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Note

Fluorination of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol in water*

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The importance of 2-deoxy-2-[^{18}F]fluoro-D-glucose in positron-emission tomography[1] (PET) and multi-tracer autoradiographical research[2] has prompted development of several synthetic methods using electrophilic[3–9] and nucleophilic[10–12] fluorinating reagents. 2-Deoxy-2-fluoro-D-mannose is also needed for the synthesis of a glycoside[13]. The electrophilic fluorinating agents used for the synthesis of fluoro sugars are xenon difluoride[4], trifluoromethyl hypofluorite[5], molecular fluorine[6], and acetyl hypofluorite[3,7–9]. We have recently reported the fluorination with molecular fluorine in an aqueous medium as a method to prepare vinyl fluoride[14]. The synthesis involved bubbling fluorine into water in the presence or absence of the appropriate starting material. On the basis of the compounds obtained, it is believed that the fluorinating agent is an electrophilic species[14].

The reaction of fluorine with 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (3,4,6-tri-*O*-acetyl-D-glucal) (**1**) in water yielded a mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α- and -β-D-glucopyranose (**5**), 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α- and -β-D-mannopyranose (**6**), as well as 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl fluoride (**3**) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (**4**). The reason for selecting **1** rather than 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal) (**2**) was the ease with which the various reaction products were isolated, and accordingly the possibility of evaluating better the products of aqueous fluorination. The components of the reaction mixture were extracted into chloroform. The hydrogen-decoupled, ^{19}F-n.m.r. spectrum of the chloroform extract containing the products of the fluorination in water showed, in the anomeric region, a doublet at δ −149.0 (relative to the signal of external $CFCl_3$) with a coupling constant of $^3J_{F,F}$ 12.2 Hz, and a doublet at δ −152.4 with a coupling

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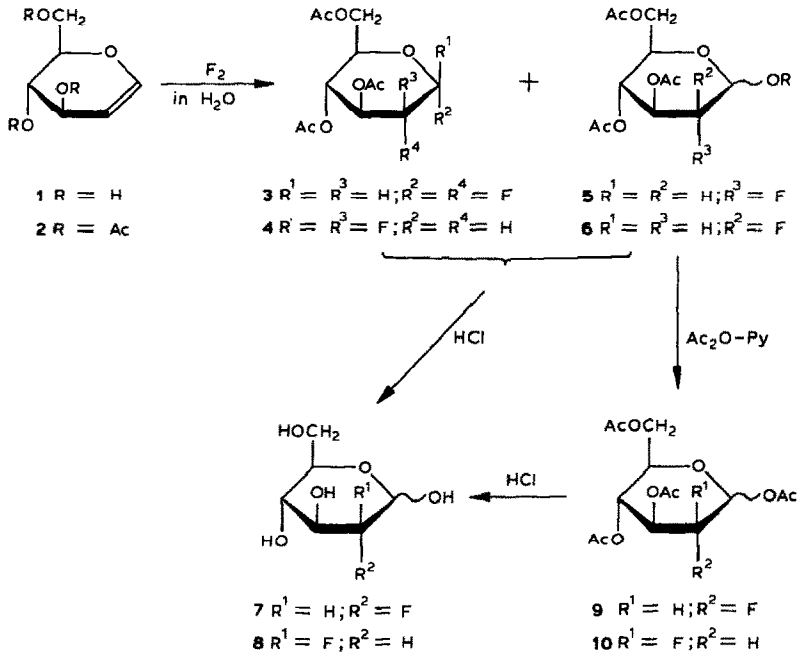

constant $^3J_{F,F}$ 18.6 Hz, in the ratio of 1:1. The former signal was coupled with a doublet at δ −222.1 ($^3J_{F,F}$ 12.2 Hz) and the latter with a doublet at δ −205.7 ($^3J_{F,F}$ 18.6 Hz) corresponding to F-2. The signals at δ −149.0 and −222.1 were attributed to compound **3** and those at δ −152.4 and −205.7 to compound **4** after comparison with the spectral data of the products of the reaction of fluorine with **1** in $CFCl_3$ reported by Ido *et al.*[6]. The ^{19}F-n.m.r., ^{1}H-decoupled spectrum of the above-mentioned chloroform extract also showed singlets at δ −200.5, 201.3, 205.2, and −223.1. These signals were assigned to **5** (β form), **5** (α form), **6** (α form), and **6** (β form), respectively, on the basis of comparison of the chemical shifts with standard values for these compounds[15]. The ratio of 1,2-difluoro to 2-deoxy-2-fluoro compounds was 1:1 in this crude mixture.

Compounds **5** and **6** were acetylated[15] into the tetraacetates **9** and **10**, respectively, and the mixture was separated by flash chromatography.

^{19}F-N.m.r. spectrometry indicated that the first fraction contained a mixture of **3** and the tetraacetate **8**, and the second fraction a mixture of **4** and the tetraacetate **9**. Hydrolysis[15] of this second fraction gave 2-deoxy-2-fluoro-α,β-D-mannose (**8**) in the ratio of α to β of 2:1. Similarly, the first fraction was hydrolyzed[5–8] to give 2-deoxy-2-fluoro-D-glucose (**7**) with the two anomers being present in equal amounts. The chemical shifts in the ^{19}F-H-decoupled spectrum were identical with those of a commercial sample of 2-deoxy-2-fluoro-D-glucose (Calbiochem-Behring Corporation, La Jolla, California 92037) and with the values of the literature[15]. All the ^{19}F-n.m.r. data agreed well with the data of the literature[5,15].

The chemical yield of the 2-deoxy-2-fluoro-hexoses **7** and **8**, relative to the

amount of fluorine used, was 32% for both compounds. In the synthesis with $[^{18}F]F_2$, the radiochemical purity of the fluorinated sugars was at least 98% as determined by thin-layer radiochromatography (t.l.r.c.). The chemical purity of the purified material exceeded 99% as determined from decoupled ^{19}F-n.m.r. spectrometry. The chemical yields are also comparable to those obtained by more classical procedures[5,15], even though only a suspension of **1** in water was possible. In the experiment with radioactive material, the final radiochemical yield of purified compounds, ^{18}F-**7** and ^{18}F-**8**, was ~12% (not corrected for decay). This result was based on the total ^{18}F-activity collected in water in a 45-min synthesis. The flash chromatography separated well ^{18}F-**3** and ^{18}F-**9** as the first fraction, and ^{18}F-**4** and ^{18}F-**10** as second fraction, as assessed by t.l.r.c. before hydrolysis and by ^{19}F-n.m.r. spectrometry after acid hydrolysis. The method described herein shows a radiochemical yield for ^{18}F-**7** comparable with those of earlier methods[3,6–9*,16].

The investigation by ^{19}F-n.m.r. spectrometry of the reaction mixture obtained after fluorine bubbling indicated that the difluoro compounds **3** and **4** are direct products of the fluorination reaction. A similar formation of 1,2-difluoro compounds was also observed for the fluorination of **1** with trifluoromethyl hypofluorite[5], and it is known that all glycal triacetates react with chlorine[17], bromine[17], and fluorine[6] in an organic solvent to form 1,2-dihalogeno compounds by *cis*-addition. The other reaction products obtained in the present work suggest the presence of electrophilic fluorine, which adds to nucleophilic C-2 of **1** and other glycals having nonprotected functional groups[18], thereby accounting for the formation of 2-deoxy-2-fluoro-D-*gluco* and 2-deoxy-2-fluoro-D-*manno* compounds. The fluorination in aqueous media described herein may also be applied to the synthesis of other fluoro compounds and other ^{18}F-labelled compounds from starting materials having unprotected functional groups. The present results show also that fluorination of **1** in an aqueous medium is not stereoselective because both fluoromanno- and fluoro-gluco-hexoses were obtained. Since the ratio between difluoro (**3** + **4**) and monofluoro (**5** + **6**) compounds was ~1:1, regardless of whether **1** was present during bubbling or added later, it is probable that a complex mechanism occurs during the fluorination reaction. However, when the starting material **1** was added after the end of fluorine bubbling, the absolute yields of the syntheses were ill-defined and difficult to reproduce. The method gave **7** and **8** in chemical and radiochemical yields comparable with those described earlier but the yield of 2-deoxy-2-fluoro-D-mannose (**8**) was much higher than those reported earlier[3–7,9,11,13,15] for other electrophilic fluorination reactions.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was performed on hard-layer silica gel plates. ^{19}F-n.m.r. spectra were recorded with spectrometers

*The yield reported in ref. 9 is for a mixture of ^{18}F-**7** and ^{18}F-**8**, see ref. 16.

operated at 280 and 75 MHz; chemical shifts are given relative to the signal of $CFCl_3$ used as external standard. All reactions were performed with fluorine in less than the equimolar amount and the yields are expressed relative to the amounts of fluorine used.

*Fluorination of 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-*D-arabino-*hex-1-enitol* (**1**). — 1:19 F_2-N_2 was bubbled into water for 8 min at a flow rate ranging from 50 mL to ~0 mL/min (expansion from a pressurized container), thus introducing ~0.1 mmol of F_2 into water. At the end of bubbling, **1** (20.5 mg, 0.14 mmol) was added and the suspension mixed for 2–3 min. In another experiment, the gas mixture was bubbled into a suspension of **1** (0.14 mmol) in water (8 mL) for 8–10 min. In both cases, the mixture was extracted with chloroform (2 × 10 mL), the extract evaporated to dryness, and the residue treated with 2:1 acetic anhydride–pyridine (2 mL) at room temperature[15]; t.l.c. (7:3 ether–hexane) showed two spots having R_F 0.6 and 0.3. The mixture was separated by flash chromatography on silica gel (40–140 mesh) in 9:11 ether–hexane to give two fractions, the first (R_F 0.6) containing 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranose (**9**) and **3**, and the second (R_F 0.3) containing a mixture of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-mannopyranose (**10**) and **4**.

The first fraction was hydrolyzed with 2M HCl for 10 min and the second fraction with 4M HCl for 20 min in a bath at 130°, as described earlier[3,6–15]. The first fraction gave, after evaporation, 2-deoxy-2-fluoro-D-glucose (**7**) (32 μmol, overall yield 32%), amorphous, m.p. 155–160°; t.l.c. (4:1 ethyl acetate–ethanol) R_F 0.58; ^{19}F-n.m.r. (β-anomer; water): δ −200.57 (m, $J_{F\text{-}2,H\text{-}2}$ 53.7, $J_{F\text{-}2,H\text{-}3}$ 14.7, $J_{F\text{-}2,H\text{-}3}$ 15.0, $J_{F\text{-}2,H\text{-}1}$ 0.8 Hz).

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.09; F, 10.43. Found: C, 39.50; H, 6.18; F, 10.48.

The second fraction gave, after evaporation, 2-deoxy-2-fluoro-D-mannose (**8**) (32 μmol, overall yield 32%), amorphous, m.p. 123–128°; t.l.c. (4:1 ethyl acetate–ethanol) R_F 0.58; ^{19}F-n.m.r. (α-anomer; water): δ −205.99 (M, $J_{F\text{-}2,H\text{-}2}$ 48.8, $J_{F\text{-}2,H\text{-}3}$ 33.4, $J_{F\text{-}1,H\text{-}1}$ 9.8 Hz; (β-anomer) δ −224.68 (m, $J_{F\text{-}2,H\text{-}2}$ 53.7, $J_{F\text{-}2,H\text{-}3}$ 29.3, $J_{F\text{-}1,H\text{-}1}$ 19.7 Hz).

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.09; F, 10.43. Found: C, 39.50; H, 6.15; F, 10.39.

Synthesis of ^{18}F-labelled compounds. — The preparation of $[^{18}F_2]F_2$ has been described elsewhere[19]. In the first set of experiments, $^{18}F_2$–F_2 (70 μmol; 0.5% in Ne) was bubbled into water containing **1** (0.14 mmol) in a suspension. In the second set of experiments, $^{18}F_2$–F_2 (~70 μmol; 0.5% in Ne) was bubbled for over 8 min at a flow rate of 50 mL/min in 8 mL of water, pH 7. At the end of the bubbling, **1** (0.14 mmol) was added and the suspension mixed for 2–3 min. The reaction mixture was extracted, the solvent evaporated, and the residue acetylated[15] and fractionated by flash chromatography on a Sep-Pak column (Waters Associates) as described above. The first fraction contained ^{18}F-**9** and ^{18}F-**3**, and the second fraction ^{18}F-**10** and ^{18}F-**4** which, on hydrolysis, gave ^{18}F-**7** and ^{18}F-**8**, respectively. The separation

of the *gluco* (**3** and **5**) from the *manno* (**4** and **6**) compounds was also performed, without conversion into the tetraacetates, by l.c. on a Partisil-5 silica gel column with 4:1 hexane–ether as eluent. The compounds were identified by comparing the ^{19}F-n.m.r. spectra after the radioactive fluorine had decayed and by comparing the R_F values on t.l.r.c. with the values obtained for nonradioactive material.

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REFERENCES

1 M. E. PHELPS, J. C. MAZZIOTTA, AND S.-C. HUANG, *J. Cereb. Blood Flow Metab.*, 2 (1982) 113–156; and references therein.
2 K. SAKO, A. KATO, M. DIKSIC, AND Y. L. YAMAMOTO, *Stroke*, 15 (1984) 896–900.
3 C.-Y. SHIUE, P. A. SALVADORI, A. P. WOLF, J. S. FOWLER, AND R. R. MACGREGOR, *J. Nucl. Med.*, 23 (1982) 899–903.
4 W. KORYTNYK AND S. VALENTEKOVIC-HORVAT, *Tetrahedron Lett.*, (1980) 1493–1496.
5 J. ADAMSON, A. B. FOSTER, L. D. HALL, AND R. H. HESSE, *J. Chem. Soc., Chem. Commun.*, (1969) 309–310.
6 T. IDO, C.-N. WAN, J. FOWLER, AND A. P. WOLF, *J. Org. Chem.*, 42 (1977) 2341–2342.
7 M. J. ADAM, *J. Chem. Soc., Chem. Commun.*, (1982) 730–731.
8 M. DIKSIC AND D. JOLLY, *Int. J. Appl. Radiat. Isot.*, 34 (1983) 893–896.
9 R. E. EHRENKAUFER, J. F. POTOCKI, AND D. M. JEWETT, *J. Nucl. Med.*, 25 (1984) 333–337.
10 S. LEVY, E. LIVNI, D. ELMALEH, AND W. CURATOLO, *J. Chem. Soc., Chem. Commun.*, (1982) 972–973.
11 W. A. SZAREK, G. W. HAY, AND M. M. PERLMUTTER, *J. Chem. Soc., Chem. Commun.*, (1982) 1253–1254.
12 T. J. TEWSON, *J. Nucl. Med.*, 24 (1983) 718–721.
13 T. OGAWA AND Y. TAKAHASHI, *J. Carbohydr. Chem.*, 2 (1983) 461–467.
14 M. DIKSIC AND P. DI RADDO, *Tetrahedron Lett.*, 25 (1984) 4885–4888.
15 J. ADAMSON, A. B. FOSTER, L. D. HALL, R. N. JOHNSON, AND R. H. HESSE, *Carbohydr. Res.*, 15 (1970) 351–359.
16 J. D. H. HERSCHEID, C. J. S. VAN RIJN, G. W. M. VISSER, AND A. HOEKSTRA, *Abstr. Proc. Int. Symp. Radiopharm. Chem., Vth*, (1984) 209–210.
17 R. U. LEMIEUX AND B. FRASER-REID, *Can. J. Chem.*, 43 (1965) 1460–1475.
18 M. DIKSIC AND D. JOLLY, *Carbohydr. Res.*, in press.
19 M. DIKSIC AND J. TODA, *Can. J. Chem.*, 61 (1983) 661–664.