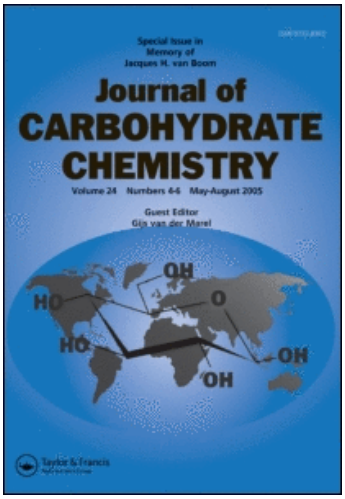

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New Synthesis of 2-Deoxy-2-fluoro-D-hexoses by Fluorination in Water

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Communication

NEW SYNTHESIS OF 2-DEOXY-2-FLUORO-D-HEXOSES BY FLUORINATION IN WATER

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Interest in fluorinated sugars labelled with {^{18}F}positron-emitting radionuclides as tracers for the measurement of glucose utilization in man by positron emission tomography[1] (PET) and in animals by autoradiography[2] has resulted in the development of numerous syntheses[3-11] of 2-deoxy-2-fluoro-D-glucose (3a). Some of these syntheses are not practical because the carbohydrate substrates for the fluorination reactions are not readily available.[9-11]

This manuscript describes the synthesis of fluorinated carbohydrates by fluorination of unprotected glycals in aqueous solution with molecular fluorine, perhaps better described as a "fluorinating species" formed by reacting F_2 with water. The feasibility of this type of reaction was suggested in a recent paper from this laboratory describing the synthesis of vinyl fluoride by fluorination in water.[12] After completion of the research described here an abstract outlining the synthesis of {^{18}F}-2-deoxy-2-fluoro-D-glucose ({^{18}F}3a) by fluorination of glucal in aqueous media appeared;[13] details of that work are not yet available.

The glycals employed in the study described here were D-glucal (1a) and D-galactal (1b). Epimers formed in the fluorination reaction were separated by high performance liquid chromatography (HPLC) using a Partisil-5 PAC column[14] and 0.0025N NaOAc -CH_3CN (18 : 82) as the elution solvent at a flow rate of 0.3 mL/min.

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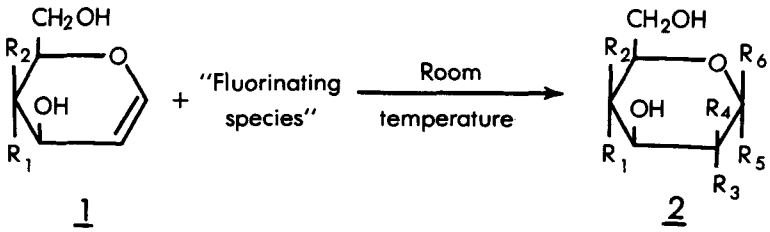
In our first set of investigations, the fluorination reactions (Fig. 1) were carried out by reacting variable amounts of glycal (0.1-0.5 mmol) dissolved in water (8 ml) with 0.07-0.150 mmol of F_2 (mixture of 5% F_2 in nitrogen) or $\{^{18}F\}F_2$ (mixture of 0.5 % $\{^{18}F\}F_2$ in neon). Fluorine mixtures were bubbled into a plastic (Teflon) container at a rate of about 50 mL/min. In the second set of investigations the solution of glycal in water was added to the "solution" of F_2 in water immediately after the bubbling of fluorine was finished.

Reactions were analyzed using: a) ^{19}F-NMR (Varian XL-200 using trifluorotrichloroethane as the external reference with ϕ = -82.204 ppm)[15] on crude reaction mixtures and on fractions of mono- and difluorinated compounds isolated by flash chromatography, b) thin layer chromatography (TLC) for reactions done with non-radioactive F_2, and c) radio-chromatography (TLRC) for reactions done with $\{^{18}F\}F_2$. Because the reactions were studied with the objective of maximizing the utilization of $\{^{18}F\}F_2$, they were all carried out with an excess of glycal. Consequently all yields given in this paper are relative to amounts of fluorine. The syntheses with $\{^{18}F\}F_2$ required around 45 min.

Both TLRC and TLC analysis (ethyl acetate-methanol, 5 : 1) of the reaction mixture derived from the fluorination of D-glucal showed two spots. ^{19}F-NMR analysis indicated that each of the spots contained two compounds. In the spot with R_f = 0.87, 2-deoxy-2-fluoro-D-glucopyranosyl fluoride (2b) and 2-deoxy-2-fluoro-D-mannopyranosyl fluoride (2a) were found in a ratio of 4.5 : 1. 1,2-Difluoro compound (2a) was identified from broad band ^1H-decoupled spectra (see Table).

2-Deoxy-2-fluoro-D-glucose (3a) (mixture of alpha and beta anomers in a ratio of 1 : 1.2) and 2-deoxy-2-fluoro-D-mannose (3b) (mixture of alpha and beta anomers in a ratio of 1.3 : 1) were found in the spot where R_f = 0.32. These structural assignments were made on the basis of ^{19}F-NMR data[3,8,16,17] given in the table.

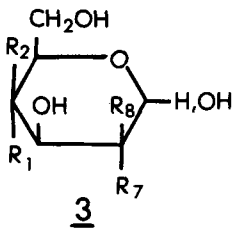
After hydrolysis with 2N HCl and removal of HCl by evaporation, compounds 3a and 3b were isolated by HPLC in a chemical yield of 40 % and 10 %, respectively. In experiments done with $\{^{18}F\}F_2$, the radiochemical yields were 18% for $\{^{18}F\}$3a and 4 % for $\{^{18}F\}$3b expressed at the end of the synthesis. The chemical purity of the purified 3a and 3b



1 2

1a: R_1= H; R_2= OH

1b: R_1= OH; R_2= H



3

2a : $R_2 = R_4 = R_6$=H; R_1=OH; $R_3 = R_5$=F

2b : $R_2 = R_3 = R_5$=H; R_1=OH; $R_4 = R_6$=F

2c : $R_1 = R_4 = R_6$=H; R_2=OH; $R_3 = R_5$=F

2d : $R_1 = R_3 = R_5$=H; R_2=OH; $R_4 = R_6$=F

3a : $R_2 = R_8$=H; R_1=OH; R_7=F

3b : $R_2 = R_7$=H; R_1=OH; R_8=F

3c : $R_1 = R_8$=H; R_2=OH; R_7=F

3d : $R_1 = R_7$=H; R_2=OH; R_8=F

FIGURE 1

was assessed by ^{19}F-NMR and showed less than 2 % of 3b present in 3a and less than 5 % of 3a in 3b when HPLC in a re-cycling mode was used.

In the fluorination reaction of galactal, three different compounds were identified on the basis of ^{19}F-NMR analysis of the crude reaction mixture. However, TLC and TLRC in the previously mentioned solvent showed only two spots with R_f = 0.70 and 0.24. The compounds corresponding to these spots were then separated by flash chromatography. The spot at 0.70 contained only 1,2-difluoro compound 2c. No compound 2d was observed. The spot with R_f = 0.24 contained a mixture of 2-deoxy-2-fluoro-D-galactose (3c) and 2-deoxy-2-fluoro-D-talose (3d). The ^{19}F-NMR assignments for 3c and 3d were made by comparing α/β relative chemical shifts of these anomers with those measured for 3a and 3b (see Table), as well as with the data from the literature.[8,16,18] After hydrolysis (as described), the reaction mixture

TABLE ^{19}F NMR Spectra Data[a]

Compound	Chemical Shifts (ppm)	Coupling Constant (Hz)					
		J_{FF}	J_{F1H1}	J_{F1H2}	J_{F2H1}	J_{F2H2}	J_{F2H3}
2a	-151.3(F-1)	19.5	53.8	24.5[b]			
2a	-205.1(F-2)	19.5				48.8	14.6
2b	-150.0(F-1)	12.4	48.8	9.8			
2b	-222 0(F-2)	12.4				48.8	24.0
2c	-153.4(F-1)	19.6	54.1	24.4			
2c[c]	-213.0(F-2)	19.6				48.9	14.6
α-3a	-200.57				0.8	48.3	15.0
β-3a	-200.41				2.9	51.6	14.7
α-3b	-206.0				7.7	51.7	32.8
β-3b	-224.5				20.0	52.0	32.0
α-3c[d]	-208.93					46.4	12.2
β-3c	-208.74				2.9	51.3	14.6
α-3d	-203.43				12.2	44.0	34.2
β-3d	-223.51				19.7	51.2	32.9

a. Chemical shifts are relative to CF_3Cl_3 (-82.204 ppm).
b. Trans orientation.
c. There is an additional coupling $J_{F2H4} = 4.9$ Hz.
d. There is an additional coupling $J_{F2H4} = 4.8$ Hz.

was found to contain only two compounds, 2-deoxy-2-fluoro-D-galactopyranose (mixture of α and β anomers in the ratio of 1.6 : 1) and 2-deoxy-2-fluoro-D-talopyranoside (with α and β in the ratio of 1.8 : 1). The ratio between 2-deoxy-2-fluoro-D-galactose and 2-deoxy-2-fluoro-D-talose was 5.3 : 1 and did not change significantly when measured after hydrolysis.

^{19}F-NMR spectra of the crude reaction mixture and the fraction with $R_f = 0.70$ had only one set of resonances (see Table) corresponding to 2-deoxy-2-fluoro-D-galactopyranosyl fluoride (2c). A very low yield of

compound 2d was reported earlier in the reaction of 3,4,6-tri-O-acetyl-D-galactal with CF_3OF[18] and XeF_2[3]. The low yield might explain why this compound was not detected in the present work.

HPLC purification was needed to obtain 3c and 3d as pure compounds. The chemical yield for the HPLC-purified fractions was 38 % and 7 % for 3c and 3d, respectively. The radiochemical yields were 16 % and 3 % for {^{18}F}3c and {^{18}F}3d, respectively.

The experiments described were repeated with glycals being added immediately after the introduction of fluorine or the ^{18}F-labelled fluorine mixtures. The chemical yields and the ratios of 1,2-difluoro to 2-deoxy-2-fluoro compounds were smaller than those described for the procedure where substrates were present in the reaction mixture during bubbling. However, the absolute amounts of 1,2-difluoro compounds were always lower when glucal was added after the end of fluorine bubbling. The absolute amounts of 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-galactose were always higher when substrates were added after the end of bubbling. The reasons for these yield differences is now being investigated.

In the fluorination reaction of both glycals studied here, fluorination in water yields mostly monofluoro compounds. Since the ratio of 3a to 3c did not differ greatly from that of 3b to 3d, the orientation on C-4 apparently does not have a major influence on stereoselectivity of the reaction.

The formation of cis-difluoro compounds in the reaction of 3,4,6-tri-O-acetyl-D-glucal with F_2 in freon-11 was explained by the addition of F_2 onto the C-C double bond following the pattern of the addition of other halogens.[5] Since the half-life of the fluorine reaction with water is 7 x 10^{-6} sec[19], and the concentration of water is much greater (~5000 times) than that of the substrate, it is unlikely that F_2 as such reacts with the substrate before reacting with water. The fluorinating "power" of the fluorine "solution" in water[21] described here and reported earlier [12] also mitigates against such a reaction. However, these results cannot exclude the possiblity that F_2 reacts with a substrate before reacting with water. The observation that the total yield of the fluorinated products is

essentially independent of the route of the fluorination suggests that the reaction mechanism is similar in both procedures.

The syntheses described here give chemical and radiochemical yields comparable to other syntheses using electrophilic substitutions as reported for the preparation of ^{18}F-labelled 3a[4,7] and non-labelled 2-deoxy-2-fluoro-D-hexoses.[3,5,6,8,16,17,21] Since the syntheses described in this manuscript are relatively short (about 45 min), they should also prove convenient when preparing a number of fluorinated compounds,[22] in particular ^{18}F-labelled 2-deoxy-2-fluoro-D-hexoses (especially {^{18}F}2-deoxy-2-fluoro-D-glucose ({^{18}F}3a), a tracer much in demand for PET medical research[1]) and other fluorinated hexoses of interest in biological research.[23]

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