

Recovery and Purification of No-carrier-added [^{18}F]Fluoride with Bis(trimethylsilyl)sulfate (BTMSS)

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(Received 28 November 1990; received for publication 1 May 1991)

No-carrier-added trimethylsilyl[^{18}F]fluoride (TMS[^{18}F]F) was rapidly liberated from a variety of dry supports containing unreactive [^{18}F]fluoride by simply heating with neat bis(trimethylsilyl)sulfate. The supports included calcium phosphate, anion exchange resins, alumina, borosilicate and porous carbon beads, to which [^{18}F]fluoride was applied by absorption or evaporation of aqueous solution. TMS[^{18}F]F was evolved essentially free of entrained moisture or excess silylating agent and was efficiently absorbed and rapidly cleaved to free [^{18}F]fluoride ion by 0.1% benzyltrimethylammonium methoxide in anhydrous methanol. Passage of this solution through a strong cation exchange column provided purified hydrogen[^{18}F]fluoride, which was subsequently trapped on a quaternary 4-aminopyridinium resin and used for heterogeneous nucleophilic radiofluorination of 1,3,4,6-tetraacetyl-beta-mannopyranose-2-triflate in 70% yield. The purified [^{18}F]fluoride ion was also used for solution phase nucleophilic labeling of ethyl [^{18}F]4-fluorobenzoate following addition of K_2CO_3 /Kryptofix and DMSO. This approach provides a simplified way to ensure high reactivity in [^{18}F]fluoride ion from cyclotron targets. It also may be used to salvage active [^{18}F]fluoride ion from insoluble complexes and radiofluorination reaction residues.

Introduction

Much understanding has been gained about the critical factors and conditions for incorporating [^{18}F]fluoride ion into organic molecules via no-carrier-added (n.c.a.) nucleophilic reactions [see reviews by Nickles *et al.* (1986); Tewson (1989); Kilbourn (1990)], but a significant element of variability remains to these reactions. Microcontamination of [^{18}F]fluoride has been cited as a major factor contributing to low and variable yields (Clark and Sylvester, 1966; Tewson, 1989; Tewson *et al.*, 1988; Kilbourn *et al.*, 1986). Metal ions apparently have the most serious effects but organic substances such as traces of solvents or chemical components of elastomer seals, plastic tubing, fittings, etc., may also cause problems, by radiolyzing to either acids (e.g. bicarbonate, formate) that neutralize the bases added for the labeling reaction, or to nucleophilic substances (e.g. NH_3 , CN^- , Cl^-) that compete with [^{18}F]fluoride for substrate. Potential entry points for trace impurities are numerous, and controlling them routinely can be a daunting task.

Purification of [^{18}F]fluoride by conversion to trimethylsilyl[^{18}F]fluoride (TMS[^{18}F]F) is an effective solution to variable fluoride quality (Taves, 1968; Hutchins *et al.*, 1985; Rosenthal *et al.*, 1985; Bosch *et*

al., 1986; Chirakal *et al.*, 1988; Gatley, 1989), but existing procedures have drawbacks which reduce their utility for routine application with cyclotron produced [^{18}F]fluoride ion. Recovery of the expensive ^{18}O enriched target water, and aqueous hydrolysis of TMS[^{18}F]F can be problematic with present silylation techniques. The latter drawback has been recognized and a nonaqueous method for cleaving TMS[^{18}F]F with potassium tert-butoxide in acetonitrile has been developed recently (Gatley, 1989). Another difficulty is volatility of the silylating reagent, usually TMSCl , which is carried along with the TMS[^{18}F]F. Since this excess reagent can both generate acid and also introduce chloride ion which may compete with [^{18}F]fluoride ion in nucleophilic reactions, it must be removed completely with a water trap placed before the TMS[^{18}F]F hydrolysis vessel. This additional stage slightly complicates the process and may lower overall recoveries of [^{18}F]fluoride ion due to hydrolysis of some TMSF by water (Rosenthal *et al.*, 1985).

The effectiveness of anion exchange resin techniques for separation of [^{18}F]fluoride from [^{18}O]water (Schlyer *et al.*, 1990; Jewett *et al.*, 1990; Jewett, 1991a) and resin-supported nucleophilic labeling reactions (Mulholland *et al.*, 1989b; Toorongian *et al.*, 1990) depends upon the [^{18}F]fluoride quality and these techniques alone may not greatly improve the

initial reactivity of [^{18}F]fluoride from the target. In examining sources of variability in resin- ^{18}F fluorodeoxyglucose (FDG) production (Toorongian *et al.*, 1990) we find that poor quality aqueous [^{18}F]fluoride does not trap well on resin, and trapped activity fails to react normally in the subsequent heterogeneous displacement reaction.

A modified silylation technique, free of the drawbacks mentioned above, was sought that could be used in conjunction with resin fluorination methods. Bistrimethylsilylsulfate (BTMSS), came under consideration as a possible reagent because of its low volatility (m.p. 41°C), strong silylating and dehydrating actions, powerful Lewis acid properties, and low nucleophilicity of sulfate counterion. BTMSS readily forms TMSF from solid alkali fluorides (Voronkov *et al.*, 1982), and BTMSS-like mixtures of mineral acids and hexamethyldisilazane have been used for recovery of [^{18}F]fluoride ion from KOAc·HOAc complexes (Chirakal *et al.*, 1988), and also in analysis of microamounts of fluoride in aluminum and silica matrixes (Tsuchiya *et al.*, 1985).

The present work examines methods for quickly separating [^{18}F]fluoride from [^{18}O]H₂O, the generation of TMS[^{18}F] from solid matrixes with neat BTMSS, and the formation, properties and reactions of purified [^{18}F]fluoride ion and H[^{18}F]F in methanol.

Experimental

[^{18}F]Fluoride was prepared by 17 MeV, 20 μA proton bombardments of 95 + % ^{18}O -enriched water (Isotec) in a 1 cc volume all-silver target (Mulholland *et al.*, 1989a). 1,3,4,6-Tetraacetyl-beta-mannopyranose-2-triflate benzyltrimethyl-ammonium methoxide (QOMe, 40% in methanol), XAD 2 (20–40 mesh) polystyrene adsorbant and Dowex 50X2-400 (H⁺) strong cation exchange resin were purchased from Aldrich. The Dowex 50 resin was washed with methanol before use. Neutral chromatographic grade 100–200 mesh alumina, CaCO₃ and tribasic calcium phosphate Ca₃(OH)(PO₄)₃, were obtained from Baker. The quaternary 4-aminopyridinium (AP) resin (carbonate form) was prepared as previously described (Toorongian *et al.*, 1990), as was the oxidized pyrolytic carbon anion exchange material (Jewett, 1991b; Voll and Boehm, 1970, 1971a, b). All yields are corrected for isotope decay and, unless otherwise noted, based on crude starting [^{18}F]fluoride.

The [^{18}F]fluoride used in these experiments in most cases was scavenged from daily clinical FDG production runs (Toorongian *et al.*, 1990) where the quality of the starting [^{18}F]activity could be independently assessed to a certain extent by the yields of FDG obtained that day. [^{18}F]Fluoride was taken from three points in the resin–FDG synthesis procedure. The first source was target water containing [^{18}F]fluoride diverted before entering the FDG synthesis. This [^{18}F]fluoride had the best reactivity of the three sources and was designated as “good”

[^{18}F]fluoride. The second source was “bad” aqueous [^{18}F]fluoride activity which had not been trapped when passed through the FDG synthesis resin column. The third source of activity, also labeled “bad” [^{18}F]fluoride, was unreacted ^{18}F -activity left on the resin column following the FDG synthesis.

Separation of [^{18}F]fluoride by absorption on solid support columns

Columns were made by loading the dry adsorbant packing into the tip of a disposable flint glass 125 mm Pasteur pipet. The packings included neutral alumina (10–20 mg, 100–200 mesh), Ca₃(OH)(PO₄)₃ (1.5–4 mg), quaternary AP resins (20–30 mg) and oxidized pyrolytic anion exchange carbon (15–20 mg). The materials were held in place by a plug of glass or polypropylene wool. Aqueous [^{18}F]fluoride (1–3 mL) was forced through the column by slight nitrogen pressure and the column was then dried briefly by a stream of nitrogen gas. The pipet tip was then crushed into the base of a 10 × 75 mm borosilicate tube to empty the column packing and absorbed ^{18}F . In some experiments, spent “FDG resin” packing with residual unreactive [^{18}F]fluoride was extruded with a metal plunger from columns into a 10 × 75 mm borosilicate test tube.

Separation of [^{18}F]fluoride by evaporation of water

A 1–1.5 mL aliquot of target water containing [^{18}F]fluoride was placed in a 13 × 75 mm borosilicate glass test tube with either ~1 mg of K₂CO₃ or ~0.5 mg of a basic calcium salt, i.e. CaCO₃ or Ca₃(OH)(PO₄)₃. A rubber cap pierced with a nitrogen gas inlet tube and a coiled teflon 0.8 mm i.d. outlet (distillation) tube was fastened over the test tube and the tube was placed in a 150°C heating block or heated with a hot air gun. The water was distilled at atmospheric pressure under a stream of nitrogen gas (~200–600 mL/min) until the test tube was completely dry, leaving behind the [^{18}F]fluoride in the test tube in a residual film. The [^{18}O]water distillate was recovered in an ice-chilled tube placed at the end of the coil. The distillation process required 3–5 min to complete.

Formation and cleavage of TMS[^{18}F]F

To a rubber stoppered test tube (silylation tube) containing [^{18}F]fluoride residue was added 200–500 μL of molten BTMSS by syringe. The stopper had a vent and a teflon outlet line that passed into the bottom of a second stoppered and vented test tube (cleavage tube) containing 2–3 mL of 0.1% QOMe (11–17 μmol) in methanol for basic cleavage of TMSF. A reusable 5 × 30 mm column of dry Na₂SO₄ or P₂O₅/Na₂SO₄ was placed in-line between the tubes to prevent aerosol particles from entering the cleavage tube. The silylation tube was heated between 120–170°C, depending on the substrate, for 1–10 min and TMS[^{18}F]F vapor was drawn off and transferred to the solution in the hydrolysis tube by

applying a gentle vacuum to the outlet vent of the cleavage tube with a 60 cc syringe. Three strokes of the vacuum syringe over a 1–2 min period were usually sufficient to transfer substantially all of the volatile radioactivity into the basic methanol solution. Cleavage of TMS[¹⁸F]F to free [¹⁸F]fluoride ion occurred at room temperature in less than 5 min from the beginning of transfer, as judged by the lack of volatile activity when the solution was heated or sparged with inert gas.

Purified [¹⁸F]fluoride solution in radiofluorinations

(A) 2-[¹⁸F]fluoro-2-deoxy-beta-glucopyranose-1,3,4,6-tetraacetate (FDGAc₄) by heterogeneous nucleophilic displacement on quaternary AP resin. The above methanolic Q[¹⁸F]fluoride/QOMe solution was passed sequentially through a 5 mm i.d. polyethylene column containing 0.5 cc of Dowex 50 for removal of excess QOMe, to form a dilute pH 5–6 solution of [¹⁸F]fluoride (“H[¹⁸F]F”), and then directly through a 4.6 mm i.d. × 1 cm HPLC guard column (stainless steel or PEEK inner surfaces) containing 30 mg of AP resin (CO₃²⁻). A 1 mL rinse of methanol was passed sequentially through the column to wash residual [¹⁸F]fluoride through the system. The [¹⁸F]fluoride adhering to the AP resin (typically > 95% of applied activity) was “activated” (methanol removed) by passing 2 mL of dry acetonitrile through the column at room temperature. A solution of 20 mg of 1,3,4,6-tetraacetyl-beta-mannopyranose-2-triflate in 1 mL of acetonitrile was next placed in contact with the [¹⁸F]fluoride-AP resin and the column temperature was raised to 95°C over a 3 min period as the triflate solution passed back and forth through the resin bed by means of remote syringe pressure applied alternately to the ends of the column. After the column temperature had remained at 95°C for 1 min, the reaction solution was collected and the column and lines were washed with 1 mL of acetonitrile. The eluted radioactivity in the combined reaction solution and washings constituted between 65–85% of the total purified methanolic [¹⁸F]fluoride applied to the resin column and TLC analysis (SiO₂; 1:1 hexane:ethyl acetate) of this eluate typically showed the product to be more than 94% pure FDGAc₄ (R_f = 0.50). Removal of the solvent followed by acid hydrolysis (1 N HCl, 15 min) quantitatively converted the radioactive product to a single spot with the same R_f as FDG (0.35–0.40; SiO₂; 95:5 acetonitrile:water).

(B) Ethyl 4-[¹⁸F]fluorobenzoate by solution phase reaction. In a typical reaction, ca 1 mL of the above methanolic H[¹⁸F]F solution, ~1 mg of K₂CO₃, 10 mg of Kryptofix 222, and 0.5 mL of dry DMSO were placed in a magnetically stirred borosilicate 3 mL volume “V-vial”. The vial was placed in a 150°C heating block, the methanol was driven off under a stream of inert gas (1–3 min) and then 10–30 mg of ethyl 4-trimethylammonioacetate triflate (Haka *et al.*, 1989) was added and the vial was

capped with a vented seal, and heat for 10–20 min. Examination of the reaction solution by TLC (SiO₂; 3:1 hexane:ethyl acetate) showed a single mobile radioactive peak that comigrated with authentic ethyl 4-fluorobenzoate (Aldrich). It constituted between 50–80% of the total plate activity, the remainder being at the origin. The overall decay-corrected yields based upon methanolic [¹⁸F]F were between 40–70%. Similar results could be obtained with this reaction by substituting Q[¹⁸F]fluoride for H[¹⁸F]F and omitting the K₂CO₃, and Kryptofix 222.

Results and Discussion

Choice of solid support

The best support for separation of [¹⁸F]fluoride from target water and subsequent liberation as TMS[¹⁸F]F appeared to be tribasic calcium phosphate. A 1.5–4 mg, 1.5 mm dia bed of this insoluble powder quantitatively trapped both good and bad quality aqueous [¹⁸F]fluoride in a single pass. Presumably, the avid absorption of inorganic fluoride is due to formation of strong Ca—F or P—F bonds. The binding interaction was rapidly disrupted by BTMSS treatment with nearly complete volatilization of [¹⁸F]fluoride as TMSF. Two minor drawbacks exist with the calcium phosphate used in these experiments, the first being its small particle size which requires care in making the columns to avoid problems with back pressure. The other problem is the presence of about 75 ppm of inorganic ¹⁹F in the commercial grades of calcium phosphate, which dilutes the specific activity of the purified [¹⁸F]fluoride slightly [4 mg of Ca₅(OH)(PO₄)₃ contributes ~17 nmol of carrier fluoride]. Use of a purer and larger size grade material would overcome these minor problems.

Alumina quantitatively absorbed both bad and good quality aqueous [¹⁸F]fluoride, but a significant fraction of the absorbed activity on Al₂O₃ could not be released by BTMSS treatment, even after prolonged heating at 170°C. Unlike calcium phosphate, Al₂O₃ did not dissolve in BTMSS and [¹⁸F]fluoride containing sites in the Al₂O₃ matrix may have remained inaccessible to silylation. It has been reported that addition of pyrophosphoric acid to aluminum containing solutions containing micro amounts of nonradioactive fluoride promotes the liberation of TMSF through “masking” or preferential complexation with the metal (Tsuchiya *et al.*, 1985). This treatment was not tried in the present study.

Mixed results were seen with aminopyridinium resins and pyrolytic carbon anion exchange beads. Both materials efficiently absorbed good quality [¹⁸F]fluoride and this activity was liberated efficiently by BTMSS treatment, but absorption of “bad” aqueous fluoride on the resin was variable and generally poor. The adhering fraction of “bad” [¹⁸F]fluoride could be efficiently volatilized as TMSF

by BTMSS, and recovery of leftover unreactive ^{18}F activity from used resin-FDG synthesis columns with BTMSS was uniformly excellent. The conclusion from these experiments is that AP resins and pyrolytic carbon anion exchange powders are not the best choice for efficient separation of poor quality aqueous ^{18}F fluoride, but any ^{18}F fluoride present on these solid supports can be recovered and purified efficiently by silylation.

Separation by water evaporation

^{18}F Fluoride was isolated quantitatively in the residue by simple evaporation of target water after adding a small amount of calcium or potassium containing base. Water losses from distillations of 1–1.5 mL liquid samples were estimated to be no greater than 10%, with most of the lost water being held up in the teflon line, needles and leur fittings that together served as the distillation “head”. This loss became negligible when the same head was used for multiple distillations. Recovery of the residual ^{18}F fluoride from the evaporation vessel walls by BTMSS was good to excellent; the best volatilization yields were found with insoluble calcium bases.

The absorptive and the evaporative techniques for separation of aqueous ^{18}F fluoride have their respective advantages: absorption is generally faster while evaporation involves fewer moving operations and may be simpler to incorporate into a routine automated procedure. The latter technique also allows direct recycling of target water without further purification. Other ^{18}F separation techniques such as electrodeposition on graphite (Alexoff *et al.*, 1989) might also be applied in combination with BTMSS silylation.

Properties and reactions of TMS ^{18}F F and methanolic ^{18}F fluoride

Gaseous TMS ^{18}F F passed through solid granular P_2O_5 and Na_2SO_4 without effect. Neither was it absorbed to any significant extent by borosilicate glass, stainless steel or passage through several meters of teflon tubing. This lack of attraction to common laboratory materials raises the possibility TMS ^{18}F F might serve as a convenient transport form of reactive ^{18}F fluoride that could be “piped” to where it was needed by gas handling systems. TMS ^{18}F F was completely and irreversibly absorbed from a gas stream by a 5×30 mm column of sodalime, or other basic solutions such as NaOMe/methanol, and KOH/aqueous methanol, in addition to QOMe. QOMe/methanol was the preferred cleavage system because it avoided completely the need for water in the cleavage reaction, and only 11–17 μmol of base were required for rapid absorption and cleavage, less than one-third the amount used in previous procedures (Gatley, 1989; Chirakal *et al.*, 1988). TMS ^{18}F F was absorbed reversibly by XAD 2 (20–60% of activity trapped on a 5×50 mm column at room temperature) and pure methanol (30–70%).

The trapping efficiencies for reversible systems were maximized at low carrier gas volumes and temperatures, and absorbed activity could be volatilized by gas purge or heating.

Methanolic solutions of purified Q ^{18}F fluoride were nonvolatile and showed no tendency to adhere to silanized or unsilanized glass, steel or plastics. After passing these solutions through Dowex 50 resin the ^{18}F fluoride became volatile under reflux or sparging conditions, consistent with it being in the chemical form of HF, but in solution it still showed no tendency to adhere to steel, plastic, Dowex 50 or, surprisingly, glass, even when the methanolic H ^{18}F F was in contact for periods longer than 1 h. This behavior conflicts with the widely reported “stickiness” of H ^{18}F F in organic solvents that prevents it from being utilized in normal laboratory glassware [Dahl *et al.* (1983); Kilbourn (1990) p. 43], and suggests that methanol effectively solvates fluoride ion or glass surfaces or both, minimizing attractions between them in some way.

The overall yield of purified H ^{18}F F from aqueous ^{18}F fluoride, isolated either by calcium phosphate absorption or distillation, was 85–90%. The predominant loss was nonvolatile activity left behind in the silylation tube. There was no pattern of significant losses greater than 5% due to activity sticking to lines, vessels (other than the silylation tube) or Dowex 50 resin, or incomplete absorption of TMS ^{18}F F by the QOMe solution.

In spite of its low order of nonspecific “stickiness”, the purified methanolic H ^{18}F F was efficiently (>95%) trapped by ionic exchange to the AP resins (CO_3^{2-}), even in cases where the solution volume and flow through the resin column were as great as 5 mL/7 s. The activity clearly was bound to the AP resin by an ionic mechanism since it was resistant to elution by pure neutral solvents but could be almost quantitatively brought off the resin by dilute solutions of Cl^- or CO_3^{2-} anions.

The reactivity of the purified ^{18}F fluoride was very good in both resin and solution phase nucleophilic radiofluorinations provided that methanol was first removed. Methanol solvation apparently inhibits ^{18}F fluoride nucleophilicity in ways similar to water, but it is much easier to remove low-boiling methanol than water. In the case of resin fluorinations the methanol was simply displaced from the resin ^{18}F fluoride by brief acetonitrile or DMSO rinses in a precisely analogous way as when using aqueous ^{18}F fluoride (Mulholland *et al.*, 1989b). For solution phase aromatic labeling reactions it was convenient to add K_2CO_3 , Kryptofix and DMSO to the methanolic H ^{18}F F, then drive off the methanol by heat, add precursor and carry out labeling reaction. The reason for adding precursor last was to prevent the loss of volatile ^{18}F -products along with the last traces of methanol. For reactions yielding nonvolatile labeled products, all ingredients could be added together initially and then methanol evaporation and

Table 1. Comparison of TMS[¹⁸F]F yields

Aqueous ¹⁸ F separation method	Separation efficiency	TMS[¹⁸ F]F formation ^a
<i>By absorption on:</i>		
Neutral alumina	Quantitative	30–60 ^b
Ca ₃ (OH)(PO ₄) ₂ ⁺	Quantitative	>90 ^c
4-AP resin, "Good" fluoride	85–99	90–98% ^c
4-AP resin, "bad" fluoride	10–50	90–98% ^c
Spent FDG synthesis resin	—	90–98% ^c
Oxidized carbon material	37–94 ^d	>90% ^c
<i>By evaporation from:</i>		
K ₂ CO ₃ /borosilicate	Quantitative	60–80% ^b
CaCO ₃ /borosilicate	Quantitative	>95% ^c
Ca ₃ (OH)(PO ₄) ₂ /borosilicate	Quantitative	>95% ^c

^aDefined as the percentage of total separated activity that was volatilized from the tube after adding BTMSS and heating. Silylation conditions. ^b140–170°C, 10 min. ^c120–130°C, 3 min. ^dTaken from Jewett (1991b). Includes both "good" and "bad" aqueous [¹⁸F]fluoride.

displacement carried out in a single heating step. It was found that both K₂CO₃ and Kryptofix must be present at the beginning of heating of reaction solutions containing methanolic H[¹⁸F]F. Attempted reactions of ethyl trimethylammonio benzoate triflate salt in the absence of K₂CO₃/Kryptofix or with K₂CO₃ alone resulted in major loss of volatile activity. In this case apparently there is insufficient dissolved K₂CO₃ in the absence of Kryptofix to deprotonate H[¹⁸F]F before it is driven out of solution by the elevated temperatures. The alternative solution phase labeling using Q[¹⁸F]fluoride without K₂CO₃/Kryptofix gave variable results; yields of ethyl 4-[¹⁸F]fluorobenzoate were good but 4-[¹⁸F]fluorobenzaldehyde yields were less than 10%. Sensitivity of benzaldehydes to the strong basic conditions of the Q[¹⁸F]fluoride/QOMe system may explain the low yields in the second case.

Conclusions

The ¹⁸F-labeling yields obtained using purified [¹⁸F]fluoride in heterogeneous and solution phase labeling reactions lie consistently in the range of the best reported yields (Kilbourn, 1990) using (presumably) good quality aqueous [¹⁸F]fluoride directly from the target. The lack of "stickiness" of either TMS[¹⁸F]F or methanolic [¹⁸F]fluoride with common laboratory materials suggest their potential usefulness as transport forms of highly reactive [¹⁸F]fluoride ion. Purification by silylation ensures the nucleophilic quality of n.c.a. [¹⁸F]fluoride and eliminates much of the effort and difficulties involved in preventing microcontamination of the water target system. The particular advantage of this approach is that it is simple and efficient enough to be used routinely as part of clinical ¹⁸F-radiopharmaceutical production.

Acknowledgements—The author thanks Drs Douglas Jewett and Michael Kilbourn for their thoughtful suggestions and review of this manuscript. This work was supported by National Institutes of Health Grant NS15655 and Department of Energy Grant DE-FG02-87ER60528.

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