

RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

The Synthesis of 2-[F-18]Fluoro-2-Deoxy-D-Glucose Using Glycals:
A Reexamination

Gerald T. Bida, Nagichettiar Satyamurthy, and Jorge R. Barrio

University of California, Los Angeles, Los Angeles, California

The reaction of [F-18]F₂ with D-glucal in water proceeds sufficiently mildly at room temperature to present marked regioselectivity. After hydrolysis, analysis by Fourier-transform ¹⁹F-NMR showed the product to consist of a mixture of 2-fluoro-2-deoxy-D-glucose (2-FDG) and 2-fluoro-2-deoxy-D-mannose (2-FDM) in a 2:1 ratio, respectively. The presence of the mannose isomer has been revealed by extension of the ¹⁹F-NMR analyses to other literature methods for 2-FDG synthesis involving the electrophilic fluorinating agent acetyl hypofluorite. Reaction of acetyl [F-18] hypofluorite, prepared by the reaction of [F-18]F₂ with solid sodium acetate trihydrate, with the appropriate glycal/solvent combination, followed by hydrolysis, has led to production of [F-18]2-FDG with a radiochemical purity of 95%.

J Nucl Med 25: 1327-1334, 1984

Fluorine-18 - labeled - 2-fluoro-2-deoxy-D-glucose ([F-18]2-FDG) has persisted as the most important radiopharmaceutical for studying local organ metabolism by positron tomography. This has dictated the need to investigate alternative syntheses, with the ultimate objectives of providing higher radiochemical yields, while at the same time reducing overall synthesis time and the complexity of the processing system. Similar objectives have been the subject of other recent reports on the synthesis of radiolabeled 2-FDG by means of electrophilic (1-8) or nucleophilic (9,10) fluorination. Our efforts to improve the synthesis of 2-FDG have included nucleophilic displacement on 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-C-nitro-D-mannitol with fluoride ion (11-13), and electrophilic fluorination of D-glucal in aqueous media with elemental fluorine (14).

Generally, reactions of elemental fluorine with organic compounds are conducted in inert organic solvents (15). Fluorinations in aqueous media are relatively uncom-

mon due to the belief that the reaction between fluorine and water is violent and difficult to control. [Examples of fluorinations in aqueous media are restricted to the preparation of N-F compounds and α -fluorination of certain nitro derivatives (16)]. A recent estimate of the reaction rate between fluorine and water at 1°C (17), and the relatively low concentrations of F₂ in inert gas (18,19) normally used in the preparation of [F-18]2-FDG, suggested the possibility of using molecular fluorine in aqueous solution as a fluorinating agent. Other observations regarding aqueous fluorinations lend additional support to the potential synthetic utility of this approach (20,21).

The reaction between F₂ and D-glucal in water revealed that the reaction is indeed regioselective for fluorine addition but shows limited stereospecificity. During the course of our investigation, the results of the reaction between aqueous D-glucal and the milder, and reportedly highly stereospecific (1-5,22), fluorinating agent acetyl hypofluorite (AcOF) were published (1), as were the results for the F₂/aqueous D-glucal reaction (23). Fluorine-19 NMR product analysis for this reaction prompted us to investigate thoroughly the behavior of F₂ and AcOF for 2-FDG production under a variety of

Received July 24, 1984; revision accepted Sept. 17, 1984.

For reprints contact: Gerald T. Bida, PhD, UCLA School of Medicine, Dept. of Radiological Sciences, Division of Biophysics, Los Angeles, CA.

experimental conditions. Results of a similar study that used HPLC for isomer analysis have recently been reported (24). The purposes of this paper, then, can be summarized as follows: (a) to report the first regio- and stereoselective addition of fluorine across a double bond in aqueous media; (b) to present data 1) showing that under certain conditions molecular fluorine is more stereoselective than AcOF and, that provokes some 2) discussion about the extent or degree of stereoselectivity of AcOF; (c) to discuss, by way of our results for product analyses through ^{19}F -NMR, the appropriateness of choice in analytical methods for 2-FDG (and similar) identification; and (d) to suggest what we believe, on the basis of our results, to be the correct avenues to pursue in finally achieving the above-mentioned objectives in the synthesis of [F-18]2-FDG.

MATERIALS AND METHODS

3,4,6-Tri-*O*-acetyl-D-glucal (TAG), acetic acid, and sodium acetate trihydrate ($\text{NaOAc}\cdot 3\text{H}_2\text{O}$) were obtained commercially and used without further purification. For the production of [F-18] F_2 , research-grade neon (>99.999%) and 1% fluorine in neon (research grade) were purchased commercially and used as received. D-Glucal was prepared as reported in the literature (25).

Electrophilic additions with D-glucal in aqueous media. [F-18] F_2 (Method A). Fluorine-18 labeled F_2 was produced by the $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$ nuclear reaction by deuteron irradiation (9.4 MeV on target, at 30 μA for 1 hr) of 0.2% fluorine in neon at a pressure of 1.37 MPa (200 psia) contained in a nickel target chamber of 190 ml volume. Fluorine-18 F_2 was bubbled (flow rate = 150 ml/min) into a Teflon reaction vessel containing an aqueous solution (2 ml) of D-glucal (40 mg, 0.27 mmol) at room temperature. Any unreacted fluorine leaving the reaction mixture was trapped in soda lime while the F-18-labeled inert-gas fraction (26) was trapped in an activated-charcoal reservoir. The resultant fluorinated product mixture was hydrolyzed in the teflon reaction vessel with 1.0 *N* HCl at 120° for ~15 min. The solution was then transferred to a column packed with AG 11A8 resin (50–100 mesh),* neutral alumina, and AG 11A8 resin, which was previously equilibrated with water (18). After the solution transfer, the reaction vessel was rinsed with water (3 \times 3 ml) onto the column, and the eluted solution collected for analysis. For those experiments in which the pH of the initial aqueous D-glucal solution was varied, HCl, acetic acid, or potassium carbonate was used.

[F-18]AcOF generated in the gas phase from $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (Method B). [Fluorine-18]AcOF was generated by passing [F-18] F_2 , prepared as described above, through a 5 mm i.d. \times 35 mm cartridge containing powdered $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (340 mg). The effluent from

the cartridge was bubbled (flow rate 150 ml/min) into a teflon reaction vessel containing D-glucal (40 mg, 0.27 mmol) in water (2 ml), and the reaction was continued as described for Method A, above.

[F-18]AcOF generated in the gas phase from KOAc/HOAc (1:1.5) (Method C). [Fluorine-18]AcOF was prepared as described in the literature (1,27,28) using a mixture of KOAc/HOAc (1:1.5) and reacted with D-glucal as described for Method B, above.

Electrophilic addition with 3,4,6-tri-*O*-acetyl-D-glucal in CFCl_3 with [F-18]AcOF generated in the gas phase from $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (Method D). Fluorine-18 AcOF, prepared as described above for Method B, was bubbled into a glass reaction vessel containing 45–50 mg (165–184 μmol) of TAG in 20 ml of CFCl_3 at room temperature. The effluent leaving the reaction vessel was trapped in soda lime followed by activated charcoal. After discharge of the target gas and helium flush of the target chamber, the fluorinated crude product solution was transferred under nitrogen pressure to a 5-ml tapered glass vessel kept at 60°C. The reaction vessel was rinsed with two 10-ml portions of CFCl_3 , which were then transferred to the tapered vessel. One ml of 1.0 *N* HCl was added to the residue and heated in an oil bath at 125°C for 20 min. The hydrolyzed mixture was then transferred onto the top of a column of ion-retardation resin/alumina column (see description above) previously equilibrated with water. The hydrolysis vessel was rinsed with two 4.0-ml portions of water onto the column, and the [F-18]2-FDG eluted from the column passed through a C-18 Sep-pak cartridge, which had been washed with 3 ml of absolute ethanol followed by 10 ml of sterile water into a vial containing 90 mg of NaCl. The resulting isotonic solution (pH \approx 7.0) was finally sterilized by passage through a Millipore filter (0.22 μm) into a sterile 10-ml multi-injection vial.

Electrophilic additions with 3,4,6-tri-*O*-acetyl-D-glucal in HOAc. For the purpose of this comparative investigation, the reported literature procedures were followed for the reaction of [F-18]AcOF, generated in the gas phase from KOAc/HOAc (1:1.5), with TAG in HOAc (Method E) (27,28) and for the reaction of [F-18]AcOF, generated in solution phase, with TAG in HOAc (Method F) (4).

Product identification and analysis. Fluorine-19 NMR spectra (proton-coupled, gated decoupled, and broadband proton-decoupled) were recorded on a spectrometer operating at 470.56 MHz, equipped with computer. All F-18-labeled samples were allowed to decay before NMR analysis. Samples were dissolved in D_2O , and deuterium in the solvent was used for field stabilization. The F-19 shifts were referenced to an external sample of hexafluorobenzene contained in a concentric capillary. All spectra were obtained by the Fourier-transform (FT) technique; relative ratios of the products observed were calculated from the electronically integrated peak areas.

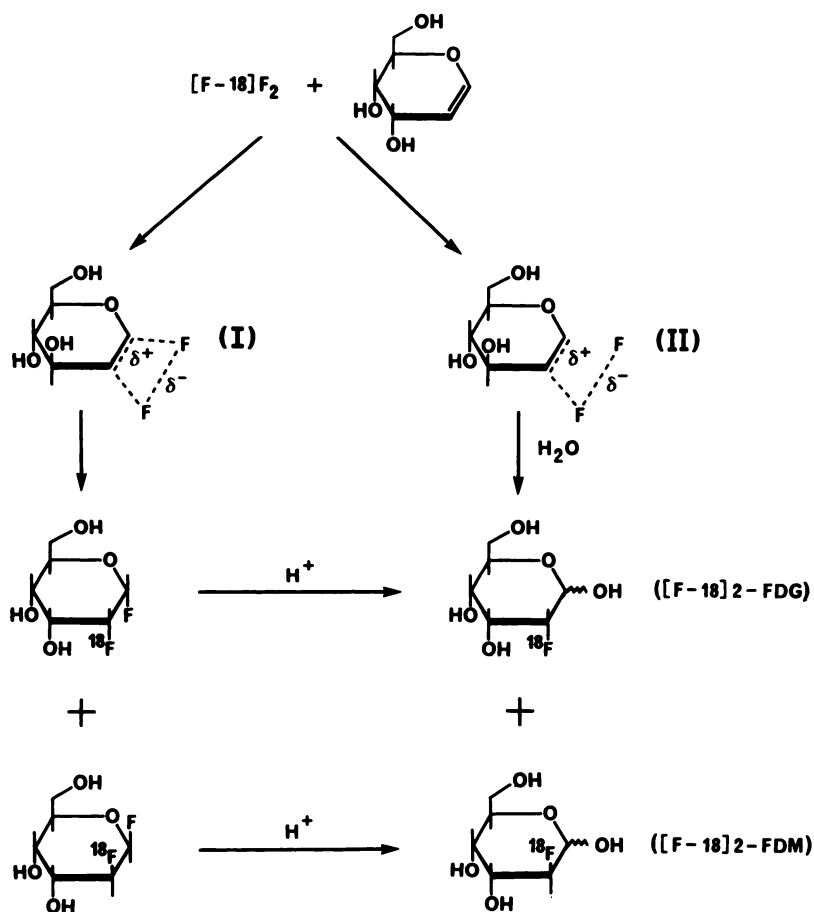


FIG. 1. Scheme and possible intermediates (30,31) for reaction of $[F-18]F_2$ with D-glucal.

Gated proton-decoupled ^{19}F -NMR spectra were obtained by computer-controlled gating of the 1H radiofrequency, and the typical 90° pulse widths were 12–15 μs for a 5-mm insert. In acquiring the $^{19}F \{^1H\}$ data, a delay time of 2–10 sec between each accumulation was used. Broad-band proton decoupling was centered at about $\delta -5.0$ referenced to tetramethylsilane in the proton spectrum. Sixteen to 64 pulses were acquired for each spectrum with a spectral window of 30,000 Hz, to give spectra with excellent signal-to-noise ratio. All spectra were recorded at $25 \pm 1^\circ C$.

Assay of the final product by TLC was done using silica gel sheets[†] developed with the following solvent systems: System A: acetonitrile/water (95:5), R_f of 2-FDG = 0.37; System B: acetonitrile/water (85:15), R_f of 2-FDG = 0.46; System C: *n*-butanol/acetic acid/water (5:1:1), R_f of 2-FDG = 0.50.

RESULTS AND DISCUSSION

Reaction of $[F-18]F_2$ with aqueous D-glucal (Method A). When F-18-labeled F_2 in neon was bubbled into an aqueous solution of D-glucal at room temperature, TLC analysis (Systems A, B, and C) of the fluorinated crude product mixture showed two peaks, one having an R_f value consistent with that reported for 2-fluorodeoxyhexoses (18,29), and the other tentatively identified as

the difluoro adduct(s) 2-fluoro-2-deoxy-D-hexopyranosyl fluoride. The reaction scheme is summarized in Fig. 1. The identification of the difluoro adduct(s) has been inferred from its chemical reactivity. When a portion of the column eluant (above) was hydrolyzed and again analyzed by TLC (solvent Systems A and B), the chromatogram showed only two peaks, one due to fluoride ion and the other having an R_f value consistent with the 2-fluorodeoxyhexose(s). These are the anticipated products from the hydrolysis of the difluoro adduct(s) (18,29). Also, an increase in the amount of 2-fluorodeoxyhexose concomitant with the disappearance of the difluoro compound was observed. Our inability to effect a TLC separation of 2-FDM from 2-FDG, or their corresponding difluoro adduct precursors, using solvent Systems A through C prevented us initially from performing an unequivocal identification of the 2-fluorodeoxyhexose(s) produced in the reaction.

After the addition of fluorine, hydrolysis of the crude reaction mixture followed by chromatographic purification (18) gave a single peak, as shown by TLC (Fig. 2, solvent System A). Subsequent product analyses were performed using ^{19}F -NMR. Other methods for product identification, e.g., gas-liquid chromatography (GLC), were not pursued for reasons to be discussed later.

Figure 3 shows a typical FT ^{19}F -NMR spectrum of the product resulting from the reaction between molec-

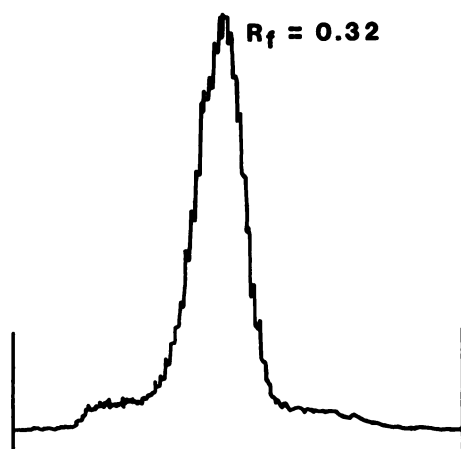


FIG. 2. Radio-TLC profile of product mixture after hydrolysis and purification for reaction of $[F-18]F_2$ with aqueous D-glucal (solvent system, acetonitrile/water (95:5)).

ular fluorine and aqueous D-glucal, after the hydrolysis and purification steps. From the observed chemical shifts, the products are identified as 2-FDG and 2-FDM by comparison (a) with authentic samples [2-FDG: δ +32.85 ppm (α -anomer) and +32.70 ppm (β -anomer); 2-FDM: δ +38.21 ppm (α -anomer) and +56.59 ppm (β -anomer), and (b) with literature values [2-FDG: δ +32.51 ppm (α -anomer) and +32.33 ppm (β -anomer); 2-FDM: δ +37.84 ppm (α -anomer) and +56.32 ppm (β -anomer)] (32). The chemical shifts found for 2-FDG were: α -anomer = δ +32.73 ppm, β -anomer = δ +32.60 ppm; and for 2-FDM: α -anomer = δ +38.08 ppm, β -anomer = δ +56.51 ppm. Further, the percentages of the two fluorosugar isomers determined by NMR peak integration were 65.4 (\pm 9.8)% for 2-FDG and 34.6 (\pm 9.8)% for 2-FDM. The ratio of 2-FDG to 2-FDM formed was found to be insensitive to the reaction temperature (up to 70°C) and pH (0.7 to 9.0; see Table 1).

Concerning the synthesis of $[F-18]2$ -FDG, the partial stereospecificity of the reaction between molecular fluorine and D-glucal in aqueous media limits its application at the present time. However, the reaction is attractive in light of its simplicity, short processing time (\sim 30 min after EOB), and good radiochemical yield (\sim 30%), and awaits the development of effective chromatographic

procedures for separation of the two epimers. In addition, this work demonstrates that carbon-carbon double-bond addition on D-glucal with fluorine in aqueous media is sufficiently mild at room temperature to present marked regiospecificity. This, in a more general context, shows the feasibility of fluorination reactions with elemental fluorine in aqueous media. Understandably, the general applicability of aqueous fluorination reactions as a synthetic tool depends largely upon the ability of the organic substrate to react with fluorine before it reacts with the solvent.

The reason(s) for the moderately predominant formation of the deoxyfluoro sugars (2-FDG and 2-FDM) over the difluoro compounds formed before hydrolysis (Fig. 1) is not clear. The fact that fluorine reacts directly with D-glucal in water is evidenced by the formation of the $[F-18]$ difluorohexoses. However, it is not clear whether formation of the 2-fluorodeoxyhexoses involves the intermediate HOF (20) or, more probably, a transition state intermediate (Fig. 1, I and II), which could be intercepted by the nucleophilic solvent water and the reaction diverted to form the 2-fluorodeoxyhexoses.

Other 2-FDG syntheses involving F_2 or AcOF (Methods B through F). From reports in the literature concerning the regio- and stereoselective nature of AcOF (1-5,27,33), it was anticipated that the ^{19}F -NMR data for the product from the AcOF/aqueous D-glucal reaction (Method C) would be consistent with the chromatographic data reported (1). However, based on the ^{19}F -NMR results for this particular reaction, we felt it imperative to investigate other existing literature methods for 2-FDG synthesis from F_2 or AcOF in order to determine the product distribution for these electrophilic fluorinations. The results of the final product analyses by FT ^{19}F -NMR for the various methods investigated are summarized in Table 2. Similar results for Methods C and F have been reported using HPLC to analyze the isomeric mixture (24).

Analysis of the product distribution for the reactions given in Table 2 points to the conclusion that stereochemical control of the carbon-carbon double-bond addition reaction depends largely upon (a) solvent polarity, (b) nature of the fluorinating agent, and (c) structure of the substrate. For example, for a statistically

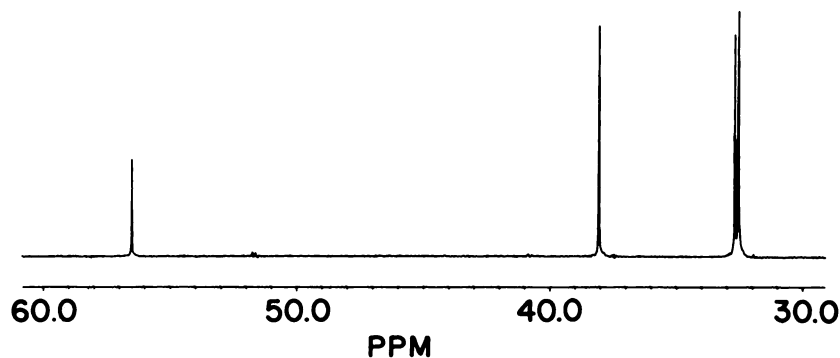


FIG. 3. ^{19}F -NMR spectrum of product mixture after hydrolysis and purification for reaction of $[F-18]F_2$ with aqueous D-glucal (Method A).

TABLE 1. EFFECT OF pH AND TEMPERATURE ON THE 2-FLUORO-2-DEOXYHEXOSE RATIO FOR THE [F-18]F₂ + AQUEOUS D-GLUCAL REACTION

| Experiment no. | pH | Temperature | % of 2-Fluoro-2-Deoxyhexoses* | |
|----------------|---------|-------------|-------------------------------|-------|
| | | | 2-FDG | 2-FDM |
| 1-6 | 8.7-9.0 | 25°C | 65.2 | 34.8† |
| 7 | 4.8 | 25°C | 68.0 | 32.0 |
| 8 | 0.7 | 25°C | 65.0 | 35.0 |
| 9 | 9.0 | 70°C | 65.0 | 35.0 |

* Determined by ¹⁹F-NMR.

† Average of 6 experiments.

significant number of experiments (n ≥ 5), F₂ is found to be more stereoselective than AcOF in its reaction with D-glucal in water (Methods A and C, respectively). This stereochemical specificity may arise from the thermodynamic stabilities of the transition-state intermediates, requiring solvent participation and leading to the different 2-fluorodeoxyhexoses.

It is anticipated that the nature of the glycal substrate will also affect the glucose-to-mannose ratio because of steric hindrance and inductive effects. Indeed, the effect of such factors has been observed (3,4). For instance, F₂ addition to D-glucal in water (Method A) is observed to be more stereospecific than AcOF addition with the same glycal/solvent combination (Methods B and C, Table 2). However, F₂ addition to TAG in CFCl₃ produces a mixture of 2-fluorogluco- and 2-fluoromannopyranosyl isomers in a 3:1 ratio (29,34), whereas AcOF addition (Method D) shows marked stereospecificity (2-FDG: 2-FDM ~20:1). Furthermore, and as an indication that the glucose-to-mannose ratio may be affected

by solvent polarity, the use of HOAc as a solvent in this reaction reduces the percentage of 2-FDG from 95% (Method D) to ~80% (Methods E and F). In fact, based on these ¹⁹F-NMR data, Method D represents the most appropriate choice of fluorinating agent, glycal substrate, and solvent for the production of 2-FDG. For most purposes the radiochemical purity of the final product (95%) may be considered sufficient, and thus the procedure can become a one-pot reaction. However, if required, epimerically pure [F-18]2-FDG can easily be obtained by chromatographic separation of the unwanted 2-fluoro-2-deoxy-tetra-O-acetylmannopyranose formed by reaction of AcOF with TAG, and subsequent hydrolysis of the glucopyranose isomer (3). Using this procedure, [F-18]2-FDG was synthesized with a radiochemical yield of 15-20%, based on the F-18 activity recovered from the target, in 60 min from EOB. The specific activity of the [F-18]2-FDG was 2.0-2.2 Ci/mmol at EOB.

Synthesis of [F-18]AcOF from NaOAc·3H₂O. The

TABLE 2. SUMMARY OF 2-FLUORO-2-DEOXYHEXOSE PERCENTAGES AS DETERMINED BY ¹⁹F-NMR AND CHROMATOGRAPHY FOR VARIOUS 2-FDG SYNTHESSES

| Method designation | Percentages of 2-Fluoro-2-Deoxyhexoses | | | |
|--------------------|--|-------------|---|-------|
| | From ¹⁹ F-NMR* (this work) | | From chromatographic procedures (previous work) | |
| | 2-FDG | 2-FDM | 2-FDG | 2-FDM |
| A | 65.4 (±9.8) | 34.6 (±9.8) | — | — |
| B | 46.0 | 54.0 | — | — |
| C | 44.4 (±4.6) | 55.6 (±4.6) | >99† | — |
| D | 95.0‡ | 5.0 | — | — |
| E | 81.3 | 18.7 | 86.2§ | 13.8 |
| F | 81.5 | 18.5 | >98¶ | — |

* For Methods A and C, the percentages are given as the mean (±2 s.d.); for all others, the percentages are the average of 2-4 experiments. The radiochemical yields for the reactions ranged between 15 and 40%.

† Percentage of [F-18]2-FDG as determined by radio-TLC and -HPLC (1).

‡ Essentially identical results were obtained with AcOF generated from NaOAc·3H₂O or KOAc/HOAc (1.0:1.5).

§ Anticipated percentages from hydrolysis of tetra-O-acetyl-2-fluorohexoses identified by GLC (27).

¶ Percentage of [F-18]2-FDG as determined by radio-TLC, -HPLC, -GLC, and by proton NMR (4).

exact mechanism for the preparation of certain acyl- and perfluoroacyl hypofluorites does not appear to be completely understood, but the presence of water seems to play a crucial role in their synthesis. For example, it has been observed that the yield of trifluoroacetyl hypofluorite (CF_3COOF) from the gas-phase fluorination of trifluoroacetic acid is markedly increased in the presence of water vapor (35). In an alternative solution-phase synthesis (36), water again is found to be necessary for formation of CF_3COOF . Apparently, solvation of the alkali metal fluoride formed in these reactions prevents nucleophilic attack of the carbonyl group, which then leads to formation of unstable species (22,36). It is not clear whether water plays a role in the gas/solution phase synthesis of AcOF (22), but in the synthesis of 2-FDG from AcOF prepared in solution (4) (Method F), its presence does not appear detrimental. For these reasons, and with the information provided on the reaction of F_2 with water (17), we investigated the possibility of generating AcOF by passing a stream of dilute F_2 (in inert gas) through a cartridge containing finely divided $\text{NaOAc}\cdot 3\text{H}_2\text{O}$. Consistent with the formation of AcOF by this method is the ^{19}F -NMR data for the adduct prepared with tetrachloroethylene.

From our experimental observations and those of others (4,35,36), we conclude that rigorous exclusion of moisture in a gas/solid phase synthesis of AcOF is unnecessary. While we have not pursued a mechanistic investigation, water—or some other nonreactive polar solvent such as acetic acid—may be necessary for AcOF formation in the reaction of F_2 with alkali acetate salts (22,28). Indeed, we have observed that passage of a dilute $[\text{F-18}]\text{F}_2$ stream through anhydrous KOAc results in almost complete retention of activity in the acetate salt. Even generation of AcOF from a KOAc/HOAc mixture can tolerate the presence of some moisture (28). This synthesis of AcOF, then, from the reaction of F_2 with an off-the-shelf reagent, $\text{NaOAc}\cdot 3\text{H}_2\text{O}$, is the easiest method yet reported for the synthesis of this versatile fluorinating agent.

The analytical method: Fourier transform ^{19}F -NMR. The selection of FT ^{19}F -NMR as the analytical method of choice was dictated by several considerations. The importance of FT-NMR as one of the most powerful tools for chemical analysis, yielding both characterization and quantification of the product, is well established. Furthermore, given the large F-19 chemical shift differences observed between 2-FDG and 2-FDM (32), ^{19}F -NMR precludes any potential ambiguities that might be encountered during an attempt to effect a good separation of carbohydrate isomers by chromatographic techniques. In this regard, we note the following:

1. With the TLC solvent systems normally reported in the literature for 2-FDG product analysis—i.e., solvent Systems A, B, and C (see Materials and Methods section)—we were unable to achieve any satisfactory

separation of 2-FDG from 2-FDM.

2. While GLC has been extensively used for qualitative and quantitative analyses, it is not immediately apparent why such a large difference in the 2-FDG-to-2-FDM ratio exists between reported analytical procedures (1,4) and these NMR results. In the case of GLC, it is possible that the trimethylsilyl derivatives of the carbohydrates could undergo thermal decomposition in the GLC column due to the high temperature required for analytical separations [as an example, see footnote (14) of Ref. (34)].

In order to ensure accurate quantitative results, heteronuclear spin-spin decoupling of the proton spins from those of fluorine by application of gated decoupling was used. Gated decoupling is commonly applied in FT-NMR in order to suppress enhancement of signal intensity due to the Nuclear Overhauser Effect (NOE) (37,38). How quantitative NMR measurements are affected by NOE is discussed elsewhere (37,39). Nondecoupled and broadband proton-decoupled spectra were obtained and compared with the gated decoupled spectrum, all for the same sample. Within the experimental limits of the peak integration, the same quantitative results were observed for all three cases.

SUMMARY

The results of this investigation have provided us with some important new information regarding (a) the chemical reactivity of F_2 in aqueous media and (b) the factors affecting the stereospecific nature of the two most common electrophilic fluorinating agents (F_2 and AcOF) used in 2-FDG synthesis. Firstly, the demonstration that addition reactions with elemental fluorine can be conducted in water will help foster additional pursuit of aqueous fluorination as a general synthetic method heretofore ignored because of a lack of sufficient understanding of the fluorine/water reaction mechanism. Secondly, the use of FT ^{19}F -NMR spectroscopy for product analysis has led to the following conclusions important to the synthesis of $[\text{F-18}]\text{2-FDG}$:

1. Because of the difficulties that still prevail for the efficient separation of 2-FDG and 2-FDM by chromatography, and the large F-19 chemical shifts observed for these species, the usefulness of a spectroscopic technique such as ^{19}F -NMR for correct product identification and quantification is clearly evident. Indeed, we believe that the reaction products of various methods for making radiolabeled 2-FDG should be analyzed by ^{19}F -NMR in the experimental stage itself, before implementing the full-scale production for human or animal applications. It is obvious, however, that routine analysis of the radiopharmaceutical preparations requires the development of simple and dependable chromatographic techniques.

2. The NMR data have shown that AcOF does not

react with D-glucal in water with any degree of significant stereospecificity.

3. The reaction of AcOF with TAG in a nonpolar medium such as CFCl_3 does proceed almost exclusively in a stereospecific manner. Even though the maximum radiochemical yield remains at 50%, the attractive features of this method are the facile generation of the electrophile, together with guaranteed provision of [F-18]2-FDG of high epimeric purity.

FOOTNOTES

* Eastman Chromagram Sheets 6061.

† Bio-Rad.

ACKNOWLEDGMENTS

The authors thank Dr. J. Yesinowski and his staff of 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. The authors also thank Dr. T. Ogawa (Riken, Tokyo, Japan) for an authentic sample of 2-fluoro-2-deoxy-D-mannose and 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-AM03-76-SF00012, NINCDS Grant No. P01-NS 15654 and NIMH Grant No. 1 R01 MH 37916.

REFERENCES

1. EHRENKAUFER RE, POTOCKI JF, JEWETT DM: Simple synthesis of F-18-labeled 2-fluoro-2-deoxy-D-glucose: Concise communication. *J Nucl Med* 25:333-337, 1984
2. ADAM MJ: A rapid, stereoselective, high yielding synthesis of 2-deoxy-2-fluoro-D-hexopyranoses: Reaction of glycols with acetyl hypofluorite. *JCS Chem Commun* 730-731, 1982.
3. ADAM MJ, PATE BD, NESSER J-R, et al: A rapid, stereoselective synthesis of fluorinated carbohydrates: Addition of acetyl hypofluorite to vinyl ether derivatives of sugars. *Carbohydr Res* 124:215-224, 1983
4. SHIUE C-Y, SALVADORI PA, WOLF AP, et al: A new improved synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose from ^{18}F -labeled acetyl hypofluorite. *J Nucl Med* 23:899-903, 1982
5. DIKSIC M, JOLLY D: New high-yield synthesis of ^{18}F -labeled 2-deoxy-2-fluoro-D-glucose. *Int J Appl Radiat Isot* 34:893-896, 1983
6. KORYTNYK W, VALENTEKOVIC-HORVAT S: Reactions of glycols with xenon difluoride: An improved synthesis of 2-deoxy-2-fluorosaccharides. *Tet Lett* 21:1493-1496, 1980
7. SHIUE C-Y, TO K-C, WOLF AP: A rapid synthesis of 2-deoxy-2-fluoro-D-glucose from xenon difluoride suitable for labelling with ^{18}F . *J Label Comp Radiopharm* 20:157-162, 1983
8. SOOD S, FIRNAU G, GARNETT ES: Radiofluorination with xenon difluoride: A new high yield synthesis of [^{18}F]2-fluoro-2-deoxy-D-glucose. *Int J Appl Radiat Isot* 34:743-745, 1983
9. TEWSON T: Synthesis of no-carrier-added fluorine-18 2-fluoro-2-deoxy-D-glucose. *J Nucl Med* 24:718-721, 1983
10. LEVY S, ELMALEH DR, LIVNI E: A new method using anhydrous [^{18}F]fluoride to radiolabel 2-[^{18}F]fluoro-2-deoxy-D-glucose. *J Nucl Med* 23:918-922, 1982
11. SZAREK WA, HAY GW, PERLMUTTER MM: A rapid, stereospecific synthesis of 2-deoxy-2-fluoro-D-glucose using the fluoride ion. *Chem Commun* 1253-1254, 1982
12. BARRIO JR, BIDA G, SATYAMURTHY N, et al: A minicyclotron based technology for the production of positron emitting labelled radiopharmaceuticals. In *The Metabolism of the Human Brain Studied with Positron Emission Tomography*, Widen L, ed., New York, Raven Press: in press
13. BIDA GT, SATYAMURTHY N, PADGETT HC, et al: [F-18]2-deoxy-2-fluoro-D-glucose: New approaches involving nucleophilic and electrophilic fluorination. Abstracts of the 5th International Symposium on Radiopharmaceutical Chemistry, Tokyo, Japan, 1984, p 213
14. BIDA GT, SATYAMURTHY N, BARRIO JR: Fluorination in aqueous media with elemental fluorine. The synthesis of [F-18]2-FDG. *J Nucl Med* 25:P125, 1984 (abstr)
15. HUDLICKY M: *Chemistry of Organic Fluorine Compounds*. London, Ellis Horwood Limited, 1976
16. SHARTS CM, SHEPPARD WA: Modern methods to prepare monofluoroaliphatic compounds. *Org React* 21:125-406, 1974
17. APPELMAN EH, THOMPSON RC: Studies of the aqueous chemistry of fluorine and hypofluorous acid. *J Amer Chem Soc* 106:4167-4172, 1984
18. BARRIO JR, MACDONALD NS, ROBINSON GD, et al: Remote, semiautomated production of F-18-labeled 2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 22:372-375, 1981
19. CASELLA V, IDO T, WOLF AP, et al: Anhydrous F-18 labeled fluorine for radiopharmaceutical preparation. *J Nucl Med* 21:750-757, 1980
20. THOMPSON RC, APPELMAN EH, SULLIVAN JC: Reaction of fluorine and hypofluorous acid with some substitution-inert complex ions in aqueous perchloric acid solutions. *Inorg Chem* 16:2921-2926, 1977
21. LAGOW RJ, MARGRAVE JL: Direct fluorination: A "new" approach to fluorine chemistry. In *Progress in Inorganic Chemistry*, Vol 26, Lippard SJ, ed. New York, John Wiley & Sons, 1979, pp 162-200
22. ROZEN S, LERMAN O, KOL M: Acetyl hypofluorite, the first member of a new family of organic compounds. *Chem Commun* 443-444, 1981
23. JEWETT DM, POTOCKI JF, EHRENKAUFER RE: Aqueous-phase electrophilic fluorination of F-18 labeled radiopharmaceuticals. Abstracts of 187th ACS National Meeting, NUCL 58, St. Louis, MO, 1984
24. HERSCHIED JDM, VAN RIJN CJS, VISSER GWM, et al: Is the addition of [^{18}F]acetyl hypofluorite to glucals really stereoselective? Abstracts of the 5th International Symposium on Radiopharmaceutical Chemistry, Tokyo, Japan, 1984, p 209
25. FRASER-REID B, WALKER DL, TAM S Y-K, et al: A rapid route to hex-1-enopyran-3-uloses. *Can J Chem* 51:3950-3954, 1973
26. BIDA GT, EHRENKAUFER RL, WOLF AP, et al: The effect of target-gas purity on the chemical form of F-18 during ^{18}F - F_2 production using the neon/fluorine target. *J Nucl Med* 21:758-762, 1980
27. JEWETT DM, POTOCKI JF, EHRENKAUFER RE: A preparative gas-solid-phase synthesis of acetyl hypofluorite. *Synth Commun* 14:45-51, 1984
28. JEWETT DM, POTOCKI JF, EHRENKAUFER RE: A gas-solid-phase microchemical method for the synthesis of acetyl hypofluorite. *J Fluor Chem* 24:477-484, 1984
29. IDO T, WAN C-N, CASELLA V, et al: Labeled 2-deoxy-D-glucose analogs. ^{18}F -labeled 2-deoxy-2-fluoro-D-glucose,

- 2-deoxy-2-fluoro-D-mannose and ^{14}C -2-deoxy-2-fluoro-D-glucose. *J Label Comp Radiopharm* 14:175-183, 1978
30. MERRITT RF: The polar fluorination of propenylbenzene. *J Amer Chem Soc* 89:609-612, 1967
31. MERRITT RF: The polar addition of molecular fluorine to acetylenes. *J Org Chem* 32:4124-4126, 1967
32. PHILLIPS L, WRAY V: Stereospecific electronegative effects. Part I. The ^{19}F nuclear magnetic resonance spectra of deoxyfluoro-D-glucopyranoses. *J Chem Soc (B)*:1618-1624, 1971
33. VISSER GWM, v HALTEREN BW, HERSCHIED JDM, et al: Reaction of acetyl hypofluorite with aromatic mercury compounds: A new selective fluorination method. *Chem Commun* 655-656, 1984
34. IDO T, WAN C-N, FOWLER JS, et al: Fluorination with F_2 . A convenient synthesis of 2-deoxy-2-fluoro-D-glucose. *J Org Chem* 42:2341-2342, 1977
35. GARD GL, CADY GH: Role of water in the reaction of fluorine with trifluoroacetic acid to produce trifluoroacetyl hypofluorite. *Inorg Chem* 4:594-596, 1965
36. ROZEN S, LERMAN O: Synthesis and chemistry of trifluoroacetyl hypofluorite with elemental fluorine. A novel method for synthesis of α -fluorohydrins. *J Org Chem* 45:672-678, 1980
37. BECKER ED: *High Resolution NMR. Theory and Chemical Applications*. New York, Academic Press, Inc., 1980, pp 206-208
38. NOGGLE JH, SCHIRMER RE: *The Nuclear Overhauser Effect. Chemical Applications*. New York, Academic Press, Inc., 1971
39. SHOOLERY JN: Some quantitative applications of ^{13}C NMR spectroscopy. *Prog NMR Spectr* 11:79-93, 1977

**SNM Radiopharmaceutical Science Council
Preparation of High Specific Activity Radionuclides for
Labeling Receptor Agents**

January 26, 1985

Las Vegas Riviera Hotel

Las Vegas, Nevada

SNM 4th Conjoint Meeting

Topics will include: fluorine-18, carbon-11, bromine-75, bromine-77 and iodine-123.

Lectures will be presented by:

Timothy Tewson, PhD, University of Texas
Joanna Fowler, PhD, Brookhaven National Laboratory
Leonard Mausner, PhD, Brookhaven National Laboratory
Arnold Friedman, PhD, Argonne National Laboratory
Manuel Lagunas-Solar, PhD, Crocker Nuclear Laboratory
Iain Trevena, PhD, Atomic Energy of Canada

For more information write:

Harold O'Brien, PhD
Los Alamos National Laboratory
CN-3, Mail Stop 514
Los Alamos, NM 87544
(505) 667-4675

DISTINGUISHED EDUCATOR AWARD

The Society of Nuclear Medicine Awards Committee is accepting nominations of individuals as possible recipients of the Distinguished Educator Award. This award is given to an individual recognized for outstanding contributions in the area of nuclear medicine education. Nominations should be supported by a curriculum vitae of the nominee and at least two (2) letters of nomination. These letters should describe briefly the contribution the nominee has made to nuclear medicine education. Although preferable, membership in the Society is not mandatory.

Please submit nominations and supporting documents to:

Leonard M. Freeman, M.D.
Society of Nuclear Medicine
475 Park Avenue South
New York, NY 10016

Deadline for nominations is December 31, 1984.