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FACTORS AFFECTING THE PURITY OF 2-DEOXY-2-FLUORO-D-GLUCOSE SYNTHESIZED FROM THE REACTIONS OF GLYCALS WITH ACETYL HYPOFLUORITE

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SUMMARY

The reactions of gaseous acetyl hypofluorite with glycals (1a-d) followed by hydrolysis with 2 N HCl give 2-deoxy-2-fluoro-D-glucose (2) and 2-deoxy-2-fluoro-D-mannose (3). The ratio of 2 to 3 depends largely on the polarity of the solvent rather than on the size of the substituents on the hydroxyl groups of glucal. The amount of 3 in the final product from the reaction of 1b-d with acetyl hypofluorite ranges from 4% in non-polar solvents (Freon-11, CCl_4, hexane) to ~ 20% in polar solvents (HOAc, MeOH, DMF, acetone).

INTRODUCTION

The 2-deoxy-2-[^{18}F]fluoro-D-glucose (2-^{18}FDG) method, first described in 1976, has generated widespread interest in the application of this technique for the measurement of regional cerebral glucose metabolism under different pathological states in humans using positron emission tomography (PET) [1-3]. The 2-^{18}FDG used for PET studies is synthesized using a number of methods including electrophilic fluorination of 3,4,6-tri-O-acetyl-D-glucal (TAG, 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol) or glucal

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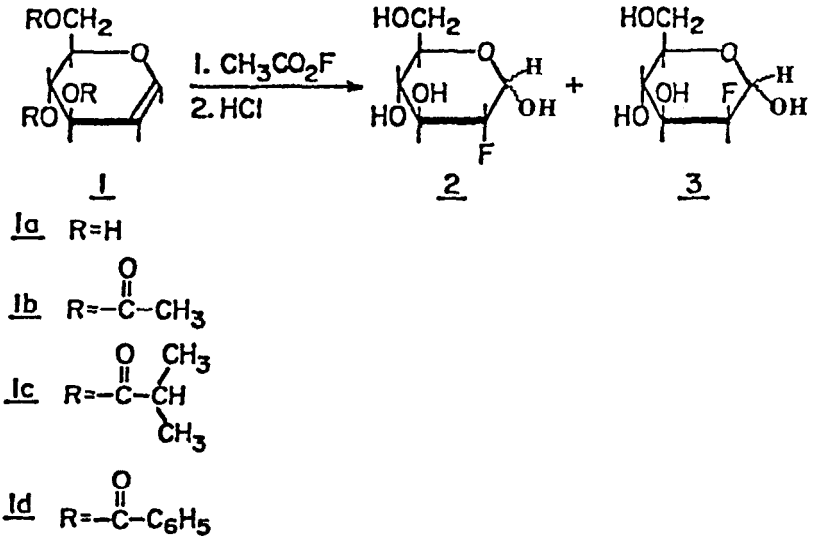
(1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol) with either molecular fluorine [4-6], xenon difluoride [7-9] or acetyl hypofluorite [10-15]. Although in each of these methods isomerically pure 2-^{18}FDG, i.e. free of 2-deoxy-2-fluoro-D-mannose (2-FDM) was claimed, it was recently discovered that varying amounts of 2-FDM were produced along with 2-FDG [6,16,17].

One reason for this oversight in the past was that there were no simple methods for the determination and separation of 2-FDG from 2-FDM. In the course of our studies on the determination of relative amounts of 2-FDG and 2-FDM produced using various synthetic methods, we have found that the reaction of acetyl hypofluorite with glucal gave more 2-FDM than with TAG (56% vs 16%), and that the reaction of acetyl hypofluorite with TAG in acetic acid gave more 2-FDM than in Freon-11 (16% vs 4%) [18]. These results suggested that the reactions of acetyl hypofluorite with glycals might depend both on the structures of the glycals and the reaction medium. We report here the steric effects and the solvent effects on the stereoselectivity of the reactions of glycals (1a-d) with acetyl hypofluorite (Scheme 1). A preliminary report of this study has appeared [19].



1

1a R=H

1b R=–C(=O)–CH3

1c R=–C(=O)–CH(CH3)–CH3

1d R=–C(=O)–C6H5

Scheme 1

EXPERIMENTAL

General Methods

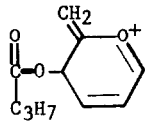
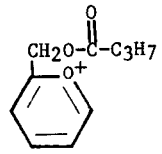
3,4,6-Tri-O-acetyl-D-glucal (TAG), benzoyl chloride, isobutyric anhydride and glucal were purchased from Aldrich Chemical Co. and Mara Specialty Chemicals respectively, and were used without further purification. Authentic 2-FDG was obtained from Calbiochem-Behring. 3,4,6-Tri-O-isobutyryl-D-glucal (1c) and 3,4,6-tri-O-benzoyl-D-glucal (1d) were synthesized by acylation of glucal with acyl anhydride and acyl chloride and characterized by IR, NMR and MS [20]. NMR spectra were taken using a JEOL MH-100 spectrometer on solutions in chloroform-d, with Me_4Si as an internal standard. IR spectra were recorded with a Perkin-Elmer Model 337 spectrometer. The mass spectra were measured with a Finnigan MAT 5100 GC/MS/DS spectrometer. Gas-liquid chromatographic analyses (GLC) were carried out with a Perkin-Elmer Sigma 300 gas chromatograph equipped with a thermal conductivity detector. A Hewlett-Packard 3390A integrator was used to integrate the peak areas. A column (6 ft x 1/8 in) containing 4% SE-30 + 6% OV-210 on chromosorb W-HP 80/100 mesh from Anspec Co., Inc., Ann Arbor, Michigan was employed, isothermal at 150°C and a flow of 15 ml/min. The 2-FDG and 2-FDM were silylated by the known method [21]. The retention times of the silylated derivatives of 2-FDG were 20 min (α) and 28 min (β), while the retention times of 2-FDM derivatives were 23 min (α) and 36 min (β) [18].

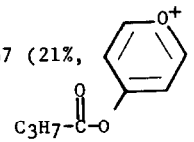
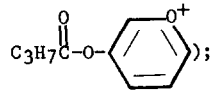
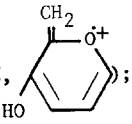
3,4,6-Tri-O-Isobutyryl-D-Glucal (TIG, 1c)

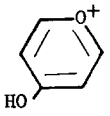
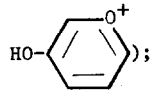
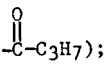
Isobutyric anhydride (2.86g, 18.1 mmol) was added to the solution of glucal (396.4 mg, 2.7 mmol) in 5 ml of pyridine at ice-bath temperature. The solution was stirred at room temperature overnight and then water was added. The water was decanted and the oil was washed with water again. The process was repeated several times and the oily residue was dissolved in ether, dried (Na_2SO_4) and the solvent was removed by evaporation to give 725 mg (16% yield) of oily compound 1c. The yield of compound 1c was not optimized.

IR: $\nu\,cm^{-1}_{max}$ 1725 (C=O); 1645 (C=C).
NMR δ_{CDCl_3} 1.1-1.2 (dd, J=3Hz, CH_3, 18H); 2.55 (m,CH, 3H); 4.3 (m,H-5, H-6, H-6', 3H), 4.8 (m, H-2, 1H); 5.3 (m, H-3, H-4, 2H); 6.45 (d,J=6 Hz, H-1, 1H).

MS: m/e (relative intensity) =

180 (12%,  or );

167 (21%,  or ); 110 (49%, );

97 (79%,  or ); 71 (57%, );

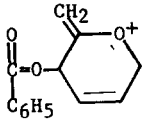
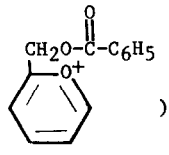
43 (100%, C_3H_7).

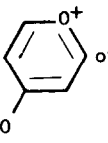
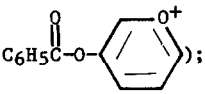
3,4,6-Tri-O-Benzoyl-D-Glucal (TBG, 1d)

Compound 1d was synthesized by the method of Lundt et al. [22] from D-glucal and benzoyl chloride in pyridine.

IR: $\nu^{cm^{-1}}_{max}$ 1710 (C=O); 1640 (C=C); 1600 (aromatic).
NMR: δ_{CDCl_3} 4.55 (m, H-5, H-6, H-6', 3H); 5.02 (m, H-2, 1H); 5.75 (m, H-3, H-4, 2H); 6.55 (d,J=6 Hz H-1, 1H); 7.75 (aromatic, 15H).

MS: m/e (relative intensity) =

214 (17%,  or );

201 (13%,  or ); 105 (100%, );

77 (34%, C_6H_5).

Fluorinations of Glycals (1a-d) with Acetyl Hypofluorite

Gaseous acetyl hypofluorite, generated by the method of Jewett et al. [17], was purged into a solution of glycal in an appropriate solvent at room temperature for ~ 10 minutes. The solvent was evaporated, the residue was suspended (or dissolved) in 3 ml of 2 N HCl and hydrolyzed at 135°C for 20 minutes. The solution was evaporated and the residue was dissolved in H_2O. An aliquot of the solution was evaporated, silylated and analyzed by GLC to determine the 2-FDG:2-FDM ratio and the α- and β-forms ratio, and the results are shown in Table 1. The ratio of the α- and β-forms of the silylated derivatives of 2-FDG was 0.9, while the ratio of 2-FDM derivatives was 2.6.

The ^{18}F-labeled compounds were synthesized by a similar method except using ^{18}F-labeled acetyl hypofluorite as the fluorinating reagent. The radiochemical yields of 2-^{18}FDG and 2-^{18}FDM were ~ 20% after silica gel column purification [10].

RESULTS AND DISCUSSION

Reactions of gaseous acetyl hypofluorite with glucal (1a) or substituted glucals (1b-d) followed by hydrolysis with 2 N HCl give 2-FDG (2) along with varying amounts of 2-FDM (3) (Table 1 and Scheme 1). The amounts of 2-FDM present in 2-FDG depend largely on the solvent polarity. In non-polar solvents (Freon-11, CCl_4 or hexane), the ratio of 2-FDG:2-FDM is ~ 95:5; in polar solvents, either protic (acetic acid, methanol) or aprotic (acetone, DMF), the ratio of 2-FDG:2-FDM is ~ 80:20. The fact that the ratio of 2-FDG and 2-FDM stays the same in protic and aprotic solvents suggests that the hydrogen bonding between the solvent and the substrate is not important. Although the exact reason(s) for this solvent effect is unclear, it may be due to either differences in the conformations of the substrates (or reaction intermediates) or the reaction mechanisms

TABLE 1

Relative Amounts (%) of 2-FDG and 2-FDM from the Reactions of Glycals with Gaseous Acetyl Hypofluorite in Different Solvents at Room Temperature[a]

Substrate	Solvent	% 2-FDG	% 2-FDM
D-Glucal (1a)	HOAc	12	88
TAG (1b)	HOAc	81	19
TIG (1c)	HOAc	76	24
TBG (1d)	HOAc	76	24
D-Glucal (1a)	Freon-11	43	57
TAG (1b)	Freon-11	96[b]	4[b]
TAG (1b)	Freon-11	94[c]	6[c]
TIG (1c)	Freon-11	92	8
TBG (1d)	Freon-11	95	5
D-Glucal (1a)	Acetone	32	68
TAG (1b)	Acetone	86	14
TIG (1c)	Acetone	76	24
TBG (1d)	Acetone	84	16
TAG (1b)	CCl_4	95	5
TAG (1b)	Hexane	96	4
TAG (1b)	CH_3OH	80	20
TAG (1b)	DMF	82	18
D-Glucal (1a)	H_2O	44	56

a The relative amounts of 2-FDG and 2-FDM were determined by GLC on a 6' x 1/8" 4% SE-30 + 6% OV-210 on chromosorb W-HP 80/100 mesh column.

b References 6 and 18.

c The reaction was run at -78°C (reference 18).

in different solvents. The mechanism of the reaction of acetyl hypofluorite with olefins remains uncertain. Whether the acetyl hypofluorite acts as a source of positive electrophilic fluorine or as a free radical is still controversial [23,24]. Rozen et al. have reported that reactions of acetyl hypofluorite with simple olefins are regiospecific and highly stereoselective [25], Visser et al. recently have demonstrated that the reactions of acetyl hypofluorite with cyclohexene [26] or with glycals (1a,b) [16] are non-regiospecific and non-stereospecific. The products isolated from these reactions arise from cis, trans and reversed cis addition of acetyl hypofluorite across the double bond of the substrates. Some of the products arise from a free radical mechanism. The results of our study could not distinguish between the ionic or free radical mechanism.

The size of the substituents (Scheme 1, R = acetyl, isobutyryl, benzoyl) on the hydroxyl groups of glucal has only a slight effect on the ratio of 2-FDG:2-FDM (Table 1). However, there are drastic steric effects on the reaction of acetyl hypofluorite whether with glucal (1a) itself or with substituted glucals (1b-d). In the case of glucal (1a) itself, the hydrogens on C-3 and C-5 in the glucal molecule which all occupy the axial positions have some steric effects on the addition of acetyl hypofluorite across the C-1, C-2 double bond and therefore it would add across the less hindered side of the molecule and gives more 2-FDM than 2-FDG. In the case of TAG (1b), the steric effects of the hydrogens on C-3 and C-5 are overcome by the bulky acetate group at C-3 which tends to shield the double bond from attack from that direction and therefore acetyl hypofluorite would add from the opposite side (less hindered side) of the C-3 acetyl group and thus give more 2-FDG than 2-FDM. Similar trends in isomer distributions have also been observed in the reaction of mercuric acetate with TAG (1b) which gives a glucose derivative whereas mercuration of glucal (1a) gives the mannose derivative as the major product [27]. The isobutyryl group (1c) and benzoyl group (1d) result in steric effects similar to those of the acetyl group and give a similar ratio of 2-FDG:2-FDM as that of 1b when the substituted glucals react with acetyl hypofluorite.

In summary, we have shown that: (1) the reactions of acetyl hypofluorite with glycals are highly stereoselective although non-stereospecific, (2) the isomeric purity of 2-FDG synthesized from the reactions of acetyl hypofluorite with glycals depends largely on the

solvent polarity rather than on the size of the substituents on the hydroxyl groups, and (3) the reaction temperature has little effect on the yield and isomeric purity of 2-FDG. Although the reactions of acetyl hypofluorite with 1b-d in Freon-11 give high ratios of 2-FDG:2-FDM, neither compound 1c nor 1d is commercially available, and compound 1d is difficult to hydrolyze. Because of the high product ratio of 2-FDG:2-FDM, and the commercial availability of TAG, the reaction of acetyl hypofluorite with TAG (1b) in Freon-11 or other non-polar solvents at room temperature is the method of choice for the synthesis of 2-^{18}FDG via electrophilic fluorinations.

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