Fluorine-18-Labeled Diethylaminosulfur Trifluoride (DAST): An F-for-OH Fluorinating Agent

Maria G. Straatmann and Michael J. Welch

Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

A new fluorinating agent was developed by incorporation of ^{18}F into diethylaminosulfur trifluoride (DAST), a reagent capable of replacing hydroxyl and carbonyl oxygen with fluorine. The DAST was synthesized using sulfur tetrafluoride and trimethylsilyldiethylamine in a freon-11 solvent at $-78°C$ and purified by reduced-pressure distillation. Labeling was then accomplished by exchange with anhydrous ^{18}F-hydrofluoric acid, which caused more than 80% of the available activity to be incorporated into the DAST. Fluorine-18-labeled methyl fluoride, ethyl fluoride, and 2-fluoroethanol were prepared from methanol, ethanol, and ethylene glycol, with yields of 20%, 25%, and 12%, respectively.

Interest in the use of radiofluorine for labeling biologic molecules has existed for some time, as its small size and C–F bond strength (107 kcal) render it a good substituent in organic molecules. Since fluorine is not likely to alter the biologic activity of a compound significantly, both F-for-H and F-for-OH substitutions at metabolically inactive sites in a molecule have been suggested (*1*). In size and electronegativity the fluorine atom resembles the hydroxyl group, however (*2*). Of the known isotopes of fluorine, only ^{18}F has a long enough half-life (110 min) to be useful as a tracer. Fluorine-18 is, moreover, a positron-emitter, which permits the use of coincidence detection techniques (*3-5*).

The essential task in a ^{18}F labeling procedure is to contain the highly reactive radiofluorine in a form that allows practical chemistry to be performed. To this end, a number of synthetic precursors incorporating ^{18}F have been developed (*6-9*). These molecules have had varying degrees of success as labeling agents in terms of ease of preparation, labeling yields, and specific activities. In no instance, however, has ^{18}F been attached to a specific F-for-OH synthetic reagent.

Recently, two reports on a family of fluoroalkyl-amine reagents called dialkylaminosulfur trifluorides have appeared in the literature (*10,11*). These re-agents are extremely useful in substituting fluorine for the carbonyl oxygen of aldehydes and ketones, and especially for the hydroxyl groups of sensitive alcohols. Phenolic hydroxyls are included as possible reactants. Primary, secondary, and tertiary alcohols all react with high yields of the unrearranged fluoride. The mild conditions under which these reactions are conducted preclude competition by ester groups or other halogens. When an F-for-OH substitution is made in an alcohol, the resulting product commonly undergoes carbonium-ion rearrangement and/or dehydration. With diethylaminosulfur trifluoride (DAST), these problems are greatly diminished (*11*). In general, fewer rearrangements occur when the fluorination reaction is carried out in an inert nonpolar solvent, although proper use of solvent polarities can lead to fluorinated products otherwise unavailable.
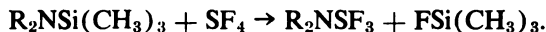
MATERIALS AND METHODS

The unlabeled dialkylaminosulfur trifluorides are prepared in an inert solvent (usually ether or freon-

11) by the dropwise addition of dialkyltrimethyl-silylamine (0.1 M) to a stirred solution of sulfur tetrafluoride (0.12 M) in the same solvent at $-78°C$:

$$R_2NSi(CH_3)_3 + SF_4 \rightarrow R_2NSF_3 + FSi(CH_3)_3.$$

The mixture is allowed to come to room temperature, and the solvent, the byproduct fluorotrimethylsilane (boiling point, 17°C), and excess SF_4 are evaporated. The residue is then distilled at reduced pressure (10,11).

DAST is reported to be a stable product that can be distilled (at 46°C and 10 mm Hg) and stored in a plastic bottle at room temperature. We enhanced the stability by storing the DAST at 0°C. Great care must be taken to avoid contamination with moisture, since large amounts of DAST react explosively with water.

Two approaches were taken to incorporate ^{18}F into DAST: (A) the use of labeled sulfur tetrafluoride, $SF_3{}^{18}F$, for the synthesis of DAST, and (B) the exchange labeling of normal DAST by elemental radiofluorine, $^{18}F^{19}F$, or hydrofluoric acid, $H^{18}F$. Preparation of these precursors is described below.

The synthesis (A) involved the addition of trimethylsilyldiethylamine (TMSDEA), in either freon-11 or methylene chloride, to a glass trap immersed in liquid nitrogen and containing $SF_3{}^{18}F$. The components were allowed to react in a bath of dry ice and acetone at $-78°C$. The resultant mixture was analyzed or, if the experiment included a labeling attempt, the compound to be labeled was added directly to the solution and reaction time allotted.

The exchange labeling (B) was conducted similarly. The ^{18}F precursor was first produced in the cyclotron, trapped in a glass trap in liquid nitrogen, and the DAST added in an appropriate solvent. Exchange was at room temperature. A wide range of solvents was examined for the exchange medium, and compounds to be labeled were introduced into the trap containing the DAST mixture (with $F^{18}F$ or $H^{18}F$) before it was opened. In some cases, the addition of these compounds followed purification of the ^{18}F-DAST by distillation.

To test the effectiveness of DAST as a fluorinating agent, several model compounds were used: ethanol, methanol, ethylene glycol, and, to a limited extent,

heptanol and benzenol. These materials were added and the respective fluorides examined for percent yields. Compounds were chosen on the basis of ease of analysis and availability of authentic samples of the fluorides. In addition, $C_2H_5{}^{18}F$ and ^{18}F-2-fluoro-ethanol can be compared in vivo with the known biologic behavior (12) of ^{11}C-ethanol, and the effect of an ^{18}F substituent evaluated.

PREPARATION AND PROPERTIES OF SF$_4$

Sulfur tetrafluoride is most conveniently synthesized in the laboratory by the reaction of sulfur dichloride with finely divided sodium fluoride at 50–70°C in a polar aprotic medium such as acetonitrile (13):

$$3\,SCl_2 + 4\,NaF \xrightarrow{CH_3CN} SF_4 + S_2Cl_2 + 4\,NaCl.$$
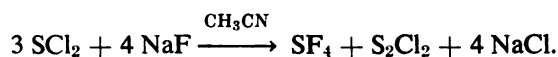
The product commonly contains 5–10% thionyl fluoride as a contaminant.

Stainless steel, copper, and nickel are all inert to SF_4. In addition, it can be manipulated with only nominal attack in well-dried Pyrex glass apparatus up to $\sim30°C$. Sulfur tetrafluoride is hydrolyzed rapidly and exothermally by aqueous media at all pH values (14):

$$SF_4 + H_2O \rightarrow SOF_2 + 2\,HF.$$
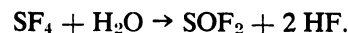
There are direct and indirect approaches to the task of incorporating ^{18}F into the sulfur tetrafluoride molecule. The direct method would be to produce a fluorine precursor that could be used in place of the sodium fluoride in the conventional synthesis of SF_4. Besides being time-consuming (a serious drawback with a short-lived nuclide), such a method involves the purification of extremely small quantities of a highly reactive and water-sensitive material requiring low-temperature distillation.

It seemed more appropriate to attempt to label SF_4 indirectly, by exchange with some form of ^{18}F. Rowland et al. reported the feasibility of producing $SF_3{}^{18}F$ by such a method (15). Both SF_4 and SOF_4 have an empty orbital that is available for easy approach by the ^{18}F atom to the central sulfur atom, permitting thermal fluorine-atom exchange. Accordingly, a mixture of neon and sulfur tetrafluoride was
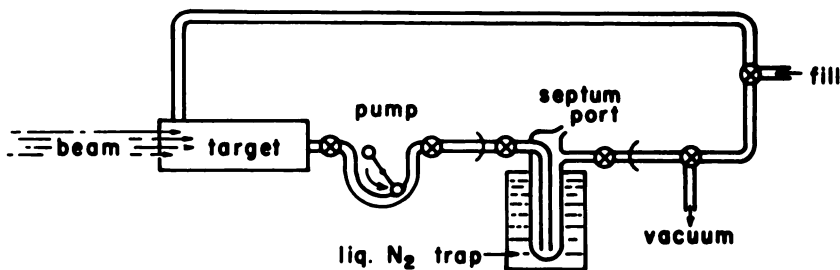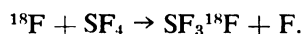

FIG. 1. Schematic diagram of irradiation system including target, pump for circulating bombardments, and glass trap in liquid-nitrogen bath.

bombarded with deuterons $[^{20}Ne(d,\alpha)^{18}F]$ to effect the reaction

$$^{18}F + SF_4 \rightarrow SF_3^{18}F + F.$$

The remaining ^{18}F precursors were prepared (A) by exchange of ^{18}F with elemental fluorine present in a bombardment gas mixture of neon and 1% natural $^{19}F_2$, or (B) by ^{18}F abstraction to form $H^{18}F$ from a bombardment gas mixture of neon containing various percentages of hydrogen.

CYCLOTRON SYSTEM

The ^{18}F for these studies was produced using the $^{20}Ne(d,\alpha)^{18}F$ reaction in the cyclotron of Washington University Medical School, a low-energy machine producing 6–8-MeV deuterons. Although the yield of ^{18}F is low (16), isotopic impurities are minimal and all are short-lived. Because the nascent ^{18}F is exceedingly reactive, the irradiation system requires special materials and construction (see Refs. 7 and 17–19, or contact the authors for details).

The cyclotron system is shown schematically in Fig. 1. A nickel-plated target chamber (later changed to monel) was used with a gas fill line and outlet line of nickel tubing. Valves (Teflon stem) were located on either side of the glass trap so that they could be easily removed from the system. Monel valves on the nickel lines minimized the exposure of the remainder of the system to air (and hence water vapor) in the absence of the trap.

All procedures for $F^{18}F$ or $H^{18}F$ included circulation of the gases during bombardment through the glass trap in a liquid-nitrogen bath. For $SF_3^{18}F$ the cold bath was added at the end of bombardment.

Studies of isotopic purity and decay rate were made after irradiation of two neon mixtures: Ne + 1% F_2 and Ne + 3% SF_4. These were irradiated by a 5-μA/hr integrated beam, gas samples were taken, and half-life determinations made. Counts were recorded with integration times of 10 sec in each case, with the total collection time equal to three half-lives of ^{18}F. Both exhibited a half-life of ~110 min.

In the case of the Ne + 1% F_2 mixture, an energy spectrum was taken using a Ge(Li) detector and multichannel analyzer with times corrected to the end of bombardment. In addition to the 0.511-MeV annihilation peak, a peak at 0.44 MeV indicated ^{23}Ne (half-life, 37.6 sec). Presumably this impurity is formed by the $^{22}Ne(d,p)^{23}Ne$ reaction, ^{22}Ne having a natural abundance of 8.82% (20).

ANALYSIS AND RESULTS

Fluorine-18-labeled sulfur tetrafluoride. All SF_4-production experiments were analyzed by a gas-chromatography instrument* with a 6-ft Poropak Q†

column operated at room temperature. Zero-grade helium‡ was used as the carrier gas, after passing through a H_2O/O_2 absorber. The effluent was passed through a thermal-conductivity detector for mass measurements and then to a flow-through window counter (21) to monitor radioactivity. Efficiency of the counter for ^{18}F was determined relative to other positron-emitters to ascertain percentages of injected activity eluted from the column (22). Retention times of interest are: SF_4, 1.7 min; SF_6, 3.9 min; peak of unknown composition, 5.2 min; and SOF_2, 7.7 min.

Rowland et al. (15) have found it impossible to chromatograph SF_4 owing to hydrolysis reactions with traces of water and hydroxyl groups on the column packing. Injecting large samples (2 cc) of unlabeled SF_4 gas, we observe 60% conversion to SOF_2; presumably this conversion takes place on the column. Thus, even though analyses show large yields of $SOF^{18}F$, assuming similar conversion occurs, one can estimate that the majority of the activity is $SF_3^{18}F$ with $SF_5^{18}F$, some $SOF^{18}F$, and a small amount of an unknown compound as impurities. The Poropak Q column did exhibit a limited lifetime for these analyses (22).

The data in Table 1 support the view that labeled SF_4 is converted to SOF_2: if a sample is withdrawn from the cyclotron system into a syringe already containing carrier SF_4, a higher percentage of $SF_3^{18}F$ is eluted from the gas chromatograph as a result of this "protection." Since addition of carrier is unacceptable if $SF_3^{18}F$ is to be used to label biologic molecules, one must introduce any compound for labeling directly into the trap. All reagents and solvents must be scrupulously dried, and no air can be tolerated until the reaction is completed.

As can also be seen from Table 1, it is not necessary to conduct the experiments using the full 10% of SF_4 in the bombardment mixture. Results are similar when 1% SF_4 is used.

FLUORINE-18-DAST

Several methods were used to assess the yields of ^{18}F-DAST produced by the various labeling techniques.

Chromatography was carried out using a Model ALC/GPC-201 liquid chromatograph with Model 6000 solvent delivery system and U6K universal L.C. injector.† For mass detection the effluent was passed through a Model R-403 differential refractometer.† At the outlet of the refractometer, flow continued through a 0.5-cc volume loop wrapped around a 2 × 2-in. NaI(Tl) crystal interfaced to the computer for radioactivity measurements.

Percentages of radioactivity eluted from the system were determined directly. A volume equal to

TABLE 1. GAS-CHROMATOGRAPHY ANALYSES OF PRODUCTS FROM Ne–SF₄ MIXTURES

SF₄ (%)	Comments	Products eluted (%)			
		SF₄	SF₆	X*	SOF₂
10	Gas sample	3.6	12.1	3.0	82.0
10	Gas into SF₄†	27.3	25.2	0.0	46.1
1	Gas sample	4.6	0.3	5.1	90.0
1	Gas into SF₄†	27.0	0.3	6.5	65.8

* X is an unidentified product.
† Gas sample withdrawn into syringe containing carrier sulfur tetrafluoride.

TABLE 2. DISTILLATION YIELDS FOR ¹⁸F-DAST IN THE NEON + 10% SF₄ SYSTEM

Irradiation time (μA-hr)	Recovered activity Total activity (mCi/mCi)*	% Activity distilled with DAST
7	3.5/8 (44%)	74
7	5.5/16 (34%)	87.7
15	9/20 (45%)	84
15	6.5/16 (41%)	88
15	3.5/8 (44%)	48
17.5	3/9.5 (32%)	86

* Activity recovered from trap out of total activity in trap at end of bombardment.

the size of the injected sample was diluted to 5 cc, and this was compared in a well counter with a 5-cc aliquot of the total collected eluate. The experiments using Ne + 1% F₂ were analyzed by liquid chromatography, using a μ-styragel column with 10-nm pore size, eluted with toluene at 0.3 ml/min. Two peaks were seen from the injection of DAST on the chromatograph; the retention times were 34 min (small percent, presumably a breakdown product) and 40 min. This system was compatible with a wide range of solvents used in attempts to dissolve DAST and provide an exchange medium for DAST + F¹⁸F. The solvents included: freon-11, toluene, acetonitrile, and diethyl ether. In addition, heptyl alcohol and benzyl alcohol, two candidates for labeling, served as solvents and reactants in experiments in which they were used, and they were analyzed in the same manner as the solvent–DAST mixtures.

A second method for determining yields of labeled DAST was the reduced-pressure distillation procedure, which was used for all systems. After the exchange reaction was completed, 1.0 ml of DAST was added to the liquid removed from the trap and the resultant mixture was distilled at 46°C and 10 mm Hg. Since some DAST was lost in the distillation apparatus, the receiving vessel was a centrifuge

tube graduated in 0.1-ml divisions. The activity after addition of the carrier DAST was compared with the activity in the receiving vessel after the distillation, a correction made for lost DAST, and the percent of activity distilling with DAST was measured. Trials of codistillation with 1,2,3-trichloropropane and trans-decalin, both with boiling points similar to that of DAST at 10 mm Hg, were also performed in the absence of carrier DAST.

A gas-chromatographic technique employing Poropak Q (9-ft column) at room temperature analyzed for ¹⁸F-DAST (18 min), ethyl fluoride (10 min), and methyl fluoride (2.3 min), with yields determined as percentages of injected activity. The oven temperature was raised to 160°C to elute ¹⁸F-2-fluoroethanol at a retention time of 7 min.

This last compound was also studied by liquid chromatography. It was eluted from a μ-Bondapak/C-18 column† by 50% acetonitrile–water at a flow rate of 1 ml/min, with a retention time of 4.7 min. The H¹⁸F is eluted with a retention time of 4.3 min. The two peaks, therefore, are not totally resolved.

Table 2 displays ¹⁸F-DAST distillation yields in the Ne + 10% SF₄ system for various irradiation conditions and reaction times. The solvent freon-11 (2 ml) and TMSDEA (0.3 ml) were frozen in the trap and the amount of activity incorporated on warming and removal from the trap is also given in the table. Attempts to evaporate the solvent, excess TMSDEA, and trimethylsilylfluoride, and label ethanol with the residue containing ¹⁸F-DAST without addition of carrier DAST were unsuccessful; only 12% of the activity remained in the residue. Reduced-pressure distillation was attempted by adding solvents having the same boiling temperature at 10 mm Hg as DAST to the trap. The same ¹⁸F sample divided into thirds yielded 88% distilled with DAST, 25% distilled with 1,2,3-trichloropropane, and none distilled with trans-decalin. The activity that distilled with 1,2,3-trichloropropane was unable to convert ethanol to ethyl fluoride.

The system using Ne + 1% F₂ for exchange labeling of DAST gave consistently poor percentages of elution of injected activity from the μ-styragel analytic column—commonly in the range of 0.5–4% eluted. Varying the solvent medium for exchange had no discernible effect. When 1 ml of unlabeled DAST was added to the trapped activity (containing CH₂Cl₂ and 0.05 ml DAST), and a reduced-pressure distillation was performed, an average of 74% of the activity distilled.

In the system using Ne + H₂, distillation of the trapped activity containing CH₂Cl₂ and 0.05 ml DAST, with an added ml of DAST, gave yields of around 85% in the distilled ¹⁸F. This liquid, when

154

0.1 ml of the ^{18}F-DAST was added to a CH_2Cl_2 solution containing 0.1 ml methanol, gave 7.8% ^{18}F-methyl fluoride. Similar treatment of ethanol yielded 14.9% of ^{18}F-ethyl fluoride, while ethylene glycol gave 8.9% of ^{18}F-2-fluoroethanol. Under similar conditions, except that the ^{18}F-DAST from the F^{18}F exchange was used, we obtained 11.5% ethyl fluoride from ethanol.

Table 3 is a compilation of the yields of ^{18}F-ethyl fluoride from the ^{18}F-DAST formed by synthetic means (Ne + SF$_4$) and distilled, and by exchange (Ne + F$_2$ or Ne + H$_2$). All samples were analyzed by elution from a Poropak Q column at room temperature. A typical chromatogram is given in Fig. 2. The mean of the results for the Ne + SF$_4$ system is 27.2% ^{18}F-ethyl fluoride; similarly 22.1% for the Ne + H$_2$ system, and 6.9% for the Ne + F$_2$ system. No ethyl fluoride was formed when DAST was not added to the solution in the trap. Similar results were seen for ^{18}F-methyl fluoride, the mean yield being 20% of the activity in the labeled product.

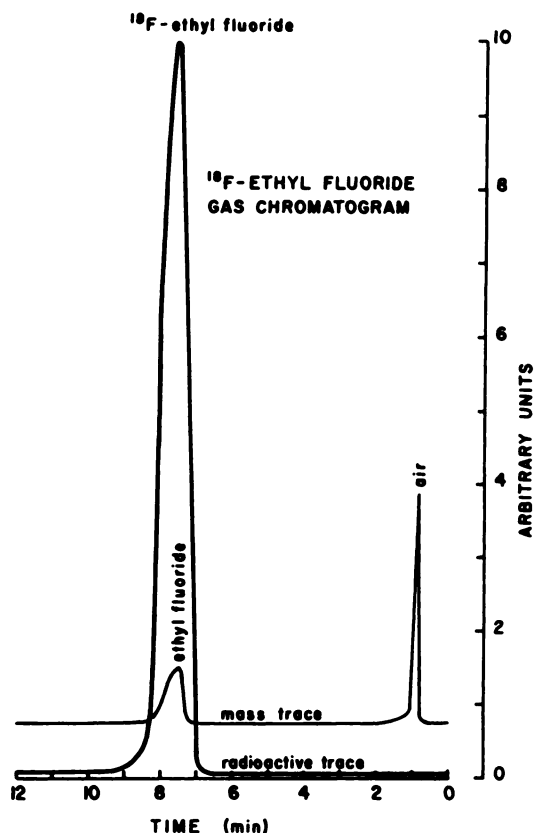Experiments to produce ^{18}F-2-fluoroethanol from

FIG. 2. Typical gas chromatogram of ^{18}F-ethyl fluoride, mass and radioactive traces, from Poropak Q at room temperature.

TABLE 3. GAS-CHROMATOGRAPHIC YIELDS OF ^{18}F-ETHYL FLUORIDE FROM ^{18}F-DAST REACTIONS

Labeling method for ^{18}F-DAST	Reactants	% Activity eluted as ^{18}F-ethyl fluoride*
Ne + 10% SF$_4$	0.1 ml ^{18}F-DAST + 0.1 ml ethanol + 1 ml CFCl$_3$	51
"	"	15.3
"	"	26
"	"	12.5
"	5 μl ^{18}F-DAST + 0.1 ml ethanol + 1 ml CFCl$_3$	21.4
"	"	14.8
"	"	49.7
Ne + 10% H$_2$	0.1 ml ^{18}F-DAST + 1 ml freon-11 + 0.1 ml ethanol	13.5
Ne + 5% H$_2$†	0.1 ml DAST + 0.5 ml hexane + 0.5 ml ethanol	16.8
Ne + 15% H$_2$†	0.1 ml DAST + 0.5 ml freon-11 + 0.5 ml ethanol	18.6
"	0.1 ml DAST + 0.5 ml CH$_2$Cl$_2$ + 0.5 ml ethanol	15.5
"	0.2 ml DAST + 0.5 ml CH$_2$Cl$_2$ + 0.5 ml ethanol	23
"	"	20.6
"	"	37
"	"	21.7
"	"	33
"	"	20.9
"	"	23
Ne + 1% F$_2$†	"	12
"	"	1.8

* Percent of total activity injected on Poropak Q eluted as $C_2H_5^{18}$F.

† All reactants added through septum on glass trap. Ethanol was added after 5 min for exchange time.

the H^{18}F-DAST system were all conducted using an irradiated gas mixture of Ne + 15% H$_2$. Yields were determined by percent of activity distilling with water (11.45 ± 4.3%, mean of experiments), and then the water fraction was analyzed by liquid or gas chromatography. Figure 3 illustrates a typical liquid chromatogram. Samples were neutralized before distillation to prevent HF from leaving the boiling flask. The mean percent of injected activity eluted as ^{18}F-2-fluoroethanol for the series was 92 ± 12%. Gas-chromatographic analyses are suspect, since it was found that 2-fluoroethanol was partially adsorbed on the Poropak Q column. The gas-chromatography analyses were used primarily to confirm the presence of ^{18}F-2-fluoroethanol.

DISCUSSION

Diethylaminosulfur trifluoride labeled with ^{18}F has been approached by three avenues: synthesis from trimethylsilyldiethylamine and SF$_3$^{18}F, by exchange with ^{19}F^{18}F, and by exchange with H^{18}F. A major stumbling block in this endeavor has been the lack of an efficient and reliable means for quantitating amounts of DAST of the order of 0.1 ml in volume. Although DAST is quite stable in large quantities, any destruction of a portion on a small scale can be
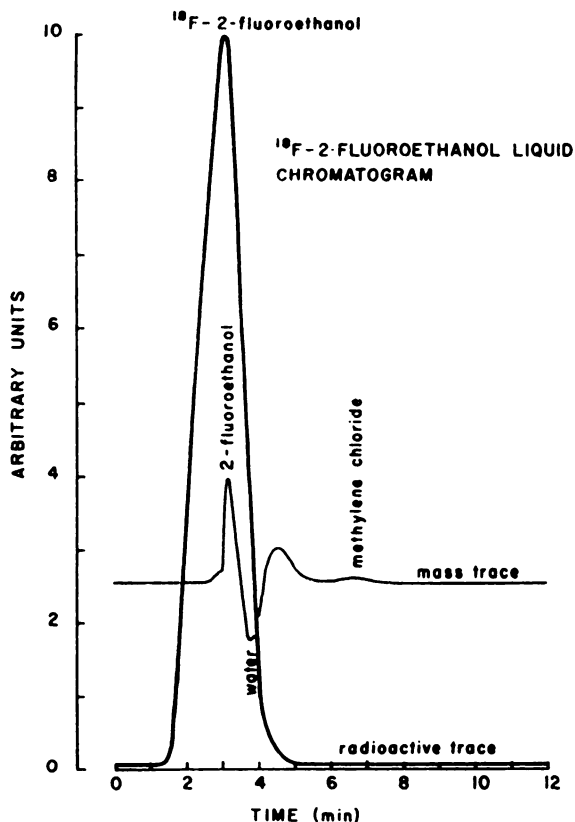
FIG. 3. Typical liquid chromatogram of ^{18}F-2-fluoroethanol, mass and radioactive traces, from μ-Bondapak/C-18 column, eluted with 1:1 acetonitrile–water.

misleading. Especially sensitive to water, DAST requires absolutely dry reagents and operating equipment, with minimum air exposure. Although a liquid-chromatography method was used to analyze the results of Ne + $F^{18}F$ labeling of DAST, there was some decomposition in the system and the amount of the decomposition product varied greatly. Since so little activity was ever incorporated into DAST as measured by this method (never more than a few percent eluted), the results were not greatly affected by this inconsistency. In further labeling attempts, however, the direct liquid-chromatographic analysis was abandoned in favor of the distillation with carrier DAST and measurement of subsequent labeling yields. The undesirability of the liquid-chromatography analytic method is illustrated by the fact that yields in the F_2 exchange system as measured by distillation with carrier DAST are most reasonable.

Synthesis of ^{18}F-DAST in the SF_4 system was confirmed by the ability to distill the activity with carrier amounts of DAST. As seen in Table 2, from 32 to 73% of the activity trapped was removed, and 85% of this activity would distill with the carrier. The ^{18}F-DAST that had been distilled was found capable of converting ethanol to ethyl fluoride. Table

3 indicates that the yields for this conversion were erratic, possibly due to the convention of adding ethanol in an open system with concomitant loss of gaseous products during the reaction, which is vigorous. The alcohol could not be added directly to the trap in this case, as SF_4 itself has the ability to effect the same F-for-OH conversion. The activity codistilling with 1,2,3-trichloropropane, as well as the residue left on evaporation, were unable to produce $C_2H_5^{18}F$. This indicates that ^{18}F-DAST made by this method would label compounds readily (sometimes in quite high yields) but that amounts of carrier unacceptable for tracer studies are also present.

There also remains some question as to whether the ^{18}F-DAST is actually synthesized or is labeled by exchange during the distillation process. In the distillation cleanup procedure, the elevated temperature could be responsible for exchange in the SF_4 method or increased exchange in the other two methods. It is known that the F_2 and HF exchange systems operate at room temperature, however, since ^{18}F-ethyl fluoride is formed from each of these methods in the absence of a distillation step.

Yields in the Ne + H_2 precursor system were not significantly affected by the amount of H_2 present in the gas mixture. Looking only at data from gas samples, when the trap contained no added reactants, with 2% of hydrogen, a high percent of non-HF components was seen; 10% hydrogen exhibited erratic trapping yields, and a series of experiments all done on the same day and having similar trapping efficiencies led to the use of 15% hydrogen as a standard concentration in subsequent investigations. Experiments in which ethanol and DAST were among the constituents in the trap gave evidence of ^{18}F-ethyl fluoride by gas chromatography. In the absence of DAST, no ^{18}F-ethyl fluoride was found. These findings further substantiate the existence of labeled DAST in this system.

Methylene chloride (dried over calcium hydride) was chosen as the solvent for this system largely for its convenience when compared to freon-11. Ether was eliminated because reaction mixtures tended to precipitate out some compound in this solvent. Trapping yields with all the solvents were similar; higher extractions were achieved when DAST was present. Whereas in the SF_4 system activity not found in the sample escaped as gas, activity in the $H^{18}F$ case adhered to the glass trap but could be rinsed out with water in most cases. Because no activity was lost to gas evolution during reaction in the trap, the overall yields of ^{18}F-ethyl fluoride by this method might be superior to those from the SF_4 system, although this fact is not reflected in the data of Table 3, where this loss is not taken into account.

156

Besides ^{18}F-methyl fluoride and ^{18}F-ethyl fluoride a third model compound was labeled by ^{18}F-DAST from the H^{18}F precursor. Middleton (10) reports that the reaction of DAST with ethylene glycol produces 1,2-difluoroethane. However, since an excess of ethylene glycol was used, some yield of 2-fluoroethanol was obtained. A number of problems were encountered in its evaluation, however. Originally it was believed that any H^{18}F would be evaporated away in the distillation process. The compounds HF and 2-fluoroethanol are not completely separated on the μ-Bondapak/C-18 column, and a small amount of one can be masked by the other. The H^{18}F is formed as a side product of the DAST-and-alcohol reaction and will trap out in water from the distillation. If the solution is neutralized before distillation, the HF is converted to fluoride and does not interfere. When no DAST is included in the reaction, no 2-fluoroethanol is found. Separating organic/aqueous layers to eliminate the CH$_2$Cl$_2$ was not successful, since this organic layer was found to contain 2-fluoroethanol. Therefore, the mixture was distilled away and the CH$_2$Cl$_2$ fraction discarded, leaving the labeled product behind.

It has been successfully shown that DAST can be labeled in high yields with ^{18}F via SF$_3$^{18}F, F^{18}F, and H^{18}F precursors. In the ^{18}F exchange reaction with DAST, the following equilibrium is found:

$$(C_2H_5)_2NSF_3 + {}^{18}F(H \text{ or } F)$$
$$\rightleftarrows (C_2H_5)_2NSF_2{}^{18}F + F(H \text{ or } F).$$
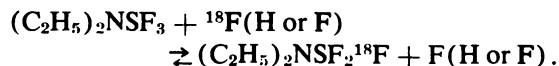
If DAST is in great excess, the equilibrium will lie to the right, but the specific activity (and labeling efficiency for reaction) of the final product will be quite low. If 0.05 ml of DAST (density, 1.16 gm/cc) is used, there is 3.7×10^{-4} moles of DAST or 1.1×10^{-3} moles of fluorine atoms. The 1% fluorine gas amounts to 3.2×10^{-3} moles or 6.4×10^{-3} moles of fluorine atoms in this system, or six times as many (stable) fluorine atoms as are found in the DAST. If 10 mCi of ^{18}F is produced, one can calculate that there are 3.52×10^{12} atoms of ^{18}F or 5.85×10^{-12} moles. This implies that carrier fluorine molecules will greatly outnumber the F^{18}F molecules, forcing the exchange equilibrium to the left, with a resultant product of low specific activity.

On the other hand, H^{18}F is carrier-free—there is no unlabeled HF before the equilibrium reaction occurs. This means that for a 10-mCi sample (containing necessarily the same number of ^{18}F atoms) the DAST is in excess and the equilibrium lies to the right, toward maximum labeling yield. The specific activity is then controlled solely by the amount of DAST used. For this reason, the HF system is far superior to the F$_2$ exchange system from a theoretical point of view, and was chosen as the best method

of producing ^{18}F-DAST. From a carrier consideration, of course, SF$_4$ is in even poorer standing when compared to the H^{18}F exchange method. Since there is a large excess of DAST relative to the ^{18}F atoms, one would expect to find only one of the three fluorine atoms in the molecule labeled. The maximum yield expected in a labeling experiment would then be about 33%. The mean yields—C$_2$H$_5$^{18}F (22.1%), CH$_3$^{18}F (20%), and ^{18}F-2-fluoroethanol (12%)—therefore represent reasonable labeling efficiencies and show the potential for labeling biologic molecules by this method via an ^{18}F-for-OH substitution.

FOOTNOTES

* Perkin-Elmer 820.

† Waters Associates, Milford, Mass.

‡ MG Scientific Gases, Modern Engineering, St. Louis, Mo.

REFERENCES

1. BLAU M: Biochemical basis of organ and tissue specificity. In Radioactive Pharmaceuticals, Andrews GA, Kniseley RM, Wagner HN, eds. USAEC Symp, Conf-651111, 1966, pp 113-118

2. TAYLOR NF: The metabolism and enzymology of fluorocarbohydrates and related compounds. In Carbon–Fluorine Compounds (A Ciba Foundation Symposium). Amsterdam, Associated Publishers, 1972, p 216

3. TER-POGOSSIAN MM, PHELPS ME, HOFFMAN EJ, et al.: A positron emission transaxial tomograph for nuclear imaging (PETT). Radiology 114: 89-98, 1975

4. PHELPS ME, HOFFMAN EJ, MULLANI NA, et al.: Application of annihilation coincidence detection to transaxial reconstruction tomography. J Nucl Med 16: 210-224, 1975

5. BURNHAM CA, BROWNELL GL: A multicrystal positron camera. IEEE Nucl Sci 19: No. 3, 201-205, 1973

6. PALMER AJ, CLARK JC, GOULDING RW: The preparation of fluorine-18 labelled radiopharmaceuticals. Int J Appl Radiat Isot 28: No. 1, 1977

7. LAMBRECHT RM, WOLF AP: Cyclotron production of radiohalogens and their use in excitation labeling. In Radiopharmaceuticals, Subramanian G, Rhodes BA, Cooper JF, Sodd VJ, eds. New York, Society of Nuclear Medicine, 1975, pp 111-124

8. ROBINSON GD: Prospects for ^{18}F-radiopharmaceuticals. In Radiopharmaceuticals, Subramanian G, Rhodes BA, Cooper JF, Sodd VJ, eds. New York, Society of Nuclear Medicine, 1975, pp 141-148

9. WELCH MJ, LIFTON JF, GASPAR PP: Production of ^{18}F for bone scanning from the ^{20}Ne(d,α)^{18}F reaction via fluorine-18 labeled nitrosyl fluoride, a selective fluorinating agent. J Nucl Med 12: 405, 1971

10. MIDDLETON WJ: New fluorinating reagents. Dialkylaminosulfur fluorides. J Org Chem 40: 574-578, 1975

11. MARKOVSKIJ LN, PASHINNIK VE, KIRSANOV AV: Application of dialkylaminosulfur trifluorides in the synthesis of fluoroorganic compounds. *Synthesis* 787–789, 1973

12. RAICHLE ME, EICHLING JO, STRAATMANN MG, et al.: Blood brain barrier permeability of ^{11}C-labeled alcohols and ^{15}O-labeled water. *Am J Physiol* 230: 543–552, 1976

13. FAWCETT FS, TULLOCK CW: Sulfur(IV) fluoride. *Inorg Syn* 7: 119, 1963

14. BOSWELL GA, RIPKA WC, SCRIBNER RM, et al.: Fluorination by sulfur tetrafluoride. *Org Reactions* 21: 1–124, 1974

15. ROWLAND FS, CRAMER JA, IYER RS, et al.: Syntheses of ^{18}F-labeled compounds by direct reactions of atomic ^{18}F. In *Radiopharmaceuticals and Labelled Compounds*, vol 1. Vienna, IAEA, 1973, pp 383–394

16. NOZAKI T, IWAMOTO M, IDO T: Yield of ^{18}F for various reactions from oxygen and neon. *Int J Appl Radiat Isot* 25: 393–399, 1974

17. MUDROVA B, SVOBODA K: Adsorption of ^{18}F on glass, polyethylene, titanium and aluminum surfaces. *Radiochem Radioanal Lett* 11: 177–185, 1972

18. BOGGS JE, VAN ARTSDALEN ER, BROSI AR: Nonexchange of F^{18} between HF and fluorinated methanes. *J Am Chem Soc* 77: 6505–6506, 1955

19. KROHN KA: *Ph.D. Dissertation, University of California, Davis, 1971.* Available from University Microfilms as Dissertation 72-3587.

20. LEDERER CM, HOLLANDER JM, PERLMAN I: *Tables of Isotopes*, 6th ed. New York, Wiley, 1967, p 160

21. CHRISTMAN DR: *Brookhaven National Laboratory Report BNL 50028*

22. STRAATMANN MG: *Master's Thesis, Washington University, 1976*

SNM GREATER NEW YORK CHAPTER
ANNUAL SPRING MEETING

March 25, 1977   Friday, 1:30–5:30 p.m.   Howard Johnson Regency Hotel   Atlantic City, N.J.

Invited speakers will discuss important *practical* advances. Enjoy an afternoon of concentrated "state-of-the-art" messages and presentations of original works.

The Spring Meeting will be held in association with 6th Annual Symposium of the Greater New York Chapter Technologist Section (March 25–26). There will be exhibitors and social functions.

For further information, contact:

David M. Milstein, M.D.
Hospital of the Albert Einstein College of Medicine
1825 Eastchester Road
Bronx, New York 10461

GREATER NEW YORK CHAPTER TECHNOLOGIST SECTION
SIXTH ANNUAL SYMPOSIUM

March 25–26, 1977   Howard Johnson Regency Hotel   Atlantic City, New Jersey

Practical and educational sessions offered at the meeting will include nuclear cardiology, gastrointestinal studies, thyroid, radiopharmaceuticals, and departmental management, as well as an extended registry review course.

The Greater New York Chapter's Annual Spring Meeting will be held in conjunction with the Technologist Section Symposium.

For further information, contact:

Margaret Iannone, MS, MT(ASCP)NM
Nuclear Medicine Service
Veterans Administration Hospital
Northport, New York 11768