

Ion Exchange Reaction of [^{18}F]fluoride with an Oxidized Carbon Surface

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[^{18}F]Fluoride was trapped from [^{18}O]water in high yield by ion exchange on a microporous carbon prepared by controlled oxidation to produce a cationic surface with an exchange capacity of about 350 $\mu\text{equiv/g}$. The [^{18}F]fluoride could be recovered by displacement with aqueous K_2CO_3 . The cationic carbon offered a dimensionally rigid matrix of high thermal stability. It was characterized with respect to chemical reactivity and selectivity for anion exchange.

Introduction

While resin based methods for nucleophilic radiofluorination offer a substantial simplification (Toorongian *et al.*, 1990) the Merrifield resin presently used has some limitations. Some of the resin-bound [^{18}F]fluoride (usually 20–30%) fails to react. The resin appears to undergo a rapid, irreversible change at about 100°C, possibly as a result of a reaction between the functionalized sites on the highly mobile polystyrene chains. It was considered that an ideal solid phase would consist of a rigid, inert network on which the reactive cationic groups were attached by flexible spacers at well separated sites. The development of microporous carbon particles for HPLC (Knox and Gilbert, 1982; Knox *et al.*, 1986) appeared to offer a convenient starting point for such a solid phase, since the carbon skeleton could be expected to be unreactive toward fluoride ion while capable of functionalization by known reactions. However, samples of a microporous amorphous carbon prepared by the method of Knox and Gilbert (1982) always adsorbed significant amounts of [^{18}F]fluoride even after extended extraction with NaOH and HF to remove all traces of silica. The work of Voll and Boehm on the introduction of cationic groups on a carbon surface by controlled oxidation (Voll and Boehm, 1970; 1971 a, b) offered an explanation for this finding. Heat treatment and oxidation of an amorphous carbon prepared by the method of Knox and Gilbert (1982) resulted in a material that efficiently extracted [^{18}F]fluoride from [^{18}O]water. The [^{18}F]fluoride could be easily removed from the carbon by ion exchange (Schlyer *et al.*, 1990; Jewett *et al.*, 1990; Jewett, 1991) for use in nucleophilic radiolabeling reactions. The preparation, characteriz-

ation and preliminary application of this material are described below.

Materials and Methods

Preparation of amorphous carbon with a high surface area

A carbon replicate was prepared by forming a phenol–formaldehyde polymer within a matrix of chromatographic grade silica, heating to form an amorphous carbon and subsequent removal of the silica (Knox and Gilbert, 1982; Knox *et al.*, 1986). Silica gel, 20 g (Davisil 635LCO1821, 60 Å pore, 150–250 micron), was dried 5 h at 150°C then mixed at 60°C with 5 g of a 10:1 molar mixture of phenol and hexamine. The powder was heated at 110°C for 2 h then at 160°C for 16 h in an oven. It was further heated 2 h at 350°C under a flow of N_2 in a quartz tube, then at 900°C for 16 h then cooled under N_2 . The powder was then heated with 4 N NaOH 1 h at 60°C in a Teflon flask to extract the silica. This extraction was repeated 3 additional times. The resulting carbon powder was further extracted 3 times with 48% aqueous HF at 60°C to remove possible traces of silica then washed well with water and dried at 100°C.

Activation of the carbon surface

Carbon powder, 10 g, prepared as above was treated by the method of Voll and Boehm (1970) to develop a partially oxidized surface. The carbon was heated 1 h at 1100°C under a flow of zero grade N_2 then cooled to room temperature under N_2 . It was maintained for 1 h in an atmosphere of dry air then stored in a closed vial.

Ion exchange extraction of [¹⁸F]fluoride

Columns were cut from appropriate lengths of 1.6 mm I.D. polyethylene or EVA tubing. Fittings consisted of 1.7 mm O.D. Teflon tubes forced into the columns. Small plugs of polypropylene wool (Aldrich) were packed into the downstream ends of the columns to retain the carbon packing. Carbon powder, 15 mg prepared as above, was suspended in water and quickly drawn into a column (1.6 mm I.D. × 30 mm; 18 mm bed length). Two approx. 200 μL volumes of water were drawn through the column by a vacuum followed by intervals of about 20 s to allow exposure of the carbon to air to ensure complete oxidation of the surface. The column was then dried 10 min at 23°C under a flow of N₂. [¹⁸O]Water, 1 mL, containing [¹⁸F]fluoride from a silver target was passed through the column at about 0.3 mL/min. The [¹⁸O]water was recovered. Then 1 mL of water containing 1 mg K₂CO₃ was passed through the column to elute the fluoride. Usually, a small column of a fibrous proton exchange resin [15 mg Toray TIN-100 H⁺; Jewett *et al.* (1990); Yoshioka and Shimamura (1983)] was connected upstream of the carbon column during the trapping step to improve trapping of the [¹⁸F]fluoride.

Measurement of ion exchange capacity of carbon samples

Carbon (100 mg) prepared as above was packed in a polyethylene column, rinsed with 2 1-mL volumes of pure water, and exposed to a flow of air for 1 min after each rinse to ensure complete oxidation of the surface. Then 3 mL 1 N HCl or NaCl were passed through the column, followed by rinsing with 10 mL water to remove all free chloride. The exchanged chloride was eluted quantitatively from the column by 100 mg LiNO₃ in 1 mL water and precipitated by 100 μL saturated aqueous AgNO₃. The AgCl was washed by centrifugation, dried and weighed. For fast semiquantitative measurements on large numbers of samples small polyethylene columns containing 10 mg of basic carbon were prepared. These were eluted by measured volumes of 1.0 mM HCl until the effluent gave a slight precipitate with saturated aqueous AgNO₃. Exchange values determined in this way (approx. 300 μequiv/g) were somewhat less than those obtained by the direct method. In experiments where the carbon samples had been treated with various reagents the samples were first rinsed with 2 N HNO₃ then with a large excess of aqueous NaOAc to convert exchangeable sites to readily exchangeable acetate groups before adsorption of chloride.

Determination of elution curves for [¹⁸F]fluoride

Microcolumns were prepared as described above containing 22 mg of basic carbon, neutral alumina, fibrous quaternary ammonium resin (TIN-200, CO₃²⁻ form) or spherical quaternary ammonium resin (Dowex IX8, 400 mesh, CO₃²⁻ form). Trace amounts

of aqueous [¹⁸F]fluoride, conditioned by passage through 20 mg of fibrous proton exchange resin, were applied to each of the columns. The columns were eluted by 3 mL water containing 1 mg/mL K₂CO₃. The effluent was collected in 100 μL aliquots and counted in an ionization detector.

Determination of exchangeable water on solid phases after drying

Samples of basic carbon or various resins (20 mg) were slurry packed in polyethylene columns and converted to the desired ionic form by an excess of NaOH or Na₂CO₃. Most of the water was removed by passing a stream of N₂ through the columns for 10 min. Tritiated water, 10 μL, 8800 dpm was applied to the columns which were then dried either by passing a stream of N₂ through them for 10 min, or by 1 mL of MeOH or MeCN. The dried columns were extracted with 1 mL of water, and the extracted radioactivity was determined by liquid scintillation counting.

Incorporation of extracted [¹⁸F]fluoride into [¹⁸F]FDG precursor

Method 1, aqueous extraction: The [¹⁸F]fluoride was extracted by the carbon by 1 mg K₂CO₃ in 1 mL water as described above. This was added to 10 mg Kryptofix-2,2,2 and 1 mg K₂CO₃ in a pyrex tube and evaporated at 110°C. Two 1 mL volumes of MeCN were added and evaporated to dryness to remove traces of water. Then 10 mg 1,3,4,6-tetra-*O*-acetyl-*O*-trifluoromethanesulfonyl-β-D-mannopyranose in 1 mL MeCN was added and the solution was heated 10 min in an oil bath at 110°C. The reaction was cooled, diluted with 9 mL water and passed through a C-18 Sep-Pak extraction cartridge. The tetra-acetyl-¹⁸F]FDG was eluted from the cartridge with EtOH and analyzed by radio TLC (hexane:EtOAc 1:1 on silica).

Method 2, MeCN extraction: The [¹⁸F]fluoride was eluted from the carbon by 1 mL 80% aqueous MeCN containing 10 mg kryptofix-2,2,2 and 1 mg K₂CO₃. The solvent was evaporated followed by 2 1-mL volumes of MeCN to remove traces of water. The incorporation reaction and radioassay were as described above.

Results and Discussion

To facilitate comparison, the procedures for the extraction of [¹⁸F]fluoride from target water by carbon were the same as those used for polystyrene-based particulate resin (Schlyer *et al.*, 1990) and fibrous resin (Jewett *et al.*, 1990). Trace amounts of [¹⁸F]fluoride were more than 99% extracted from pure water. Extraction of [¹⁸F]fluoride from target water was always lower, ranging from 37 to 94% for a 15 mg carbon column alone. If a column of a fibrous proton exchange resin [15 mg, Jewett *et al.* (1990)] was placed upstream of the carbon column,

trapping of [¹⁸F]fluoride was always greater than 95%. This same observation was made for extraction of [¹⁸F]fluoride with Merrifield resins. After the extraction the proton exchange columns retained a small amount of [¹⁸F]fluoride corresponding to their hold-up volume of water. In addition they contained a small amount of radioactivity (<0.1% of the total) with a half-life of at least several days that could not be rinsed off by pure water. Such proton exchange columns may be a general solution to the problem of poor [¹⁸F]fluoride trapping encountered with some targets. Of the [¹⁸F]fluoride trapped on the carbon, 96–99% was eluted by 1 mg K₂CO₃ in 1 mL water.

Solutions of electrolytes in wet organic solvents were used in an attempt to find an extraction solution that would be easier to evaporate than water. Recoveries of the trapped [¹⁸F]fluoride were as follows: 1 mg K₂CO₃ in 1 mL 95% aqueous MeOH, 85%; 10 μmol tetrabutylammonium hydroxide in 1 mL MeCN, 36%; 2 mg K₂CO₃ and 20 mg Kryptofix 2,2,2

in 2 mL 84% aqueous MeCN, 62%. Recoveries were thus lower than for comparable solvent mixtures with fibrous resins (Jewett *et al.*, 1990). It appears that the strength of the ion pair between fluoride and the cationic surface groups of the carbon is stronger than that between fluoride and the quaternary ammonium groups of polystyrene-based resins. This is supported by the results of attempts to carry out direct nucleophilic exchange between mannose triflate and [¹⁸F]fluoride on a dry carbon surface. Under conditions where an exchange of about 70% would occur for a Merrifield type resin (Toorongian *et al.*, 1990) no exchange of [¹⁸F]fluoride from the carbon surface was detected.

Figure 1 compares the elution of trace amounts [¹⁸F]fluoride by aqueous K₂CO₃ (1 mg/mL) from basic carbon, neutral alumina and quaternary ammonium polystyrene resins. The site accessibility for the carbon is comparable for the polystyrene resins as indicated by the sharp elution profile. This is in

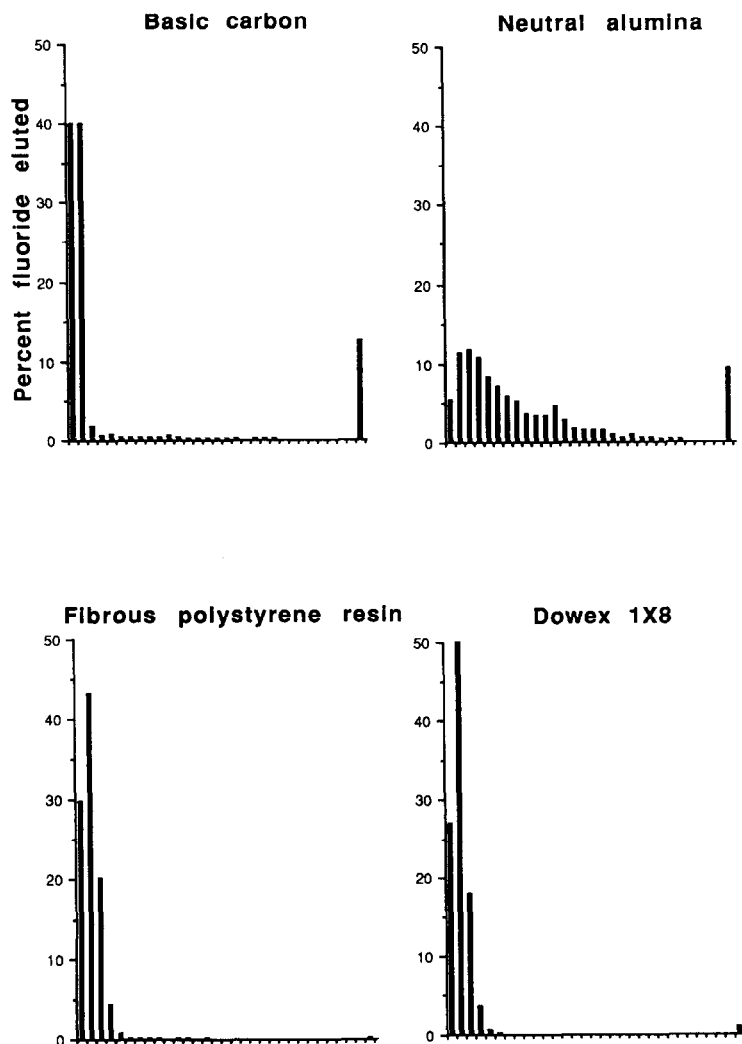


Fig. 1. Elution of [¹⁸F]fluoride by aqueous K₂CO₃ from a variety of anion exchangers. Each bar represents one 50 μl fraction of eluant. The bar at the far right represents the percent of the total [¹⁸F]fluoride remaining on the column after elution.

agreement with the performance of microporous carbons in HPLC and supports the assumption that such materials may offer a suitable basis for solid phases for nucleophilic radiofluorination. As with the neutral alumina the basic carbon bound some of the [^{18}F]fluoride irreversibly (9.3 and 12.5%, respectively). The fraction of irreversibly bound fluoride dropped when a larger fraction of the target water was applied to the column indicating that the concentration of such sites is small.

Figure 2 summarizes the results of Voll and Boehm (1970, 1971a, b) on the transformations and ion exchange reactions occurring on an amorphous carbon surface. Since the cationic groups were created on the carbon surface by incorporation of oxygen, an attempt was made to produce gaseous [^{18}F]HF by reducing the surface of the carbon, after fluoride incorporation, by hydrogen at elevated temperatures. However, no displacement of [^{18}F]fluoride into H_2 could be detected even at 500°C . Nor did any displacement of the [^{18}F]fluoride occur with N_2 or N_2O up to 500°C . With CH_3Cl displacement began at 300°C , and a sudden burst of displacement of most of the radioactivity from the column occurred as heating was continued. The radioactive material so displaced partitioned between water and CH_2Cl_2 in a ratio of about 12:1 indicating that it was in the form of HF than CH_3F .

Because of the apparent chemical and thermal stability of the cationic groups on the carbon the latter was treated with a number of reagents to characterize that stability. When a sample of the carbon activated by water and exposure to air was heated briefly to a dull red under N_2 in a quartz tube little or no loss of exchangeable sites was measured. Thus, drying basic carbon at elevated temperatures to remove traces of water is possible, whereas styrene based anion exchanged resins are rapidly degraded by heating. Concentrated aqueous persulfate, periodate and permanganate completely removed the cationic sites after 8 h. Thiosulfate gave little or no reduction. Methanolic NaBH_4 gave partial reduction after 10 min (from 350 to $150\ \mu\text{equiv/g}$). Brief exposures to concentrated HCl or HNO_3 did not remove the functionality. Heating the carbon with 1 N NaOH 1 h at 90°C resulted in partial removal of the functionality (from 350 to $180\ \mu\text{equiv/g}$).

Selectivities of the cationic groups on carbon toward various ions, determined by competition with Cl^- for exchange sites, were similar to those

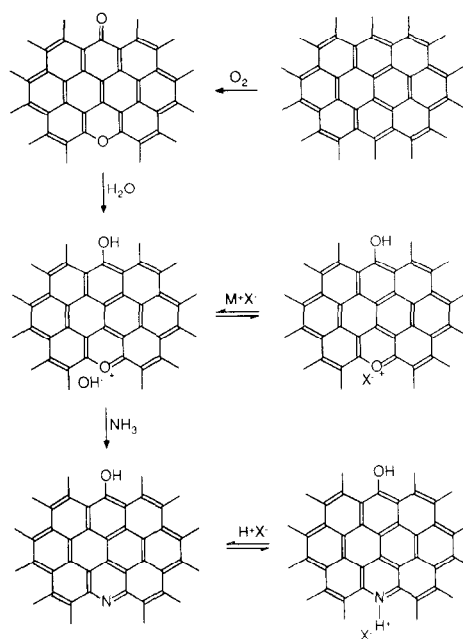


Fig. 2. Representation of the reactions producing basic exchange sites on an amorphous carbon surface, and of ion exchange reactions thereon [after Voll and Boehm (1971b)].

observed for quaternary ammonium groups on crosslinked polystyrene resins (toluene sulfonate > nitrate > citrate > formate > acetate \cong carbonate \cong bicarbonate \cong fluoride \cong hydroxide.) However, the chloride exchange capacities summarized in Table 1, indicate that the exchangeable sites on carbon do not all behave simply as stable, isolated cations as is the case with quaternary ammonium groups on polystyrene, i.e. the capacity for exchange of chloride from 1 N HCl was much greater than that from 1 N NaCl. Further, although Voll and Boehm (1971b) found that exposure of basic carbon to aqueous ammonia results in the substitution of nitrogen for half of the oxygen (Fig. 1), the resulting exchangeable sites do not behave as isolated pyridine groups. The ammonia-treated basic carbon adsorbs chloride from 1 N NaCl and also [^{18}F]fluoride from target water, whereas crosslinked polyvinyl pyridine (Reillex 402, Reilly Industries) does neither.

Other carbon samples, were heat treated as above in an attempt to develop detectable levels of cationic functionality. Neither a graphitized carbon fiber (Panex 320K, Zoltek, Inc.) nor a graphitized carbon black prepared as an HPLC phase (Shandon PCG

Table 1. Adsorption capacity of basic carbon samples and ion exchange resins for chloride from aqueous HCl and NaCl

Solid phase	Functionality	Cl ⁻ Exchange capacity, $\mu\text{equiv/g}$		Extracts fluoride from water?
		From HCl	From NaCl	
Basic carbon	Oxonium $^+\text{OH}^-$	350	140	Yes
Basic carbon ammoniated	Pyridine (?)	400	126	Yes
Polyvinyl pyridine	Pyridine	7700	Trace	No
AG 1X2	$\text{NR}_4^+ \text{OAc}^-$	3800	3500	Yes

Table 2. Amount of exchangeable water ($\mu\text{g}/20\text{ mg}$) remaining on solid phases after exposure to different drying agents. N_2 flow was for 10 min. Volume of MeOH or MeCN was 1 mL

Solid phase	Drying agent	Drying	
		temperature ($^{\circ}\text{C}$)	μg Exchangeable H_2O remaining
Basic carbon	N_2	23	45
Basic carbon	N_2	110	35
Basic carbon	MeOH	23	8
TIN 100 H^+	N_2	23	292
Dowex 1X8, 400 mesh, CO_3^{2-}	N_2	23	866
TIN 200 CO_3^{2-}	N_2	23	267
TIN 200 CL^-	N_2	23	56
TIN 200 OH^-	N_2	23	130
TIN 200 CO_3^{2-}	MeOH	23	0
TIN 200 CO_3^{2-}	MeCN	23	11
Merrifield aminopyridinium CO_3^{2-}	MeCN	23	2

102, 150 m^2/g) showed appreciable adsorption of [¹⁸F]fluoride after treatment. It is probable that graphitization renders the carbon surface resistant to the two-step oxidation required to produce the cationic surface (Voll and Boehm, 1970).

As a material for the routine extraction of [¹⁸F]fluoride for the labeling of radiopharmaceuticals the carbon prepared above was comparable to a polystyrene-based particulate resin (Schlyer *et al.*, 1990) or fibrous resin (Jewett *et al.*, 1990) reported previously. The lower exchange capacity was not a disadvantage since the amount of resin used in the published procedures apparently had a large excess of exchange capacity. Table 2 shows the amount of exchangeable water remaining after different drying procedures. Basic carbon was more readily dried by dry N_2 than either a particulate polystyrene resin [Dowex, 1, CO_3^{2-} , Schlyer *et al.* (1990)] or a fast fibrous anion exchange resin [TIN 200, CO_3^{2-} , Jewett *et al.* (1990)]. However, a small amount of water was tightly bound and was not removed by N_2 even at 110 $^{\circ}\text{C}$. As with the other resins, essentially all exchangeable water was rapidly removed by anhydrous MeOH or MeCN.

[¹⁸F]Fluoride extracted by basic carbon from [¹⁸O]water and eluted by aqueous K_2CO_3 was incorporated into the FDG precursor 1,3,4,6-tetra-*O*-acetyl-*O*-trifluoromethanesulfonyl- β -D-mannopyranose in good yield (95% recovery of fluoride: 80% incorporation). Carbonic acid at 52 atm was also a satisfactory electrolyte for elution of [¹⁸F]fluoride from basic carbon (Jewett, 1991).

Because of the low surface area and hence low ion exchange capacity of solid carbon surfaces, cationic surface groups would not be expected have an effect on the equilibrium of electrosorption of fluoride on glassy carbon electrodes from target water (Alexoff *et*

al., 1989). However, a kinetic effect may be possible. Understanding the possible role of surface functionality may lead to better control of electrosorptive methods for the extraction of [¹⁸F]fluoride.

Because of the similar results obtained with the basic carbon anion exchanger and the polystyrene-based resins and because of the expense of producing the former on a small scale, its use is not indicated for the current practical anion exchange methods for the recovery of [¹⁸F]fluoride. However, the higher chemical and thermal stability of the basic carbon may permit the development of new methods for handling [¹⁸F]fluoride. Further, carbon, because of its combination of inertness and electrical conductivity, will be an important component of new systems for handling fluorine-18, and an understanding of its interaction with fluoride ion will aid in such application.

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