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# ALTERNATIVE SYNTHESIS OF NO-CARRIER-ADDED 2-DEOXY-2-[$^{18}$F]FLUORO-D-GLUCOSE USING [$^{18}$F]FLUORIDE ION

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## SUMMARY

Two alternative routes to no-carrier-added synthesis of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose (2-$^{18}$FDG) involving nucleophilic displacements of methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranoside (1) and 1,6-anhydro-3,4-di-O-benzyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranose (2) are described. The triflates (1 and 2) reacted with aminopolyether (Kryptofix 222) supported potassium [$^{18}$F]fluoride and tetra-n-butylammonium [$^{18}$F]fluoride in acetonitrile to give methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-[$^{18}$F]fluoro-β-D-glucopyranoside (3) and 1,6-anhydro-3,4-di-O-benzyl-2-deoxy-2-[$^{18}$F]fluoro-β-D-glucopyranose (4), respectively. The displacement yield with 1 was consistently higher than that with 2. Hydrolysis of 3 with 6N HCl, followed by passage through an ion retardation resin column and a neutral alumina column, gave 2-$^{18}$FDG in 34-43% overall radiochemical yield without correction for decay. Removal of the protecting groups from 4 with 6N HCl or 50% $CH_3SO_3H$ led to incomplete hydrolysis. The total preparation time was about 80 min from start of the radiofluorination.

**Key Words:** radiofluorination, no-carrier-added, methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranoside, 1,6-anhydro-3,4-di-O-benzyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranose, 2-deoxy-2-[$^{18}$F]fluoro-D-glucose

## INTRODUCTION

In recent years there has been continuing interest in developing improved methods for the synthesis of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose (2-$^{18}$FDG) because of its increasing importance in the field of nuclear medicine for studies of regional glucose metabolism in man (1). Electrophilic additions of [$^{18}$F]$F_2$ (2) and [$^{18}$F]$CH_3CO_2F$ (3) to glucals are the most widely used methods for the preparation of 2-$^{18}$FDG for medical research. These electrophilic processes starting from [$^{18}$F]$F_2$, however, entail the inherent loss of 50% of the fluorine activity and lead to the formation of 2-deoxy-2-[$^{18}$F]fluoro-D-mannose (2-$^{18}$FDM) as a by-

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product (4-6). Recently, attention has come to be paid to synthetic procedures based on [$^{18}$F]fluoride ion which, in principle, offers the potential of utilizing all the available fluorine in substitution reactions. Several sources of [$^{18}$F]fluoride are available, one of the most common now being the $^{18}$O(p, n)$^{18}$F reaction using an $^{18}$O-enriched water target (7). Published reports based on nucleophilic approaches to the synthesis of 2-$^{18}$FDG involve the use of methyl 4,6-O-benzylidene-3-O-methyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranoside (8), 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-C-nitro-D-mannitol (9), and methyl 4,6-O-benzylidene-β-D-mannopyranoside 2,3-cyclic sulfate (10) as starting materials. The first two methods had a relatively low radiochemical yield (~10%). The latter, the most widely studied, gave a radiochemical yield of 40% or less, although there was a difficult step in removing the glycosidic methyl group of the substrate. A simpler nucleophilic fluorination has recently been developed using the displacement of the aminopolyether potassium complex ([K/2.2.2.]$^{+}$$^{18}$F$^{-}$) on 1,3,4,6-tetra-O-acetyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranose, followed by acid hydrolysis, to give 2-$^{18}$FDG with an uncorrected radiochemical yield of a maximum 50% (11).

In our laboratory, synthesis of unlabeled 2-FDG has been achieved in high yield by two different routes including nucleophilic fluorination of the $C_2$-triflate function of protected mannose derivatives as the substrate molecules (12, 13). In concurrent work, these protected triflates have been examined as alternative substrates for the preparation of no-carrier-added (n. c. a.) 2-$^{18}$FDG by [$^{18}$F]fluoride ion treatment.

## RESULTS AND DISCUSSION

Two different mannose derivatives, methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranoside (1) and 1,6-anhydro-3,4-di-O-benzyl-2-O-(trifluoromethanesulfonyl)-β-D-mannopyranose (2), were chosen as substrates for the initial displacement reaction leading to the synthesis of n. c. a. 2-$^{18}$FDG, which were suggested in our previous reports on the synthesis of unlabeled 2-FDG (12, 13). Nucleophilic fluorine from the water target was used in the form of n. c. a. tetra-n-butylammonium [$^{18}$F]fluoride ($^{18}$F-TBAF)

Scheme 1

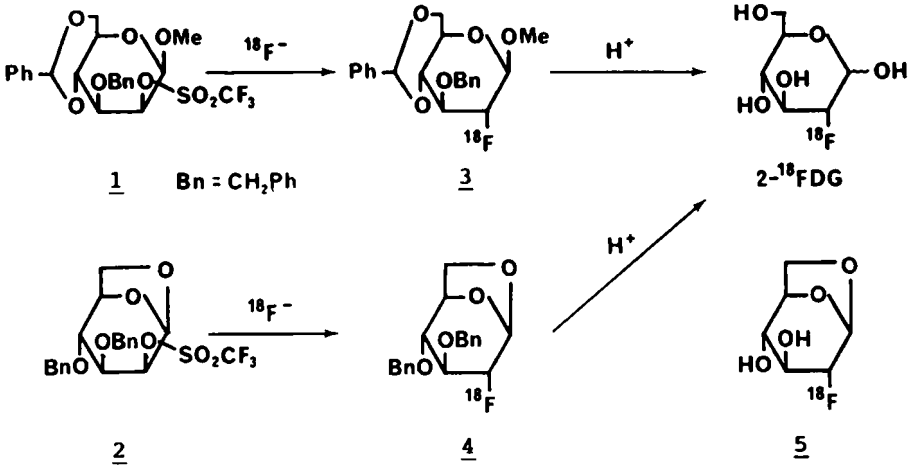


Table 1

Radiochemical yields of $^{18}$F-labeled intermediates (3 and 4) from the reaction of [$^{18}$F]fluoride with triflates (1 and 2)[a]

| Triflate | Reaction vessel | [$^{18}$F]fluoride | Yield (%)[b] |
|---|---|---|---|
| 1 | Pyrex | [K/2.2.2.]$^{+18}$F$^-$ | 3 (15 - 18) |
| | TPX[c] | $^{18}$F-TBAF | 3 (46 - 56) |
| | TPX | [K/2.2.2.]$^{+18}$F$^-$ | 3 (59 - 66) |
| 2 | Pyrex | $^{18}$F-TBAF | 4 (12 - 18) |
| | TPX | $^{18}$F-TBAF | 4 (21 - 28) |
| | TPX | [K/2.2.2.]$^{+18}$F$^-$ | 4 (52 - 54) |

a) Reactions were carried out at 75°C for 20 min in acetonitrile
b) Percentage of activity in the product fraction relative to the initial activity of the [$^{18}$F]fluoride (not corrected for decay)
c) Polymethylpentene vial

and [K/2.2.2.]$^{+18}$F$^-$. Although there is a claim that tetraalkylammonium salts are susceptible to decomposition at higher temperatures (14), $^{18}$F-TBAF has been successfully used at elevated temperatures as evidenced by good yields in some nucleophilic reactions (15-17). The latter complex has recently been found to be extremely useful in the preparation of $^{18}$F-radiopharmaceuticals at n. c. a.

level (18, 19). The results in the radiofluorination step with these triflates in dry acetonitrile at 75°C for 20 min using different vessel material are summarized in Table 1. The displacement of the triflate groups in both 1 and 2 was highly dependent on the reaction vessel material used here, with a polymethylpentene (TPX) vessel giving consistently higher yields than a Pyrex vessel. This supports further our previous result that a TPX vessel material is useful as a reaction vessel in nucleophilic substitution reaction at n. c. a. level (17). When the contents of the TPX vessel were extracted with n-hexane - dichloromethane (1:1), the amount of activity remaining on the wall of the TPX vessel was only 2-5% of the total activity. A significant difference in the displacement yield between the use of the two $^{18}$F-reagents was observed. $^{18}$F-TBAF was relatively less reactive with both substrates, even using a TPX vessel. The use of the combination of K$^{18}$F and Kryptofix 222 resulted in consistent and higher yields of the desired fluorinations with both substrates. HPLC and TLC analyses of the crude reaction mixtures extracted with n-hexane - dichloromethane (1:1) showed that the attack of [$^{18}$F]fluoride to the substrates is a single reaction leading exclusively to the corresponding $^{18}$F-intermediates. Thus the reaction of 1 with [K/2.2.2.]$^{+18}$F$^-$ in acetonitrile using a TPX vessel, followed by HPLC, gave 3 in 59-66% isolated radiochemical yield with a processing time of about 40 min. Under the similar conditions the isolated radiochemical yield of 4 from the triflate (2) in several experiments was never greater than 54%, indicating the preference of 1 over 2 as starting material in the initial displacement reaction.

The deprotection by hydrolysis of the $^{18}$F-intermediate (3) proceeded by heating with 6N HCl and a 20 min period was required to remove all the protecting groups. Thus the route involving the radiofluorination of 1 with [K/2.2.2.]$^{+18}$F$^-$ in a TPX vessel and subsequent hydrolysis with 6N HCl provided access to 2-$^{18}$FDG in 37-43% overall radiochemical yield (without correction for decay), whereas the same procedure using $^{18}$F-TBAF gave slightly lower yield (34-37%) of 2-$^{18}$FDG. The total preparation time was about 80 min. On the other hand, repeated attempts to convert the $^{18}$F-intermediate (4) into 2-$^{18}$FDG by heating with 6N HCl or 50% $CH_3SO_3H$ resulted in incomplete reaction: The 2-$^{18}$FDG

was contaminated with 9-12% of 1,6-anhydro-2-deoxy-2-[$^{18}$F]fluoro-β-D-glucopyranose (5) as determined by TLC. Evidently, the synthetic route using the triflate (2) is not a suitable one for the preparation of 2-$^{18}$FDG because of difficulty in effecting the cleavage of the 1,6-anhydro bridge.

When the 2-$^{18}$FDG solution obtained through the $^{18}$F-intermediate (3) was analyzed by TLC (silica gel, $CH_3CN:H_2O$ = 95:5) and HPLC (Waters, Carbohydrate Analysis Column; $CH_3CN:H_2O$ = 85:15), the radiochemical purity was at least 97% in several preparations. The only contaminant was a small amount (~3%) of the 1,6-anhydro glucopyranose (5) as might be suspected under the acidic conditions used. A typical TLC chromatogram obtained by adding authentic carriers as standard is shown in Fig. 1.

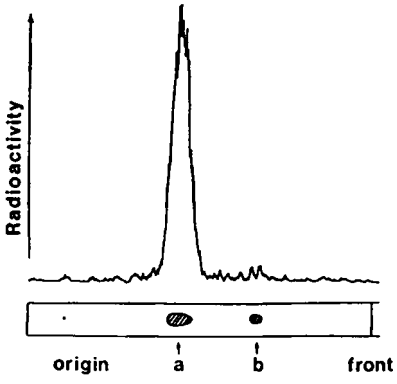


Fig. 1

A typical TLC chromatogram of an aqueous solution of 2-$^{18}$FDG obtained by hydrolysis of 3 with 6N HCl. Solvent system: $CH_3CN$ - $H_2O$(95:5) a: 2-FDG; b: 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose

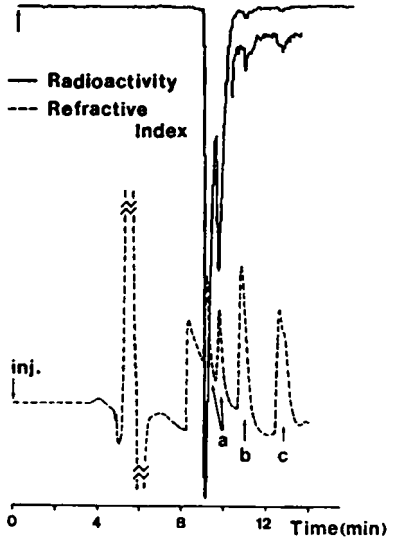


Fig. 2

A HPLC chromatogram of the ether extract obtained after peracetylation of the 2-$^{18}$FDG. Mobile phase: n-hexane - AcOEt(1:1) Flow rate: 1 mL/min; a: tetraacetate of 2-FDG; b: 3,4-di-O-acetyl-1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose; c: tetraacetate of 2-FDM

We have previously observed using $^{19}$F-NMR spectroscopy that interconversion of 2-FDG and 2-FDM is caused by the action of strong acids (20). There was, therefore, the possibility of contamination by a partial epimerization to 2-$^{18}$FDM at the stage of the acid deblocking process. The amount of 2-$^{18}$FDM

present in the 2-$^{18}$FDG obtained through the $^{18}$F-intermediate (3) was evaluated by conversion to the peracetylated derivatives and subsequent HPLC analysis. HPLC analysis of the reaction mixtures showed the presence of four radioactive peaks, as shown in Fig. 2, which was obtained by adding authentic materials as standard. Besides the three peaks expected for the peracetylated $\alpha$and$\beta$ forms of the 2-$^{18}$FDG and the peracetylated derivative of the 1,6-anhydro glucopyranose (5), a very small peak with a longer retention time corresponding to the peracetylated 2-$^{18}$FDM was found. However, this constituted only less than 0.5% of the radioactivity, thus indicating that under the conditions used the degree of epimerization of 2-$^{18}$FDG to 2-$^{18}$FDM is negligibly small.

In conclusion, the synthetic route to n. c. a. 2-$^{18}$FDG involving [$^{18}$F]fluoride ion displacement on 1 in a TPX vessel followed by hydrolysis with 6N HCl produce a greater radiochemical yield than those described by Levy et al (8) and Beeley et al (9), and is comparable to a method developed by Tewson or its modifications (10, 21). The radiochemical purity of the final product was at least 97% with the inevitable contaminants being small amount of the 1,6-anhydro glucopyranose (5) and 2-$^{18}$FDM: This level of purity is acceptable for medical use. With respect to radiochemical yield and synthetic time, however, this method dose not appear to be superior to that recently developed by Hamacher et al (11). Nevertheless, we can say that the methodology described here constitutes an alternative route to n. c. a. 2-$^{18}$FDG using [$^{18}$F]fluoride ion.

## EXPERIMENTAL

Authentic samples of 2-FDG, 2-deoxy-2-fluoro-D-mannose (2-FDM), and their tetraacetates were prepared by the methods reported earlier (12, 22). 1,6-Anhydro-2-deoxy-2-fluoro-$\beta$-D-glucopyranose was prepared in 50% yield from 2-FDG by treating 2-deoxy-2-fluoro-6-O-tosyl-D-glucopyranose with sodium hydroxide (23); mp 127-129°C (lit. 129-130°C (24)); Anal. Calcd for $C_6H_9FO_4$: C, 43.91; H, 5.53. Found: C, 43.91; H, 5.54. 3,4-Di-O-acetyl-1,6-anhydro-2-deoxy-2-fluoro-$\beta$-D-glucopyranose was prepared by acetylation of the corresponding 3,4-diol compound with acetic anhydride in pyridine in the usual manner (24). Unless

stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. Acetonitrile was distilled from $CaH_2$. High performance liquid chromatography (HPLC) was performed using a Waters Liquid Chromatograph System equipped with either a 254 nm U.V. absorbance detector (Model 441) or a differential refractometer (R401). The effluent from the column was continuously monitored for radioactivity using NaI(Tl) scintillation detector system. Thin layer chromatography (TLC) was performed on silica gel 60 $F_{254}$ (Merck): Products were co-spotted with authentic samples and, after development, spots were visualized by spraying with aqueous $H_2SO_4$ followed by heating, and activity distribution on the plates were measured by a TLC Radiochromatogram Scanner (Aloka). Conditions for all chromatographic separations are given in the following experimental sections. The radioactivity was also quantified with a Capintec Radioisotope Calibrator (CRC-30). The radiochemical yields are expressed at the end of the synthesis (not corrected for decay) relative to the amount of the [$^{18}$F]fluorinating agent measured as total radioactivity present in the reaction vessel.

**Preparation of [$^{18}$F]fluorinating agents**

Fluorine-18 was produced from 6-8% enriched [$^{18}$O]$H_2O$ by the $^{18}O(p, n)^{18}F$ reaction as described previously (17). A TPX (polymethylpentene) vial (Wheaton, Scientific, USA) and Pyrex vial were used as suitable vessels for the preparation of [$^{18}$F]fluorinating agents and subsequent displacement reactions of the triflates. Tetra-n-butylammonium [$^{18}$F]fluoride ($^{18}$F-TBAF) was prepared by the following treatment of the irradiated water. The aqueous [$^{18}$F]fluoride ion (1-1.5 mCi, 0.3-0.4 mL) was placed in the vessel containing a 10-20 $\mu$L (3.5-7 $\mu$mol) of 10% tetra-n-butylammonium hydroxide in water, and taken to dryness under a stream of argon at 100-110°C. The residue was further dried by coevaporation with acetonitrile (0.5 mL x 2). Aminopolyether (Kryptofix 222, Merck) supported potassium [$^{18}$F]fluoride ([K/2.2.2.]$^{+18}F^-$) was similarly prepared by the addition of $K_2CO_3$ (1.5 mg, 10 $\mu$mol) and Kryptofix 222 (8 mg, 21 $\mu$mol) to the irradiated water (16, 19).

**[$^{18}$F]Fluoride ion displacement of the triflates (1 and 2)**

A solution of the triflate (1 or 2) (10 mg) in dry acetonitrile (250 μL) was added to a TPX or a Pyrex vial containing the $^{18}$F-TBAF or [K/2.2.2.]$^{+18}$F$^-$ (0.5-1.3 mCi). The reaction vessel was capped and heated at 75°C for 20 min. After the solvent was evaporated with a flow of argon at 100°C, the residue was extracted with n-hexane - $CH_2Cl_2$ (1:1) ( 500 μL). The extract was injected onto a HPLC column (Partisil M9 10/50, PAC, 50 cm, Whatman; detectors: U.V. at 254 nm and radioactivity) attached a precolumn (silica gel 30μ). Elution with n-hexane - ethyl acetate (3:1) gave the $^{18}$F-labeled intermediate (3) (flow rate: 4 mL/min, $R_t$ = 13 min) or (4) (flow rate: 5 ml/min, $R_t$ = 12 min). The identities of these intermediates were verified by HPLC and TLC comparison with authentic samples. The radiochemical yields are listed in Table 1. The radiochemical purities of the intermediates were found to be >99% by TLC (n-hexane:ethyl acetate = 3:1, $R_f$ of 3 = 0.34, $R_f$ of 4 = 0.32). The time required in these radiofluorinations and subsequent isolations by HPLC was about 40 min.

**Hydrolysis of 3 and 4 to 2-$^{18}$FDG**

The $^{18}$F-intermediates (3 and 4) obtained using a TPX vessel were subjected to the following hydrolysis. The fraction of the $^{18}$F-labeled intermediate (3) (300-800 μCi) from HPLC was collected in a 5 mL Pyrex vial and the solvents were evaporated under a stream of argon at 100°C. To the residue was added 6N HCl (500 μL), and the vial was capped and heated at 110-115°C for 20 min. The reaction was cooled briefly in water prior to opening and water (1 mL) was added. The acid solution was passed through a AG11A8 ion retardation resin column (6 x 1.3 cm) and a neutral alumina column (0.5 x 1.3 cm) to remove any fluoride ion: These columns had been previously equilibrated with water. By this procedure, an aqueous solution of 2-$^{18}$FDG was obtained in a volume of 4-5 mL of water with overall radiochemical yields of 34-43% at the end of synthesis. The overall synthesis time was about 80 min from start of the radiofluorination of the triflate (1).

The $^{18}$F-intermediate (4)(200-850 μCi) was similarly treated with 6N HCl (500 μL) or 50% $CH_3SO_3H$ (500 μL) at 110-115°C for 12-20 min. After the hy-

drolysate was worked up as described above, an aqueous solution of 2-$^{18}$FDG was obtained in a volume of 4-5 mL of water with overall radiochemical yield of up to 35%. TLC ($CH_3CN$:$H_2O$ = 95:5) showed that this solution contained 9-12% of 1,6-anhydro-2-deoxy-2-[$^{18}$F]fluoro-β-D-glucopyranose (5).

**HPLC and TLC analyses of 2-$^{18}$FDG**

The 2-$^{18}$FDG obtained by hydrolysis of 3 with 6N HCl was analyzed by both TLC ($CH_3CN$ - $H_2O$ = 95:5) and HPLC (Carbohydrate Analysis Column, Waters; mobile phase: $CH_3CN$ - $H_2O$ (85:15); flow rate: 1 mL/min; detectors: refractive index and radioactivity). Analyses of several preparations showed that the radiochemical purity of 2-$^{18}$FDG ($R_t$ = 5.9 min, $R_f$ = 0.38) was at least 97% . The only significant radioactive impurity ($R_t$ = 3.2 min, $R_f$ = 0.63), accounting for about 3% of the total radioactivity, was always found in this solution. This material was identified as 5 by HPLC and TLC (Fig. 1) comparison with authentic material.

**HPLC analysis through conversion of the 2-$^{18}$FDG fraction to peracetylated derivatives**

An aqueous solution of the 2-$^{18}$FDG obtained by hydrolysis of 3 with 6N HCl and purification through a resin and an alumina columns was evaporated to dryness. To the residue (100 μCi) was added acetic anhydride (400 μL) and pyridine (200 μL). The mixture was heated at 75°C for 30 min. After cooling, water (2 mL) was added and the acetylated products were extracted with ether (2 mL). The recovery of radioactivity in the ether extract was about 97% (decay corrected). An aliquot of the extract (20 μL) was injected onto a HPLC column (ERC-silica-1282, ERMA Optical Works Ltd., detectors: refractive index and radioactivity) using n-hexane - ethyl acetate (1:1) as the mobile phase at a flow rate of 1 mL/min. The chromatogram showed the presence of four radioactive peaks(Fig. 2). The first two peaks had $R_t$ (8.8 and 9.5 min) of authentic tetraacetate of 2-FDG and the third peak having a $R_t$ of 10.8 min corresponded to 3,4-di-O-acetyl-1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose. In addition, a small radioactive peak ( <0.5%) eluted at $R_t$ of 12.4 min was identified as 1,3,4,6-tetra-O-acetyl-2-deoxy-2-[$^{18}$F]fluoro-D-mannopyranose by comparison with authentic sample.

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