V^2	V^2, ${}^2T_3$, V_3
β-Ribofuranose	${}_2T^3$	V_2; ${}_2T^3$, V^3
β-Xylofuranose	${}_2T^3$, V^3	V_3, ${}_3T^4$, V^4
α-Arabinofuranose	${}_1T^5$	${}^2T_3$, V_3, ${}_3T^4$

In the first three compounds agreement is reasonably close, especially for the β-ribofuranose. A major difference, however, is evident in the α-arabinofuranose derivative. The conformation for this latter compound predicted by the present study, is supported by Bishop and Cooper (32). Significantly, conformations for the tetraesters differ from those favoured by the fluorinated derivatives. This is not suprising, since the low pseudorotation barrier makes conformational mobility - which is governed by the non-bonded interactions - very sensitive to changes in substituents at a carbon centre of the furanose ring.

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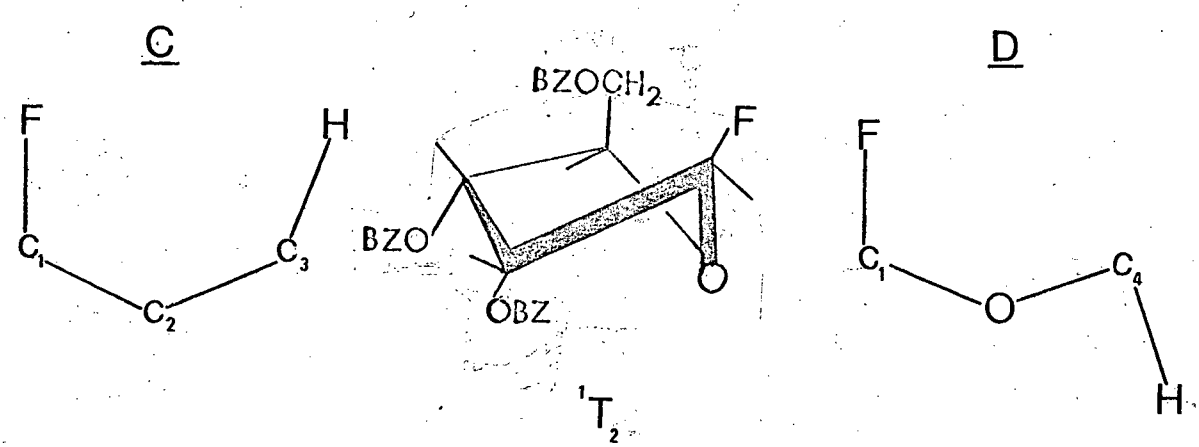
*See Reference 28b.

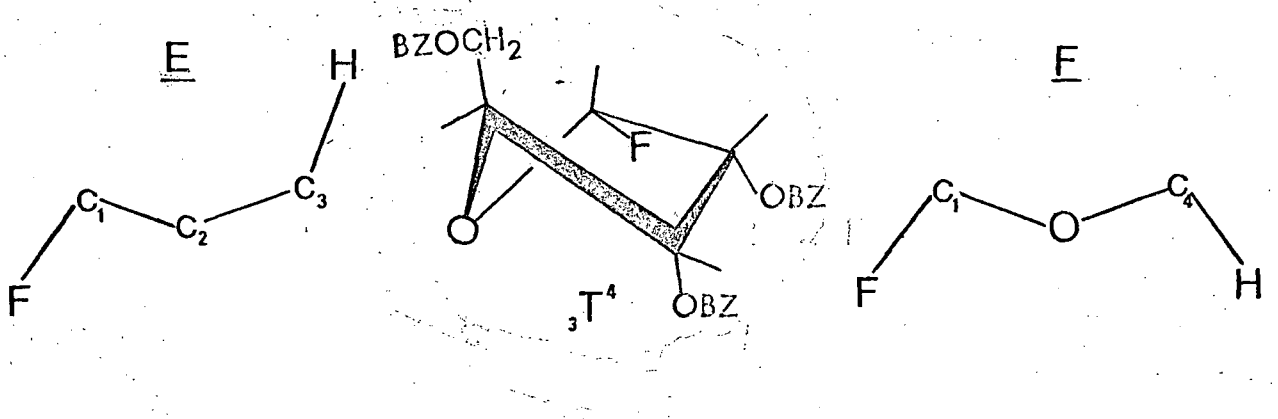
Assignment of a restricted conformation cycle to these molecules allows one to correlate the observed long-range $^{1}H-^{19}F$ coupling constants with the stereospecificity of interacting nuclei (45). For β-ribofuranosyl fluoride (XVIII) with a $^{1}T_{2}$ conformation, a long-range four bond coupling is observed following the geometry shown in C for $^{4}J_{3,F}$ and in D for $^{4}J_{4,F}$.



$^{4}J_{H,F}$ = 2.2 Hz.

$^{4}J_{H,F}$ = 6.6-7.3 Hz.

On the other hand α-ribofuranosyl fluoride (XIX) with conformation $_3T^4$ has geometries corresponding to E and F for $^4J_{3,F}$ and $^4J_{4,F}$ respectively.



$^4J_{H,F}$ = 0 Hz. $^4J_{H,F}$ = 1.0-1.8 Hz.

E and F are also identical to geometries observed for the same $^4J_{H,F}$ couplings in α-arabinofuranosyl fluoride (XXIII). The $_2T^3$ conformation of β-xylofuranosyl fluoride (XXIV) has a geometry for $^4J_{3,F}$ similar to E, while $^4J_{4,F}$ is identical to D.

The long-range coupling $^4J_{F,4}$ through oxygen is consistently large, when the two coupled groups are in a trans orientation (as in D), while this coupling is small, when the interacting groups are in a cis orientation (as in F). The latter orientation approaches a "planar M

relationship" (57). Hence, for the D-ribofuranose sugars the β fluoride exhibits this long-range coupling, while the α fluoride does not. The magnitude of these long-range couplings leads one to be optimistic of their application to configurational and conformational elucidation of furanosyl fluorides. Interestingly, when examining the $^{4}J_{F,3}$ couplings, an opposite effect is observed. The "planar M" or cis geometry of the interacting groups has a larger coupling than the trans arrangement. Hall has shown from a study of pyranosyl fluorides (45) that $^{4}J_{H,F}$ couplings through carbons only, are larger when in the "planar M" configuration than when in the non-planar arrangement*. To rationalize this reverse effect observed here for long-range ^{1}H-^{19}F couplings through oxygen, one can suggest the possibility that the signs of these ^{4}J couplings have changed and the "planar M" arrangement still has a larger coupling (-1.0 to -1.8 Hz.) than the coupling through the "trans arrangement" (-6.6 to -7.3 Hz.). Although this suggestion leads to some consistency in the observations of $^{4}J_{H,F}$ couplings, the signs of these four bond couplings through oxygen must be proven conclusively before any definitive statements can be made about the steric requirements of these

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*In pyranosyl fluorides for ^{1}H-^{19}F couplings, the sign of the $^{4}J_{e,e}$ coupling is positive, while that of the $^{4}J_{e,a}$ is negative (See Reference 45).

couplings*.

Finally, some comments should be made about the geminal $^{1}H-^{19}F$ coupling. The range of 58 to 64 Hz. for the anomeric $^{1}H-^{19}F$ couplings for furanosyl fluorides is significantly larger than the same $^{2}J_{H,F}$ coupling of ca. 50 Hz. for pyranosyl fluorides (9,31). Furthermore, the observation that the geminal $^{1}H-^{19}F$ coupling in the 3,6-anhydro ring of compound VI - where no hetero-atom is adjacent to the carbon containing the nuclei involved in the coupling - is 50.4 Hz., suggests that ring size alone does not account for the difference in geminal $^{1}H-^{19}F$ couplings between furanose and pyranose rings. A possible explanation for the change in size of these geminal couplings may arise from the orientation of the oxygen lone pairs to the anomeric fluoride (54).

The limited number of compounds available for this study restricted one from making incisive statements about the effect of substituents at the C_2 position of the geminal $^{1}H-^{19}F$ coupling. Suffice to say that an acetoxy or benzoyloxy group at C_2, which is trans to the fluorine atom on the anomeric carbon, tends to decrease the size of the geminal $^{1}H-^{19}F$ coupling. For instance, β-ribofuranosyl fluoride has a smaller $^{2}J_{H,F}$ coupling than α-ribofuranosyl fluoride, while

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*For 1α, 2α-O-isopropylidene-3β-O-acetyl-4β-cyano-tetrahydrofuran-1α, 2α, 3β-triol, Pachler has shown (See Reference 58) that $J_{1,3}$ and $J_{1,4}$ - the latter of which involves a long-range coupling through oxygen - are both small and have a negative sign.

the α-arabinofuranosyl fluoride geminal coupling is smaller than both of the ribo anomers.

This present investigation attempted to assign conformations to furanosyl fluorides by application of both ^{19}F and ^{1}H n.m.r. By using several basic assumptions, together with heteronuclear decoupling and computer programming, this objective was achieved to the extent of assigning a restricted number of conformers to each molecule. However, it has become very evident that previous investigations added confusion to matters because of oversights in defining the limitations of their studies. It is hoped that this thesis, by stating definitions and assumptions used in this investigation, demonstrates some of the limits in assigning conformations to furanose sugars. Indeed, since the energy barrier to pseudorotation for five membered rings is of the same order as that for the rotation of ethane, it is questionable - for the case of five membered rings - whether one should even use the term "conformation" in the same sense as it is applied to cyclohexane (53). Instead, one should be considering furanose forms in the same terms as that of ethane, where rotamers are somewhat analogous to pseudorotational forms.

EXPERIMENTAL

GENERAL METHODS

(a) The structural formula associated with each compound are given on flow sheets in Sections A and B.

(b) Optical rotations were measured in a Bendix ETL-NPL Automatic Polarimeter (type 143A) using a 4.0 cm. or a 0.5 cm. cell. All optical rotations were measured using chloroform solutions.

(c) Micro-analysis was carried out by Mr. P. Borda of the U.B.C. Chemistry Department.

(d) Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected.

(e) All ^{1}H n.m.r. spectra were measured with a Varian HA-100 spectrometer operating in either the frequency sweep or field sweep mode using tetramethylsilane (T.M.S.) as internal reference. Proton chemical shifts are all reported in the τ scale.

(f) All ^{19}F n.m.r. spectra were measured at 94.071 M.Hz. using a Varian HA-100 spectrometer with trichlorofluoromethane (freon 11) as internal reference. The spectrometer was used in either the HR-mode or in the locked field sweep mode using the "infinite offset" modification of Douglas (59) - further modified by Mr.

R. Burton of this Department. Chemical shifts are reported in p.p.m. from Freon 11.

3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (IIa):- 150 g. of glucose (anhydrous) was shaken with 1 l. of acetone, 120 g. of zinc chloride and 15 ml. of 85% phosphoric acid for 30 hours, and worked up in the usual manner (60) to give 85 g. (57%) of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (I); m.p. 112° (lit. (60) 112°-113°).

Acetylation was carried out by shaking 70 g. of I, 50 ml. pyridine and 45 ml. of acetic anhydride for several minutes. The solution was allowed to stand at room temperature for 10 hours then poured into ice-water, extracted thrice with chloroform and the extracts dried over Na_2SO_4. Evaporation at reduced pressure yielded a light yellow syrup which crystallized in aqueous ethanol to give 63 g. of IIa; m.p. 53°-54° (lit. (61) 55°).

3-O-acetyl-1,2-O-isopropylidene-α-D-glucose (IIIa):- 40 g. of IIa and 75 ml. of 20% acetic acid were heated at 60°. Thin layer chromatography (t.l.c.) was used to follow the reaction. After 4 hours, the reaction was completed. Work-up involved the evaporation of the reaction mixture at reduced pressure, occasionally adding ethanol to ensure the removal of all the

acetic acid. Crystallization from aqueous ethanol afforded 32 g. (94%) of IIIa; m.p. 124°-126° (lit. (62) 125°-126°).

5,6-di-O-mesyl-3-O-acetyl-1,2-O-isopropylidene-α-D-glucose (IVa):- 20 g. of IVa were dissolved in 25 ml. of dry methanol and heated on a steam bath. 0.1 N sodium methoxide was added until the boiling solution remained alkaline. The solution was refluxed further for 30 minutes and then poured into 250 ml. of water. Upon standing overnight at 0°, 0.9 g. (61%) of V precipitated; m.p. 114°-115°. The ^{1}H n.m.r. spectra was identical to that observed for 5-O-tosyl-3,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (X) except for the aromatic region. This tosyl derivative (X) was prepared in an identical manner as compound V listed above, but using 5,6-di-O-tosyl-3-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose as a precursor. Yield of X was 56%; m.p. 135° (lit. (5) 135°-136°).

3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (IIb):- 25 g. of I, 160 ml. of benzyl chloride and 80 g. of anhydrous potassium hydroxide were stirred and heated at 110° for 4 hours. The solution was cooled, 300 ml. of water added, and then extracted several times with cold water and evaporated at reduced pressure. Treatment with charcoal-celite resulted in a light orange syrup of IIb (63); yield 26 g. (78%).

3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose IIIb):-
Using the method of Goldstein and Smith (64), 26 g. of IIb was hydrolized in quantitative yield to a colourless syrup IIIb. ^{1}H n.m.r. showed the removal of one isopropylidene group via integration of resonances from the τ 8.3-8.5 region.

5,6-di-mesyl-3-O-benzyl-1,2-O-isopropylidene-α-D-glucose (IVb):-
4 g. of IIIb and 3 g. of mesyl choride in 15 ml. of pyridine were allowed to stand overnight. Work-up as in previous mesylation reactions, afforded 3 g. (54%) of non-crystalline IVb. ^{1}H n.m.r. indicated the presence of two methyl groups (from mesyl substituents) at τ 6.2.

SYNTHESIS OF 5-FLUORO-3,6-ANHYDRO-1,2-O-ISOPROPYLIDENE-α-L-IDOFURANOSE (VI)

(a) From 5,6-di-O-mesyl-3-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose (IVa):- 5 g. of IVa and 5 g. of anhydrous potassium fluoride were refluxed for 2 hours in 50 ml. of anhydrous ethylene glycol. During this time, white crystals sublimed out onto the condenser wall. The darkened solution was poured into ice water and extracted thrice with chloroform. The combined extracts were dried over Na_2SO_4 and concentrated to give crude crystals.

The crude and sublimed crystals from the condenser wall were placed in a sublimation apparatus to yield 1.21 g. (48.4%) of VI; m.p. 96.5°-97.5° (Found C, 53.12; H, 6.21; O, 31.37; F, 9.31. Calculated for $C_9H_{13}O_4F$: C, 52.94; H, 6.37; O, 31.56; F, 9.11 %). $[\alpha]_D^{22}$ = 13.5° (c. 1.97).

(b) From 5-O-mesyl-3,6-anhydro-1,2-isopropylidene-α-D-glucofuranoside (V):- 1 g. of V and 1 g. of anhydrous potassium fluoride in 25 ml. of dry ethylene glycol were refluxed for 1 hr. The reaction mixture was worked up as in (a) above. Sublimation yielded 0.55 g. (75.3%) of VI; m.p. and mixed m.p. of 96.5°-97.5°.

(c) From 5,6-di-O-mesyl-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose(IVb):- 1.5 g. of IVb and 1.5 g. of potassium fluoride (anhydrous) in 30 ml. of dry ethylene glycol were refluxed until sublimed product was observed in the condenser (1 hour). The dark solution was treated in a similar manner as (a) above. 0.25 g. of VI were recovered (45.5%); m.p. & mixed m.p. of 96.5°-97.5°.

By ^{19}F n.m.r., another product containing fluorine was observed in the mother liquors, but could not be isolated. The ^{19}F n.m.r. consisted of a triplet at +234 p.p.m. upfield from freon 11, suggesting a primary fluoride. The proton spectra indicated one mesyl group (τ 6.2), an isopropylidene group (τ 8.0-8.2), and the benzyl group (τ 1.9-2.8) remaining. This product was tentatively assigned to 6-fluoro-5-O-mesyl-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose.

OTHER ATTEMPTED FLUORINATIONS OF IVa

(a) Using potassium fluoride and potassium hydrogen difluoride:- 2 g. of IVa and 1 g. each of anhydrous potassium fluoride and potassium hydrogen fluoride were refluxed for 2 hours in dry ethylene glycol. Severe charring occurred and a white gas (presumably hydrogen fluoride) evolved. Work-up in the usual manner resulted in a small amount of starting material as the only discernible product.

(b) Using tetra-n-butyl ammonium fluoride:- 2 g. of IV and 4 g. of $Bu_4N^+F^-$ (16) were refluxed for 2 hours in 20 ml. of acetonitrile. Water was added and the precipitated crystals filtered. Product was identified as V (does not contain fluorine); m.p. & mixed m.p. 114°-115°.

1,2-di-O-acetyl-5-fluoro-3,6-anhydro-L-idofuranose (VIII):- 500 mg. of VI in 25 ml. of 30% acetic acid were placed on a steam bath. The hydrolysis was followed by t.l.c. (3 hours) to give a quantitative yield of colourless syrup VII. ^1H n.m.r exhibited no isopropylidene resonance.

To 300 mg. of VII in 10 ml. of pyridine were added 2 ml. of acetic anhydride. The solution was left at room temperature

overnight, then poured into 100 ml. of ice-water and extracted with chloroform. Evaporation of the extracts at reduced pressure afforded a light yellow syrup. T.l.c. showed only one spot in a variety of elutants (benzene/ether; $CHCl_3$/MeOH; and EtOAc/pet. ether). V.P.C. could resolve only one broad peak (column packing of 5% butanediol succinate on 60-80 Diataport S).

^{19}F n.m.r., however, showed two fluorine resonances at + 176.1 p.p.m. and + 180.0 p.p.m. upfield from freon 11 in chloroform; the latter having approximately twice the area of the former. Both ^{19}F chemical shifts are characteristic of secondary fluorides.

^{1}H n.m.r. gave two sets of peaks in the anomeric region; at τ 3.45, a quartet having ca. twice the area of the doublet observed at τ 3.65. Thus, one has an indication from the n.m.r. that both anomeric acetates are present, however until the mixture has been separated, it would indeed be presumptuous to assign any multiplets to a specific anomer.

5-O-benzoyl-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (IXa):-

2 g. of V were refluxed with 10 g. of sodium benzoate in 150 ml. of dimethyl formamide in the usual manner (65). Crystallization from aqueous ethanol afforded 1.1 g. (50.3%) of IXa; m.p. 83° (lit. (65) 83°-84°). ^{1}H n.m.r. showed the removal of the mesyl

peak at τ 6.2 and appearance of an aromatic resonance at τ 1.9-2.8 in chloroform.

3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (IXb):-

1.1 g. of IX a were dissolved in a minimum amount of dry methanol and 0.1 N sodium methoxide added until the solution became basic. After refluxing for an hour, the solution was neutralized with solid carbon dioxide and then extracted with chloroform. Evaporation at reduced pressure gave 0.6 g. (83%) of IXb; m.p. 105° (lit. (65) 105°-107°); ^{1}H n.m.r. indicated removal of the aromatic resonance.

5-O-mesyl-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose (IXc):-

0.5 g. of IXb and 1 g. of mesyl chloride in 10 ml. of pyridine were allowed to stand overnight. Work-up in the usual manner followed by recrystalization from aqueous methanol afforded 0.55 g. (79.5%) of IXc; m.p. 129°-130.5° (Found C, 42.69; H, 5.58; S, 11.12; Calculated for $C_{10}H_{16}O_7S$: C, 42.80; H, 5.70; S, 11.4 %). $[\alpha]_D^{22}$ = 31° (c. 2.25).

GENERAL FLUORINATION PROCEDURE USING HYDROGEN FLUORIDE

The tetra-acetate or tetra-benzoate derivative of the furanose sugar (500 mg.) was added slowly to a small amount (1 ml.) of hydrogen fluoride in a polyethylene flask surrounded by an acetone-dry ice bath. The reaction mixture was swirled several times and allowed to warm to room temperature (20 Min.). The reactants were poured slowly into a beaker containing 100 ml. of super-saturated sodium bicarbonate solution and 100 ml. of ethyl ether. After neutralization was accomplished, the ether layer was separated, dried over Na_2SO_4 and evaporated to give a syrup. Purification was accomplished by column chromatography (Silicar CC 7) using 25% ethyl acetate/75% pet. ether as elutant.

In the manner described above the following furanosyl fluorides were prepared for ^{19}F n.m.r. and ^{1}H n.m.r. investigations:

(a) 5-O-benzoyl-3,6-anhydro-2-O-acetyl-β-L-idofuranosyl fluoride (XII):- prepared from a sample of 5-O-benzoyl-3,6-anhydro-1,2-di-O-acetyl-L-idofuranose (VII) kindly provided by Dr. John F. Manville. ^{19}F n.m.r. shows two sextets split by 60 Hz. at + 120.6 p.p.m.

upfield from freon 11.

From a similar reaction which was quenched after half the usual reaction time, ^{19}F n.m.r. showed, in addition to the resonance observed for XII, two doublets split by 60 Hz. at + 138 p.p.m. upfield from freon 11. This multiplet was assigned to 5-O-benzoyl-3,6-anhydro-α-L-idofuranosyl fluoride (XI). In this instance the reaction mixture contained 70% of XII and 30% of XI.

(b) 2,3,5-tri-O-acetyl-β-D-xylofuranosyl fluoride (XXIV).

(c) 2,5-di-O-acetyl-β-D-glucuronolactone fluoride (XVII):- prepared from a sample of 1,2,5-di-O-acetyl-β-D-glucuronolactone (XVI) kindly provided by Dr. John F. Manville.

2,5-di-O-benzoyl-β-fluoro-D-glucuronolactone (XIV):-

(i) 750 mg. of 1,2,5-tri-O-benzoyl-D-glucuronolactone (55) were reacted with anhydrous hydrogen fluoride in the manner described above. Crystallization occurred after two days at 0° C. in dry Et_2O/pentane. ^{19}F n.m.r. gave two triplets split by 60 Hz. at

+ 117.9 p.p.m. upfield from freon 11. The mother liquors also showed only this fluorine resonance. 290 mg. of white crystalline XIV (46.2%) were isolated; m.p. 132°-134° (Found C, 62.18; H, 4.13; F, 5.05: Calculated for $C_{20}H_{15}O_7F$: C, 62.18; H, 3.89; F, 4.92 %). $[\alpha]_D^{22}$ = 64° (c. 1.28).

(ii) 1 g. of 1,2,5-tri-O-benzoyl-D-glucuronolactone were added to 20 ml. of saturated Br_2/acetic acid solution. The mixture was stirred until all the sugar was dissolved, then allowed to remain at room temperature for four hours. The reaction mixture was slowly added to 100 ml. of saturated sodium bicarbonate solution and quickly extracted several times with chloroform. Drying over Na_2SO_4 afforded a light brown syrup from which ^1H n.m.r. indicated the removal of one benzoate group. The product was tentatively assigned to 2,5-di-O-benzoyl-β-bromo-D-glucuronolactone (XV). Due to the lability of the bromides, the syrup was reacted immediately with 0.5 g. of silver fluoride in 20 ml. of acetontrile. The solution was stirred for 1 hour, filtered and evaporated at reduced pressure. The product could not be isolated, but from the fluorine spectra of the mother liquors, a small resonance was observed at + 118 p.p.m. upfield from freon 11 (two triplets) which was identical to the fluorine spectra for compound XIV.

5-O-benzoyl-3,6-anhydro-2-O-acetyl-β-L-idofuranosyl fluoride (XII):-

1.1 g. of VII was added to a saturated Br_2/acetic acid solution at 0° C. and stirred at room temperature for 2 hours. Five times the volume of saturated sodium bicarbonate solution was added and the mixture quickly extracted thrice with chloroform. The extracts were dried over Na_2SO_4 and then evaporated at reduced pressure to yield a light brown syrup XIII. Dry acetonitrile (20 ml.) and 0.5 g. of silver fluoride were immediately added and the mixture stirred for 1 hour. The silver bromide precipitated and excess silver fluoride was filtered off and the clear solution reduced to a syrup in vacuo. ^{19}F n.m.r. showed two sextets separated by 60 Hz. at + 120.6 p.p.m. upfield from freon 11.

The following furanosyl fluorides were generously donated by Christian Pedersen (48) for use in this investigation:

(a) Tri-O-benzoyl-β-D-ribofuranosyl fluoride (XVIII).

(b) Tri-O-benzoyl-α-D-ribofuranosyl fluoride (XIX)

(c) 2-O-acetyl-3,5-di-O-benzoyl-β-D-ribofuranosyl fluoride (XX).

(d) 3-O-acetyl-2,5-di-O-benzoyl-β-D-ribofuranosyl fluoride (XXI).

(e) 5-O-acetyl-2,3-di-O-benzoyl-β-D-ribofuranosyl fluoride (XXII).

(f) Tri-O-benzoyl-α-D-arabinofuranosyl fluoride (XXIII).

APPENDIX

APPENDIX A

COMPUTER PROGRAMS

During the course of this investigation, there was an increasing awareness that many of the compounds studied did not exhibit strictly first order spectra, but often involved second order effects, which make the observed chemical shifts and coupling constants different from the true values. The computer programs were used to check both the assigned analysis and also in some cases to refine the coupling constants and chemical shifts to their true values.

(1) TWØSUM*

This program was written in FØRTRAN IV for an IBM 7044 computer and can handle a maximum number of six spins with an upper limit of 100 energy levels and 600 transitions. There are two modes of operation, the first involves entering guesses of the shifts and coupling constants into the program until one achieves a computed spectrum close enough to the one observed, such that an unambiguous assignment of observed transitions to pairs of energy levels can be made. The output of a histogram plot simulating the calculated spectrum facilitates this stage of the operation. The second mode of operation assigns these transitions to their experimental frequencies and produces an optimum set of energy levels. Then, the shifts and couplings are refined by an iterative

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*Graciously provided by Dr. John Martin, University of Alberta, Edmonton, Alberta.

method to fit these optimized energy levels. The output gives a listing of these refined couplings and shifts together with the error involved in matching the transitions.

(2) LACØØN III

LACØØN III was kindly provided by Aksel Bothner-By* and was written in FØRTRAN IV and used for systems involving up to seven spins. As with TWØSUM, the program has two operational modes, one involving the introduction of "guess" shifts and couplings to generate an assigned set of frequencies and transitions. The other mode uses an iterative procedure to match the experimental and observed spectra by a least squares criterion. The core size of the IBM 7044 restricts the number of iterations in this last stage.

(3) SMASH

The plot routine SMASH was written by John Coulthart** for the calcomp plotter and used in conjunction with LACØØN III to provide a simulation of the calculated n.m.r. spectra.

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APPENDIX B

HETERONUCLEAR DECOUPLING

The advantages of using fluorine as a probe for conformational analysis are often limited by the presence of a multitude of couplings between fluorine and other nuclei in the molecule. These extra couplings may complicate the spectrum to such an extent that analysis becomes difficult. In this present investigation, such problems were overcome by application of fluorine double resonance.

One of the first successful applications of heteronuclear decoupling was made by Bloom and Schoolery (67) who observed the fluorine spectra of Na_2PO_3F while irradiating phosphorous. Conformational free energies of deuterium labelled cyclo-octane have been determined by Anet (68) using deuterium decoupling to remove the effects of quadrupole broadening in the proton spectra. Similarly, Bovey (23) simplified the ^{19}F spectra of cyclohexyl fluoride by irradiating protons and used this spectra to determine the relative free energies of the two conformations for the molecule. The application of heteronuclear decoupling to these and other nuclei has been recently reviewed by McFarlane (69).

The heteronuclear decoupler unit used for this study

was built by Mr. R. Burton of this Department for a Varian HA-100 Spectrometer (70). Essentially, the unit involved a modification of the Varian V-4333 probe, by means of a double-tuner-probe-adapter, for observing ^{1}H at 100 MHz., while irradiating ^{19}F. The ^{19}F decoupling frequency is produced by a Hewlett Packard Frequency Synthesiser (Model 5105A) with a maximum output frequency of 500 MHz. and which is coupled to a Hewlett Packard Synthesiser-Driver (Model 230A).

All heteronuclear decoupling applied to the molecules in this thesis involves continuous wave decoupling (i.e. using a single coherent radiofrequency). The maximum band width, which can be effectively irradiated under continuous wave conditions, is ca. 80 Hz.*

A typical heteronuclear decoupling experiment was performed as follows: First, the correct decoupling frequency was found by setting the HA-100 recorder at a central position (in the ^{1}H spectra) between two peaks arising from a ^{1}H-^{19}F coupling. Usually, the H_1 resonance was used because of its large geminal ^{1}H-^{19}F coupling and its low field chemical shift. The power was adjusted to almost the maximum level and then

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*Using "noise decoupling", this band width of irradiation can be increased considerably (See References 70 and 71).

the decoupler frequency altered in stages. As the frequency of the synthesiser approaches the decoupling frequency, the pen response increases. The final frequency adjustments were accomplished by scanning the decoupled H_1 resonance several times until the smallest line width (i.e. the largest peak intensity) was produced.

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NOTE

The naming of compound VI as 5-fluoro-3,6-anhydro-1,2-O-isopropylidene-α-L-idofuranose is used in this thesis and in our laboratory as a matter of convenience for visualization of structure. However, by I.U.P.A.C. nomenclature, compound VI should be correctly designated as 3,6-anhydro-5-fluoro-1,2-O-isopropylidene-β-L-idofuranose.