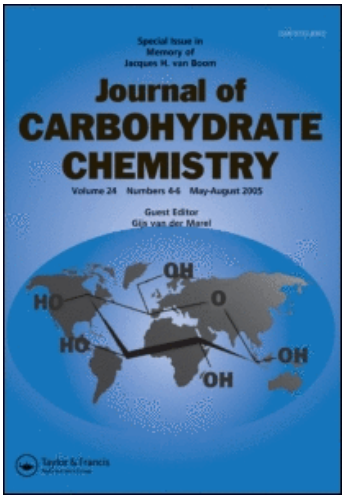

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

On the Stereoselectivity of Fluorine and Acetylhypofluorite Additions to Glycals: The Synthesis of 2-Deoxy-2-Fldorohexoses

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To cite this Article Satyamurthy, N. , Blda, G. T. , Padgett, H. C. and Barrio, J. R.(1985) 'On the Stereoselectivity of Fluorine and Acetylhypofluorite Additions to Glycals: The Synthesis of 2-Deoxy-2-Fldorohexoses', Journal of Carbohydrate Chemistry, 4: 4, 489 — 512
To link to this Article: DOI: 10.1080/07328308508082672
URL: http://dx.doi.org/10.1080/07328308508082672

J. CARBOHYDRATE CHEMISTRY, 4(4), 489-512 (1985)

ON THE STEREOSELECTIVITY OF FLUORINE AND ACETYLHYPOFLUORITE ADDITIONS TO GLYCALS: THE SYNTHESIS OF 2-DEOXY-2-FLUOROHEXOSES

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Received July 11, 1985 - Final Form October 20, 1985

ABSTRACT

Electrophilic syn additions of fluorine and acetylhypofluorite across double bonds in 3,4,6-tri-O-acetyl-D-glucal (1a) and D-glucal (1b) followed by acid hydrolysis gave mixtures of 2-deoxy-2-fluoro-D-glucose (8) and 2-deoxy-2-fluoro-D-mannose (9). These addition reactions were conducted in various solvents with a view to investigating the reaction mechanism based on the product distribution analysis by ^{19}F NMR. Tight ion pair intermediates (4 and 5) have been invoked to explain the stereospecific characteristics of the addition of fluorine or acetylhypofluorite to glycals. The relative stabilities of these intermediates control the product distributions and are governed by a) the anomeric effect (axial vs equatorial preference of C(1) electronegative substituents in pyranose rings), b) dipole-dipole interactions of the lone pairs of electrons on the ring oxygen and the electronegative substituents on C(2), and c) the gauche relationship that exists between the C(2) fluorine and polar groups in the molecule. The overall contribution of these three factors largely depends upon the polarity of the solvent. A rationale for the ^{19}F NMR chemical shifts as well as the anomeric distributions of the α and β anomers of 2-FDG (8) and 2-FDM (9) has been proposed.

 0732-8303/85/0404-0489$3.50/0

INTRODUCTION

In the last decade, enormous efforts have been devoted to the synthesis of 2-deoxy-2-fluoro-D-glucose (2-FDG).[1-22] One of the reasons for this interest is the fact that the fluorine-18 (positron emitter, half-life 109.7 min) labeled analog of 2-FDG remains as the most useful radiopharmaceutical for the noninvasive assessment of regional cerebral and myocardial metabolism in humans by positron emission tomography (PET).[23-28]

Electrophilic additions of fluorine (F_2)[29] and acetylhypofluorite (AcOF)[3,7,12,14,15,17] across the double bond in glycals are the most widely used methods for the synthesis of 2-FDG. The chemical (and radiochemical with F-18 labeling) purity of 2-FDG generally has been ascertained by chromatographic techniques,[6,7,12,15,20,21] but a recent evaluation[3] by ^{19}F NMR of the products from several reported methods for the synthesis of 2-FDG revealed the presence of various amounts of 2-deoxy-2-fluoro-D-mannose (2-FDM) for the first time in the final preparation. Similar studies using chromatographic techniques[30] confirm the ^{19}F NMR results.

The reactions of a few selected glycals with halogens (other than fluorine)[31-34] and interhalogens[35] have been studied from the standpoint of stereochemistry of the additions. However, a similar study of the reactions of F_2 or AcOF has not yet been reported. With the advent of small, relatively inexpensive particle accelerators for the production of biomedically useful short-lived radioisotopes,[36,37] it is anticipated that PET will establish itself as a viable diagnostic tool in clinical nuclear medicine.[38] If F-18 labeled 2-FDG is to continue as the most utilized radiopharmaceutical for PET, a mechanistic understanding of the common synthetic reactions used for its preparation is highly desirable. This is particularly true for the electrophilic additions to glycals. In this work, we offer an explanation for the effect of solvent polarity on the stereochemical course of the electrophilic addi-

tion of F_2 or AcOF to 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (3,4,6-tri-O-acetyl-D-glucal, TAG, 1a) and 1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (D-glucal, 1b).

In the discussion that follows, a generic mechanism is proposed that involves formation of tight ion pair intermediates and the factors that affect the stability of these intermediates. Subsequently, the stereochemical course of the 2-deoxyfluorohexose formation is then discussed.

The second part of the discussion deals with the observed equilibrium percentages of the α and β anomers of 2-FDG and 2-FDM and their ^{19}F NMR chemical shifts.

RESULTS AND DISCUSSION

The synthetic procedures used for this study involve the reaction of dilute F_2 (0.2% in Neon) or AcOF (generated in the gas phase)[3,39] with the glycal 1a or 1b in various solvents. The stereospecificity of these electrophilic additions was determined by ^{19}F NMR after acid hydrolysis of the intermediate products 6 and 7. Electrophilic fluorinations with F_2 and AcOF included reactions with the following glycal/solvent combinations: 1) 3,4,6-tri-O-acetyl-D-glucal (TAG) in freon ($CFCl_3$), acetic acid, acetonitrile and cyclohexane, and 2) D-glucal in water, acetic acid and acetonitrile. Product distributions for the electrophilic fluorination of the glycal/solvent combinations chosen are summarized in Table 1. In all cases, only two major products were observed: 2-FDG and 2-FDM; their ^{19}F NMR chemical shifts were identical to literature values.[40]

I. Proposed Mechanism.

It is now well established that the electrophilic additions of fluorine and hypofluorites across activated carbon-carbon double bonds occur in a syn manner and an ionic [41-47] rather than

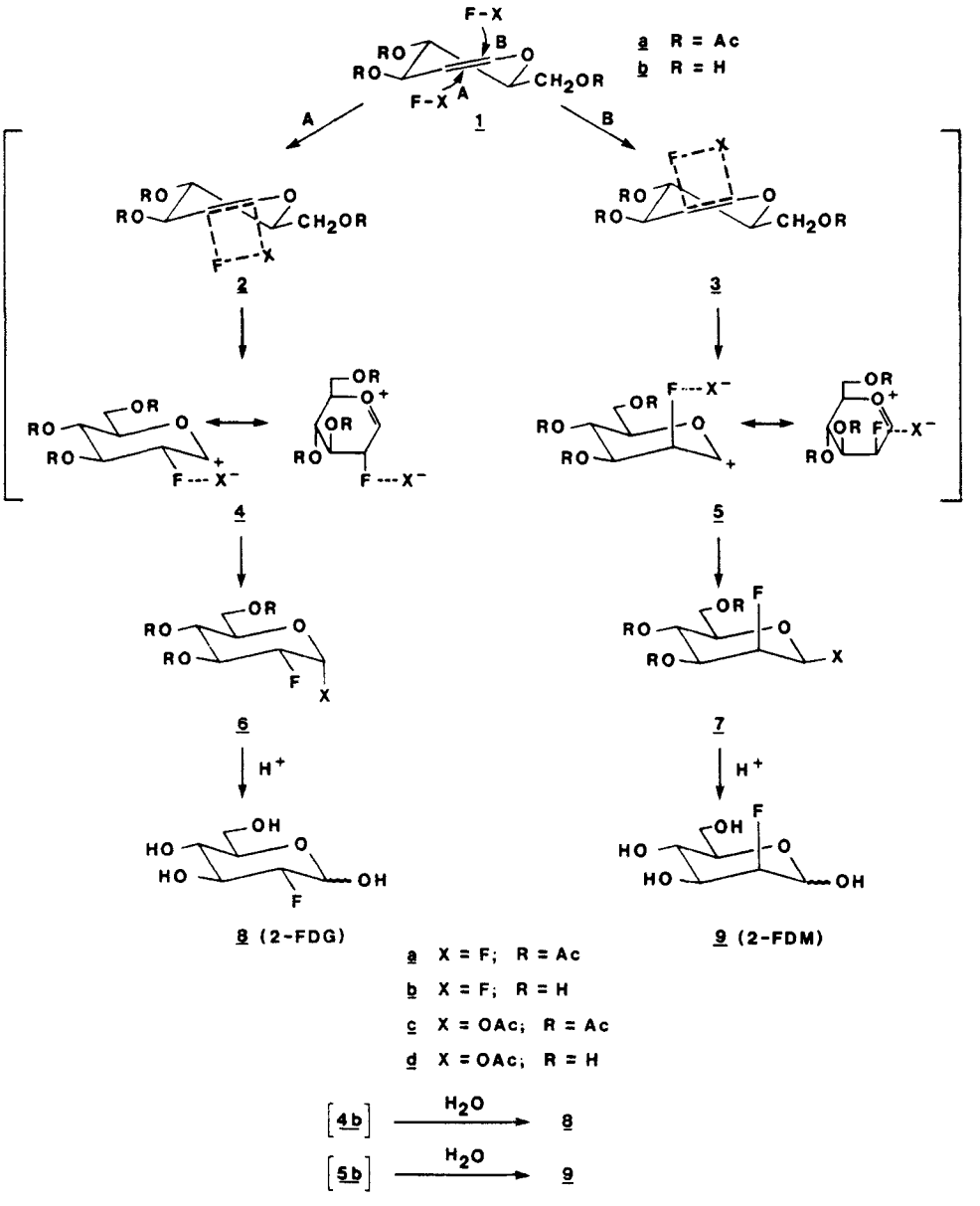
TABLE 1. Effect of Solvent and Substrate on the Product Distribution of Electrophilic Fluorination with Glycals.

Substrate	Solvent	Electrophile	Percentage of 2-FDG	Percentage of 2-FDM
D-glucal	H_2O	F_2	65	35
	H_2O	AcOF	45	55
	HOAc	F_2	62	38
	HOAc	AcOF	23	77
	CH_3CN	F_2	66	34
	CH_3CN	AcOF	29	71
TAG	HOAc	F_2	50	50
	HOAc	AcOF	81	19
	CH_3CN	F_2	51	49
	CH_3CN	AcOF	78	22
	C_6H_{12}	F_2	69	31
	C_6H_{12}	AcOF	93	7
	$CFCl_3$	F_2	73	27
	$CFCl_3$	AcOF	95	5

a radical[48] mechanism has been proposed for these reactions. Based on these observations, a probable reaction mechanism for the addition of F_2 and AcOF to TAG (1a) and D-glucal (1b) to give 2-FDG and 2-FDM is given in Scheme 1.

The double bond in the glycal 1 [49-52] could be syn approached by the fluorinating agent (F_2 or AcOF) in two different directions, path A and path B, to give tight ion pairs 4 and 5 by way of the four-centered transition states 2 and 3, respectively. The carbocations in the tight ion pairs could collapse either to syn addition products 6 and 7 or to their corresponding resonance hybrids, the oxocarbonium ions.[33] The ion pairs 4 and 5 could also be intercepted by neutral nucleophiles, such as water, present in the reaction medium leading to the formation of products. Acid hydrolysis of 6 and 7 would then lead to 2-FDG (8) and 2-FDM (9), respectively.

Interestingly, when F_2 was bubbled into a solution of D-glucal (1b) in water, analysis of the products by ^{19}F NMR indicated the presence of a mixture of the syn difluoro adducts 6b and 7b and 2-fluorohexoses 8 and 9. The 1,2-difluoro adducts presumably result from the rapid collapse of the tight ion pairs 4b and 5b. The possible formation of the 2-deoxyfluorohexoses by the in situ hydrolysis of the difluoro adducts in the reaction medium is eliminated because the difluoro adduct 6b and other related difluoro compounds have been isolated as stable products[53] and the hydrolysis of 6b and 7b to give 8 and 9 requires strong acids.[3,15,20,21] Also, the addition of 'FOH' (possibly formed by the reaction of fluorine with water[54]) to the double bond in D-glucal to give 8 or 9 could be reasonably ruled out on two grounds. First, no fluorohexose could be detected by ^{19}F NMR in the reaction mixture when D-glucal was immediately added after the reaction of fluorine with water (see EXPERIMENTAL), on the contrary to a recent report.[55] Second, it has been shown that HOF could be polarized[56] as $HO^{\delta+}$ $F^{\delta-}$ and, hence, F^- would prefer to attack the relatively less electron rich anomeric carbon of the



SCHEME I

glycal 1,[35] leading to 1-fluorohexoses rather than the 2-fluoro-derivatives. Thus, it is reasonable that the relatively stable carbocations 4b and 5b are intercepted by the nucleophile, i.e. water, to give 8 (2-FDG) and 9 (2-FDM), respectively. These reaction features are consistent with the proposed ionic (vs. radical) mechanism (Scheme 1) and are supported by numerous polar addition reactions of fluorine and other hypofluorites across activated carbon-carbon multiple bonds.[41-47]

Recently, it has been reported that the reaction of AcOF with TAG (1a) in acetic acid followed by acid hydrolysis gives only 2-FDG (8).[7,12,15] This seemingly remarkable degree of stereo-specificity was rationalized by the attack of the AcOF on the less hindered side of the double bond in the glycal.[8,15] Careful analysis of the Drieding model of TAG, however, did not seem to indicate steric crowding around the double bond sufficient to lead to stereospecific reaction. In this regard, the reactions of TAG and D-glucal in various solvents with AcOF were carried out and the results compared with the corresponding reactions with F_2. The data furnished in Table 1 clearly indicate that the stereo-selectivity of AcOF addition reactions depends largely upon the polarity of the solvent. In general, a solvent effect is considered as evidence for dipole-dipole interactions[57,58] and hence, the stereospecificity of AcOF towards the glycals may not only depend on steric factors around the double bond but also electro-static interactions. The relative ease of formation of the ion pairs 4 and 5 in different solvents should thus control the ratio of 2-FDG (8) to 2-FDM (9).

II. Stability of Reaction Intermediates and Product Formation.

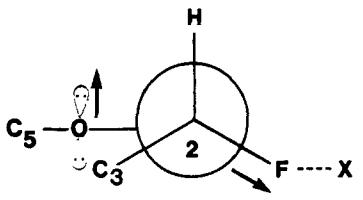
With the final statement above in mind, we now pursue an explanation of the observed results given in Table 1. To help chart the course of the discussion, this section will be further subdivided in order to appropriately focus the concepts presented below.

A. Reaction of AcOF with TAG.

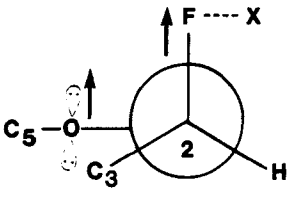
Solvents of low polarity such as freon or cyclohexane lead to predominant formation of 2-FDG in the reaction of AcOF with TAG. In solvents of low polarity, path A would be favored over path B since the intermediate 4c would preferentially collapse to give product 6c, which has an axial C-1 acetoxy group. Based on the anomeric effect,[59-61] it would be expected that 6c would be more stable than 7c and its formation would thus be facilitated.

In terms of system energetics, the anomeric effect corresponds to destabilization of conformations with polar bonds placed between two electron pairs[62,63] and dipole-dipole interactions as well as electrostatic interactions have been invoked as possible sources.[64-66] Thus preferential axial orientation of X in 6 (10) could, at least in part, be explained as due to the favorable gauche disposition of the C(1)-X (X=OAc) bond to one of the oxygen lone pairs of electrons, whereas placing a polar C(1)-X bond between two electron pairs as in 7(11) has a destabilizing effect. These interactions are analogous to those observed in different conformations of fluoromethanol.[62]

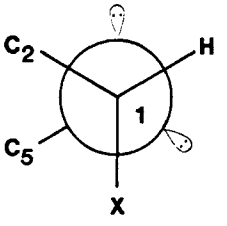
The relative stabilities of the intermediates 4 and 5 due to dipole-dipole interactions could also help in rationalizing the product distribution for the reaction of TAG with AcOF in non-polar solvents. In 4 (12), the group moments due to C(5)-O-C(1) and C(2)-F···X (X=OAc) would be roughly in opposing directions and, hence, the net dipole moment would be smaller than that in 5 (13), where the corresponding moments are aligned in the same direction. Dipole-dipole stabilization of intermediate 5 (13) in non-polar solvents (freon or cyclohexane) is precluded, and the ion pair 4 would then be preferred. The anomeric effect and the dipolar interaction are solvent dependent.[64] An increase in solvent polarity tends to decrease the relative magnitude of the anomeric effect by way of accommodating dipole-dipole interactions, such as the one that exists in 5 (13).[67] The results reported in Table 1 for reactions of AcOF with TAG are in agreement with these explanations. The greater preference for the ion



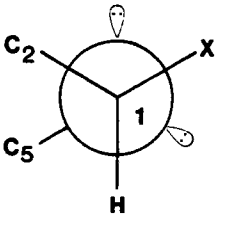
4a-d (12)



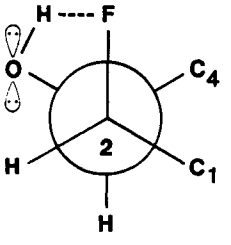
5a-d (13)



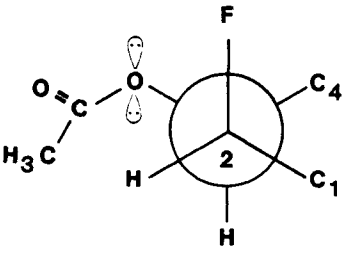
6 (10)



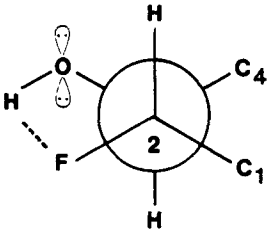
7 (11)



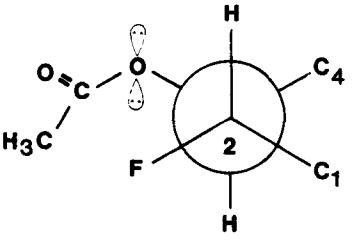
5d (14)



5c (15)



4b, 4d (16)



4a (17)

pair 4 in freon or cyclohexane decreases somewhat as the solvent polarity increases in CH_3CN and HOAc. This is evidenced by the increase in the proportion of 2-FDM (9) from 5% in $CFCl_3$ to 20% in HOAc. These results also parallel the observations and explanations for the reaction of chlorine with TAG in different solvents.[31,32]

B. Reaction of F_2 with TAG.

The reaction of F_2 with TAG in $CFCl_3$ has been shown to give a mixture of the difluoro adducts 6a and 7a in which the former predominates.[29] No explanation has been offered for this observation, however. The data in Table 1 show that fluorine is certainly less stereoselective than acetylhypoflourite with TAG. Drieding models clearly indicate that the double bond in TAG is almost equally accessible to F_2 via paths A and B (Scheme 1) due to the relatively small size of the fluorine molecule. Thus the reaction of F_2 with TAG in CH_3CN or HOAc yields a mixture of 2-FDG and 2-FDM in 1:1 ratios. A more comprehensive account of additional factors affecting the stability of intermediates involved in the reaction of F_2 with TAG in these two solvents is given later in the discussion (Section II.F.). As observed in the reaction of AcOF with TAG, preferential formation of 2-FDG occurred with decreasing solvent polarity. As explained above (II.A.), this is due to the increase in the magnitude of the anomeric effect and the suppressed dipole-dipole interaction in freon and cyclohexane, which favor the ion pair 4 over 5, and lead to formation of 2-FDG in higher proportion.

C. Preferential Formation of 2-FDM in Reactions of AcOF with D-Glucal.

The reaction of D-glucal (1b) in water with AcOF followed by acid hydrolysis has been reported to yield 2-FDG (8) exclusively.[6] However, a re-examination of this reaction and product identification by ^{19}F NMR spectroscopy conclusively proved that

the reaction is hardly stereospecific.[3] It would be expected, based on the above rationalizations, that in polar solvents the reaction of AcOF with D-glucal would not display the marked stereoselectivity reported towards the formation of 2-FDG.[6] In fact, the reaction of AcOF with D-glucal in CH_3CN and HOAc gave a remarkable reversal of product stereochemistry found in the corresponding reactions with TAG. Again, this preference can be attributed to the relative stabilities of the ion pairs 5d and 4d in the polar solvents.

In polar solvents, oxygen in the pyranose ring would experience a more favorable gauche interaction with the axial fluorine in the ion pair 5d (13) than with the equatorial fluorine in 4d (12), in which the oxygen is anti to it. A nuclear-electron attraction between the fluorine nucleus and the lone pairs of electrons on oxygen predominating over other electronic effects, termed the gauche effect,[63,68-73] is responsible for this phenomenon. As expected, this effect also depends on the polarity of the solvent and the electronegativity of the interacting groups.[71-75] This effect is responsible for the gauche conformations of the products in the reaction of hypofluorites with stilbenes and is reported to operate in the transition states leading to the products.[46] Similar stabilizing gauche interactions are possible in both 4d (16) and 5d (14) for the C-2 fluorine with the hydroxyl oxygen on C-3 of D-glucal. However, polar solvents would tend to favor the ion pair 5d over 4d due to the greater tolerance of the dipole-dipole interactions as already explained.

D. Product Distributions for Reactions of AcOF with Glycals in Polar Solvents.

When comparing the reactions of AcOF with D-glucal and TAG in polar solvents (Table 1), a complete reversal in epimer formation is observed with nearly the same ratio in each case (D-glucal vs TAG). These vast differences could be explained by the relative

stabilities of the ion pairs 5d (14) and 5c (15). The magnitude of the gauche effect due to the interaction of the axial fluorine in 5d (14) with the hydroxyl oxygen on C-3 would be expected to be larger than the corresponding effect in 5c (15) due to the partial destabilizing inductive effect on the lone pairs of electrons on the acyloxy oxygen by the acetyl group, thereby decreasing the gauche interaction with the fluorine atom. Moreover, stabilization of 5d (14) is also possible via intramolecular hydrogen bonding of the C-3 hydroxyl with C-2 fluorine in CH_3CN, although this is not certain in HOAc. In H_2O, intermolecular hydrogen bonding of the hydroxyl groups in D-glucal with the solvent will dominate, eliminating the intramolecular hydrogen bonding and also decreasing the gauche effect. Hence, in the case of the reaction of AcOF with D-glucal, the preference for the formation of 2-FDG should be comparatively decreased in going from water to acetonitrile. These rationalizations derive support from the analogous situation that exists in 2-fluoroethanol and its corresponding acetate wherein the gauche form of the former has been shown, both by spectroscopic techniques and force field calculations, to be more stabilized than the gauche form in the latter, for reasons similar to those outlined above.[76]

E. Preferential Formation of 2-FDG in the Reaction of F_2 (vs AcOF) with D-Glucal.

It is interesting to compare the results of the reactions of F_2 with those of AcOF when D-glucal is used as substrate. Reactions of F_2 with D-glucal gave a higher ratio of 2-FDG to 2-FDM. The relative stabilities of the ion pairs 4b and 4d, based on the anomeric effects due to fluorine and acetoxy groups, would explain this observation. The strongest anomeric effect in carbohydrates would be expected from the polar interactions of oxygen and an anomeric fluorine, the most electronegative substituent.[77] The quantitation of the anomeric effects due to fluorine

in these derivatives in various solvents has not been made. However, in general, the anomeric effect due to the halogens (2.7-3.2 kcal mol^{-1})[78] is greater than that due to an acetoxy group (0.9-1.4 kcal mol^{-1}).[61] Hence, it is reasonable to expect the ion pair 4b to be more stable than 4d, thus explaining the greater percentage of 2-FDG in the case of the reaction of F_2 with D-glucal.

F. Comparison of Reactions of F_2 with Glycals in Polar Solvents.

It is a priori surprising that F_2 could display higher stereoselectivity towards D-glucal in CH_3CN or HOAc than towards TAG in the same solvents. The intermediate 4a, originating from TAG, is stabilized by the anomeric effect and the gauche interaction of C-3 acetoxy group with the C-2 fluorine, 4a (17), whereas the dipolar effect would tend to favor stabilization of the ion pair 5a in polar solvents. The 1:1 ratio of 2-FDG:2-FDM in the case of the reaction of F_2 with TAG in CH_3CN and HOAc indicates that probably the two opposing effects mentioned above tend to cancel each other. However, in the case of the reaction of D-glucal with F_2, formation of the ion pair 4b (16) is energetically favored over 4a (17) due to a stronger gauche interaction[74,75] between the fluorine and C-3 hydroxyl oxygen. It is gratifying to see that this is also consistent with the experimental observations, which show a higher tendency for formation of 2-FDG in the reaction of F_2 with D-glucal than with TAG in polar solvents.

III. Anomeric Distributions and their ^{19}F NMR Chemical Shifts for 2-FDG and 2-FDM.

From the ^{19}F NMR data for the 2-deoxyfluorohexoses, an interesting pattern for the α and β anomers of these hexopyranoses emerged. In Table 2, the equilibrium percentages of the α and β anomers of 2-FDG and 2-FDM in D_2O at 25°C are listed along with

TABLE 2. Percentage Composition of Anomers

Compound	α	β
2-FDG[a]	45.7	54.3
2-FDM[a]	66.0	34.0
D-Glucose[b]	36.0	64.0
D-Mannose[b]	69.0	31.0
2-deoxy-D-arabino-hexopyranose[b]	47.5	52.5

a. Present study.

b. Ref. 80,81.

the corresponding values for D-glucose, D-mannose and 2-deoxy-D-arabino-hexopyranose (which has no C-2 hydroxyl group). It is seen that the introduction of an axial fluorine at C-2 in 2-deoxy-D-arabino-hexopyranose increases the population of the α anomer from 47.5% to 66%, whereas an equatorial fluorine decreases it to 45.7%. Similar trends are observed for the introduction of hydroxyl groups as in the cases of D-mannose and D-glucose (Table 2).[79-81] The similarities between the C-F and C-OH bond lengths and polarization could probably be responsible for this observation.[82]

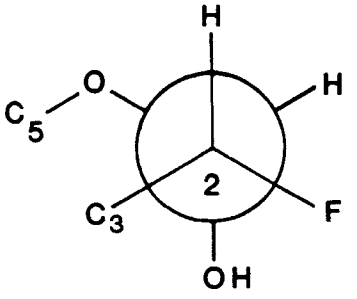
The ^{19}F NMR chemical shifts for the α and β anomers of 2-FDG and 2-FDM are reported in Table 3. The small difference (0.13 ppm) in the chemical shifts between the α (18) and β (19) anomers of 2-FDG has been explained as due to the similar gauche relationship that exists between the C-2 fluorine and C-1 hydroxyl group in both the anomers.[40] A gauche relationship also exists between the C-2 fluorine and the ring oxygen in the α anomer of 2-FDM (20). However, the C-2 fluorine atoms in 18 and 19 are deshielded by about 5 ppm in comparison to the fluorine in 20. We feel it is more likely that the deshielding arises due to the W-coplanar arrangement of the C-2 equatorial fluorine and C-4 equatorial

TABLE 3. Chemical Shift Data

Compound	Anomer	Chemical Shift δ ppm	$\delta_\beta - \delta_\alpha$ ppm
2-FDG	α	+32.73	
	β	+32.60	- 0.13
2-FDM	α	+38.08	
	β	+56.51	+18.43

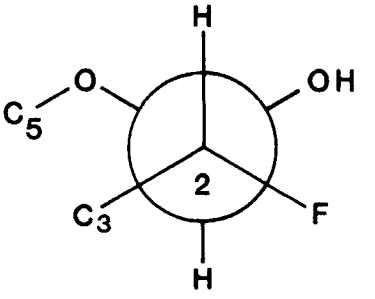
hydroxyl group in 18 and 19. The axial fluorine in 2-FDM cannot have such a deshielding interaction with any hydroxyl group in the molecule. An analogous W planar effect has been shown to be responsible for the ~ 5 ppm deshielding of the C-3 fluorine in the β anomer of 3-fluoro-3-deoxy-D-glucose in comparison to its counterpart in the α anomer.[40]

A large chemical shift difference (18 ppm) exists between the anomers of 2-FDM, unlike the case of 2-FDG. It has been reasoned that the relative deshielding observed in the α anomer of 2-FDM (20) is due to the vicinal trans diaxial arrangement of the fluorine and the hydroxyl group.[40] However, it is more likely that the fluorine in the β anomer (21), which has two gauche interactions, one with the pyranose ring oxygen and the other with the equatorial anomeric hydroxyl oxygen, is more shielded than its counterpart in the α anomer, having one gauche interaction. Further, it is not surprising that the gauche effect[63] causes more shielding of fluorine since it stems from the nuclear-electron attraction between the fluorine nucleus and lone pair of electrons on oxygen leading to more shielding of the fluorine nucleus.



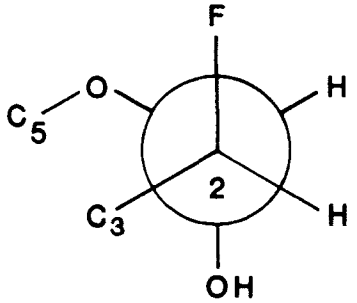
18

2-FDG α-anomer



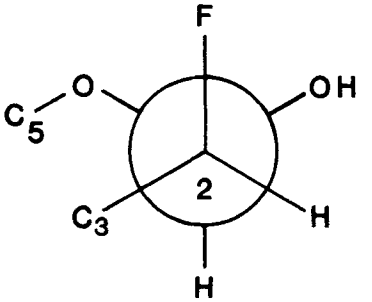
19

2-FDG β-anomer



20

2-FDM α-anomer



21

2-FDM β-anomer

CONCLUSION

In conclusion, and from the data, the following observations can be made: i) With the exception of the reaction between F_2 and TAG in either HOAc or CH_3CN, all reactions display some degree of stereospecificity. ii) With the exception of the reaction between F_2 and D-glucal, for a given electrophile/glycal combination, preferential formation of one epimer versus the other increases with

decreasing solvent polarity; 2-FDG being favored in the case of reaction of TAG with AcOF. The most striking observation is the substrate effect for reaction of AcOF in the polar solvents HOAc and CH_3CN. In the case of D-glucal, 2-FDM formation is favored by nearly a factor of 4; whereas 2-FDG is favored for reaction with TAG by nearly the same ratio.

These rationalizations represent a first attempt at a mechanistic understanding of the formation of these deoxyfluorosugars from electrophilic additions on glycals, considerations which have heretofore been ignored. The utility of these proposed ideas extends beyond its academic value. Since fluorine-18 labeled 2-FDG will predictably continue as the most used radiopharmaceutical for PET, it is reasonable to expect further efforts in the direction of its routine synthesis. The present study may, therefore, serve as a template to model these future efforts due, in part, to the instrinsic predictive value inferred from the reactions in this work.

EXPERIMENTAL

General Procedures. Inverse gated proton decoupled (no NOE) ^{19}F NMR spectra were recorded on a Bruker WM-500 spectrometer operating at 470.56 MHz (for fluorine-19 nucleus) equipped with an Aspect 2000 computer by the computer controlled gating of the proton radiofrequency. The typical 90° pulse widths were 12-15 μs with repetition times of 2-10s for a 5-mm insert. The spectra were recorded in the Fourier transform mode with a spectral width of at least 30 kHz and, from the integrated peak areas, the relative ratios of 2-FDG and 2-FDM were calculated. Deuterium oxide was used as the solvent for all the samples and the deuterium in the solvent was utilized for field-frequency stabilization. A coaxial capillary containing hexafluorobenzene was used as an external reference and positive signs were assigned for the chemical shifts upfield of the standard as used by Phillips and Wray

for the fluorohexoses.[40] All spectra were recorded at 25°C after anomeric equilibrium was established.

D-Glucal was prepared as reported by Fraser-Reid et al,[83] recrystallized from ethyl acetate and stored at 0°C. 3,4,6-Tri-O-acetyl-D-glucal (Aldrich) was recrystallized from ethyl acetate/hexane. Acetonitrile, acetic acid, cyclohexane, sodium acetate trihydrate (Aldrich, Gold label) and water (Burdick & Jackson, HPLC grade) were used as received. Freon 11 (Matheson) was distilled from P_2O_5. One percent fluorine in neon (Matheson) was diluted to 0.2% with research grade neon.

Reaction of AcOF with TAG (1a) and D-glucal (1b). Acetylhypofluorite in the gas phase was prepared by passing 0.2% F_2 (200 μmol) in Ne through a cartridge of $NaOAc.3H_2O$ or a KOAc:HOAc mixture as described in the literature.[3,39] The effluent from the cartridge was bubbled (flow rate ~150 mL/min) into a solution of 1a or 1b (200-270 μmol) in the appropriate solvent (15 mL) at room temperature. The solvent was evaporated in a rotary evaporator and the residue was hydrolyzed with HCl (1.0 N, 1 mL) at 120°C for 20 min. The reaction mixture was cooled to room temperature and transferred to a column, packed successively with 0.7 cm i.d. x 5.5 cm of ion-retardation resin AG 11A8 (Bio-Rad, 50-100 mesh), neutral alumina and AG 11A8 resin, that had been pre-equilibrated with deionized water.[20] The column was eluted with deionized water (10 mL) and the eluent passed through two C-18 Sep-pak cartridges (Waters Associates) in tandem that had been previously washed with MeOH (3 mL) followed by water (10 mL). The eluent was evaporated in a rotary evaporator at room temperature to give crystalline mixtures of 2-FDG (8) and 2-FDM (9) in 70-80% yield. The product was dissolved in D_2O for NMR analysis and the chemical shift data are provided in Table 3.

Reaction of F_2 with TAG (1a) and D-glucal (1b). Fluorine (200 μmol, 0.2% in Ne) was bubbled into a solution of 1a or 1b in appropriate solvents at room temperature and the reaction was continued as described above.

Reaction of F_2 with D-glucal in water. Into a solution of D-glucal (200 μmol) in water (2 mL), F_2 (200 μmol) diluted with Ne (0.2%) was bubbled. The solvent was evaporated at room temperature in a rotary evaporator and ^{19}F NMR analysis of the residue indicated the presence of a mixture of 2-FDG (8), 2-FDM (9) (Table 3) the difluoro adducts 6b [$\delta_{F(1)}$= -16·15ppm; $\delta_{F(2)}$= +37·11ppm; $J_{F(1)F(2)}$= -20·4Hz] and 7b [$\delta_{F(1)}$= -16·52ppm; $\delta_{F(2)}$= +56·62ppm; $J_{F(1)F(2)}$= -17·7Hz].

Reaction of F_2 with water followed by the addition of D-glucal. Fluorine (200 μmol, 0.2% in Ne) was bubbled (flow rate ~150 mL/min) into deionized water (4 mL) at room temperature. A solution of 1b (200 μmol) in water (1 mL) was immediately added to it. The solvent was evaporated after 15 min and the residue hydrolyzed with 1N HCl (1.0 mL) at 120°C for 20 min. The reaction mixture was neutralized by passing through an ion-retardation resin/alumina column as described above and the column was eluted with water (10 mL). Analysis of the residue by ^{19}F NMR after solvent evaporation did not indicate the presence of any fluorohexoses.

ACKNOWLEDGMENTS

We thank the Southern California Regional NMR Facility at the California Institute of Technology, supported by NSF Grant CHE 79-16324 and Dr. P. Card (E.I. Dupont, Delaware), for their help in obtaining the ^{19}F NMR spectra. We are indebted to Dr. N. MacDonald and the staff of the UCLA Biomedical Cyclotron for their assistance. This work was supported by U.S. Department of Energy Contract No. DE-AC03-76-SF00012, NINCDS Grants No. PO1-NS 15654 and 9 RO1 NS20867-08 and NIMH Grant No. 1 RO1 MH 37916.

REFERENCES AND FOOTNOTES

1. T. Haradahira, M. Maeda, Y. Kai and M. Kojima, J. Chem. Soc., Chem. Commun., 364 (1985).

2. T. Haradahira, M. Maeda, Y. Kai, H. Omae and M. Kojima, Chem. Pharm. Bull., 33, 165 (1985).

3. G. T. Bida, N. Satyamurthy and J. R. Barrio, J. Nucl. Med., 25, 1327 (1984).

4. G. T. Bida, N. Satyamurthy, H. C. Padgett and J. R. Barrio, J. Label. Comp. Radiopharm., 21, 1196 (1984).

5. P. A. Beeley, W. A. Szarek, G. W. Hay and M. M. Perlmutter, Can. J. Chem., 62, 2709 (1984).

6. R. E. Ehrenkaufer, J. F. Potocki and D. M. Jewett, J. Nucl. Med., 25, 333 (1984).

7. M. J. Adam, T. J. Ruth, S. Jivan and B. D. Pate, Int. J. Appl. Radiat. Isot., 35, 985 (1984).

8. M. J. Adam, B. D. Pate, J.-R. Nesser and L. D. Hall, Carbohydr. Res., 124, 215 (1983).

9. T. Tewson, J. Org. Chem., 48, 3507 (1983).

10. C.-Y. Shiue, K.-C. To and A. P. Wolf, J. Label Comp. Radiopharm., 20, 157 (1983).

11. S. Sood, G. Firnau and E. S. Garnett, Int. J. Appl. Radiat. Isot., 34, 743 (1983).

12. M. Diksic and D. Jolly, Int. J. Appl. Radiat. Isot., 34, 893 (1983).

13. T. Tewson, J. Nucl. Med., 24, 718 (1983).

14. H. C. Padgett, J. S. Cook and J. R. Barrio, J. Nucl. Med., 24, P121 (1983).

15. C.-Y. Shiue, P. A. Salvadori, A. P. Wolf, J. S. Fowler and R. R. MacGregor, J. Nucl. Med., 23, 899 (1982).

16. S. Levy, D. R. Elmaleh and E. Livni, J. Nucl. Med., 23, 918 (1982).

17. M. J. Adam, J. Chem. Soc., Chem. Commun., 730 (1982).

18. W. A. Szarek, G. W. Hay and M. M. Perlmutter, J. Chem. Soc., Chem. Commun., 1253 (1982).

19. S. Levy, E. Livni, D. Elmaleh and W. Curatolo, J. Chem. Soc., Chem. Commun., 972 (1982).

20. J. R. Barrio, N. S. MacDonald, G. D. Robinson, Jr., A. Najafi, J. S. Cook and D. E. Kuhl, J. Nucl. Med., 22, 372 (1981).

21. J. S. Fowler, R. R. MacGregor, A. P. Wolf, A. A. Farrell, K. I. Karlstrom and T. J. Ruth, J. Nucl. Med., 22, 376 (1981).

22. W. Korytnyk and S. Valentekovic-Horvat, Tetrahedron Lett., 1493 (1980).

23. M. E. Phelps, Semin. Nucl. Med., 11, 32; A.P. Wolf. ibid., 2 (1981).

24. M. Reivich, D. Kuhl, A. P. Wolf, J. Greenberg, M. E. Phelps, T. Ido, V. Casella, J. S. Fowler, E. Hoffman, A. Alavi, P. Som and L. Sokoloff, Circ. Res., 44, 127 (1979).

25. M. E. Phelps, S.-C. Huang, E. J. Hoffman, C. Selin, L. Sokoloff and D. E. Kuhl, Ann. Neurol., 6, 371 (1979).

26. M. E. Phelps, H. R. Schelbert and J. C. Mazziotta, Annals Int. Med., 98, 339 (1983).

27. H. R. Schelbert, L. Benson, M. Schwaiger and J. Perloff, Cardiol. Clinics, 1, 501 (1983).

28. M. E. Phelps, D. E. Kuhl and J. C. Mazziotta, Science, 211, 1445 (1981).

29. T. Ido, C.-N. Wan, J. S. Fowler and A. P. Wolf, J. Org. Chem., 42, 2341 (1977); T. Ido, C.-N. Wan, V. Cassella, J. S. Fowler, A. P. Wolf, M. Reivich and D. E. Kuhl, J. Label Comp. Radiopharm., 14, 175 (1978).

30. C. J. S. Van Rijn, J. D. M. Herscheid, G. W. M. Visser and A. Hoekstra, Int. J. Appl. Radiat. Isot. 36, 111 (1985); C. - Y. Shiue, J. S. Fowler, A. P. Wolf, D. Alexoff and R. R. MacGregor, J. Label Comp. Radiopharm., 22, 503 (1985).

31. P. Boullanger and G. Descotes, Carbohydr. Res., 51, 55 (1976).

32. K. Igarashi, T. Honma and T. Imagawa, J. Org. Chem., 35, 610 (1970).

33. R. U. Lemieux and B. Fraser-Reid, Can. J. Chem., 43, 1460 (1965).

34. R. U. Lemieux and B. Fraser-Reid, Can. J. Chem., 42, 532 (1964).

35. L. D. Hall and J. F. Manville, Can. J. Chem., 47, 361 (1969).

36. J. R. Barrio, G. Bida, N. Satyamurthy, H. C. Padgett, N. S. MacDonald and M. E. Phelps in; "The Metabolism of the Human Brain Studied with Positron Emission Tomography"; T. Greitz, D. H. Ingvar and L. Widen, Eds.; Raven Press, New York, 1985, p. 113.

37. A. P. Wolf and W. B. Jones, Radiochim. Acta, 34, 1 (1983).

38. M. E. Phelps and J. C. Mazziotta, Science, 228, 799 (1985).

39. D. M. Jewett, J. F. Potocki and R. E. Ehrenkaufer, Synth. Comm., 14, 45 (1984).

40. L. Phillips and V. Wray, J. Chem. Soc. (B), 1618 (1971).

41. R. F. Merritt, J. Org. Chem., 31, 3871 (1966).

42. R. F. Merritt, J. Org. Chem., 32, 4124 (1967).

43. R. F. Merritt, J. Am. Chem. Soc., 89, 609 (1967).

44. D. H. R. Barton, Pure and Appl. Chem., 49, 1241 (1977).

45. R. H. Hesse, Isr. J. Chem., 17, 60 (1978) and ref. cited therein.

46. S. Rozen and O. Lerman, J. Org. Chem., 45, 672 (1980); S. Rozen, O. Lerman and M. Kol, J. Chem. Soc., Chem. Commun., 443 (1981).

47. S. Rozen and R. Filler, Tetrahedron, 41, 1111 (1985).

48. K. K. Johri and D. D. Desmarteau, J. Org. Chem., 48, 242 (1983).

49. L. D. Hall and L. F. Johnson, Tetrahedron, 20, 883 (1964).

50. A. A. Chalmers and R. H. Hall, J. Chem. Soc., Perkin Trans., 2, 728 (1974).

51. M. Rico and J. S. Antoro, Org. Mag. Res., 8, 49 (1976).

52. K. Vangehr, P. Luger and H. Paulsen, Carbohydr. Res., 70, 1 (1979).

53. W. Korytnyk, S. Valentekovic-Horvath and C. R. Petrie III, Tetrahedron, 38, 2547 (1982).

54. E. H. Appelman and R. C. Thompson, J. Am. Chem. Soc., 106, 4167 (1984).

55. M. Diksic and D. Jolly, J. Carbohydr. Chem., 4, 265 (1985).

56. M. H. Studier and E. H. Appelman, J. Am. Chem. Soc., 93, 2349 (1971); E. H. Appelman, R. C. Thompson and A. G. Engelkemeir, Inorg. Chem., 18, 909 (1979).

57. C. B. Anderson and D. T. Sepp, J. Org. Chem., 32, 607 (1967).

58. C. B. Anderson and M. P. Geis, Tetrahedron, 31, 1149 (1975).

59. "Anomeric Effect. Origin and Consequences"; W. A. Szarek and D. Horton, Eds.; ACS Symposium Series 87, Washington, D.C., 1979.

60. R. U. Lemieux in; "Molecular Rearrangements"; Paul de Mayo, Ed.; Interscience, New York, 1964, p. 709.

61. K. S. Vijayalakshmi and V. S. R. Rao, Carbohydr. Res., 29, 427 (1973).

62. S. Wolfe, A. Rauk, L. M. Tel and I. G. Csizmadia, J. Chem. Soc. (B), 136 (1971).

63. S. Wolfe, Acc. Chem. Res., 5, 102 (1972).

64. E. L. Eliel, Angew. Chem. Int. Ed. Engl. 11, 739 (1972).

65. S. David, O. Eisenstein, W. J. Hehre, L. Salem and R. Hoffman, J. Am. Chem. Soc., 95, 3806 (1973).

66. O. Eisenstein, N. T. Anh, Y. Jean, A. Devaquet, J. Cantacuzene and L. Salem, Tetrahedron, 30, 1717 (1974).

67. R. J. Abraham and E. Bretschneider in; "Internal Rotation in Molecules"; W. J. Orville-Thomas and M. Redshaw, Eds.; John Wiley & Sons, New York, 1974, p. 481.

68. L. Radom, W. L. Lathan, W. J. Hehre and J. A. Pople, J. Am. Chem. Soc., 95, 693 (1973).

69. L. Phillips and V. Wray, J. Chem. Soc., Chem. Commun., 90 (1973).

70. N. S. Zefirov, Tetrahedron, 33, 3193 (1977).

71. N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov and S. Wolfe, Tetrahedron, 34, 2953 (1978).

72. R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer and M. K. Kaloustian, J. Am. Chem. Soc., 94, 1913 (1972).

73. M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia and E. L. Eliel, J. Am. Chem. Soc., 98, 956 (1976).

74. A. Laforgue and T. Theophanides, J. Mol. Struct., 22, 125 (1974).

75. K. G. R. Pachler and P. L. Wessels, J. Mol. Struct., 6, 471 (1970).

76. N. L. Allinger, D. Hindman and H. Honig, J. Am. Chem. Soc., 99, 3282 (1977) and ref. cited therein.

77. G. A. Jeffrey and J. H. Yates, J. Am. Chem. Soc., 101, 820 (1979).

78. C. Romers, C. Altona, H. R. Buys and E. Havinga in; "Topics in Stereochemistry"; Vol. 4; E. L. Eliel and N. L. Allinger, Eds.; Wiley-Interscience, New York, 1969, p. 39.

79. M. Rudrum and D. F. Shaw, J. Chem. Soc., 52 (1965).

80. S. J. Angyal, Aust. J. Chem., 21, 2737 (1968).

81. S. J. Angyal, Angew. Chem. Int. Ed. Engl., 8, 157 (1969).

82. A. A. E. Penglis, Adv. Carbohydr. Chem. Biochem., 38, 195 (1981).

83. B. Fraser-Reid, D. L. Walker, S. Y.-K. Tam and N. L. Holder, Can. J. Chem., 51, 3950 (1973).