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# Labelling of the CFC-alternative, 2*H*-heptafluoropropane (HFC 227ea), with fluorine-18

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**Abstract**

Various reactions of no-carrier-added $K^+$-aminopolyether 2.2.2-[$^{18}$F]fluoride were examined for labelling the CFC-alternative, 2*H*-heptafluoropropane (HFC 227ea), with the positron-emitting radioisotope, fluorine-18 ($t_{1/2}$ = 109.7 min). Reaction with 2*H*-hexafluoroisopropyl tosylate incorporated less than 2% of the radioactivity into [2-$^{18}$F]HFC 227ea and about 12% into three other volatile products. Reaction with hexafluoropropene led to a high incorporation of fluorine-18 (80%) into four radioactive products, namely the desired [1-$^{18}$F]HFC 227ea, [$^{18}$F]hexafluoropropene, [$^{18}$F]perfluoro-isohex-2-ene and an unknown, in a molar ratio of 5:4:38:3, respectively. Although reaction with 1-iodo-2*H*-hexafluoropropane gave [1-$^{18}$F]HFC 227ea in a much higher radiochemical yield (50% decay-corrected), the best radiochemical yield (80% decay-corrected) was obtained by exchange with HFC 227ea. The mechanistic bases of the results are discussed. An efficient fully shielded and automated procedure was devised for labelling HFC 227ea with fluorine-18 in high radioactivity, based on the successful exchange reaction and GC purification. [1-$^{18}$F]HFC 227ea was obtained in high radiochemical purity (>99%) and high chemical purity (>98.4%) at 80 min from the start of radiosynthesis. This product is suitable for studies of the disposition of HFC 227ea in vivo.

*Keywords:* 2*H*-Heptafluoropropane; HFC 227ea; Fluorine-18; Exchange labelling; Mass spectrometry; Reaction mechanisms

## 1. Introduction

2*H*-Heptafluoropropane (HFC 227ea) is being proposed as an alternative to ozone-depleting bromofluorocarbons (Halons) and chlorofluorocarbons (CFCs) in several applications, including use as fire extinguishants and aerosol propellants [1,2]. This compound is also being considered as a propellant in metered-dose inhalers for the administration of drugs [3–5]. This raises questions about the biological fate and distribution of HFC 227ea when inhaled by humans. The example of a recent study [5,6] on the CFC-replacement, 1,1,1,2-tetrafluoroethane (HFA 134a) indicates that the fate of HFC 227ea in vivo might be investigated similarly by whole-body $\gamma$-counting after labelling the fluorocarbon with the positron-emitting radioisotope, fluorine-18 ($t_{1/2}$ = 109.7 min). Thus, it was of interest to develop a method for labelling HFC 227ea in high radiochemical yield, radiochemical purity and chemical purity with fluorine-18.

The $^{18}$O(p,n)$^{18}$F reaction on $^{18}$O-enriched water is established as an efficient method for the production of high radioactivities of fluorine-18 as [$^{18}$F]fluoride at high specific radioactivity [7]. Moreover, there are now efficient procedures for reclaiming the $^{18}$O-enriched water and for converting the [$^{18}$F]fluoride into salts that are powerfully nucleophilic radiofluoridation reagents in organic solvents (e.g. Ref [8]). One of the most widely used of these reagents is the [$^{18}$F]fluoride of potassium cation-aminopolyether 2.2.2 ($K^+$-APE 2.2.2) [9]. Here we report our study of the use of this reagent to label HFC 227ea with fluorine-18 for potential application in studies of its distribution in vivo.

## 2. Experimental details

### 2.1. Chemicals

Hexafluoropropene, HFC 227ea, 2*H*-hexafluoroisopropyl tosylate and 1-iodo-2*H*-hexafluoropropane were purchased from Fluorochem Ltd. Potassium fluoride, anhydrous potassium carbonate, 4,7,13,16,21,24-hexaoxa-1,10-diazacyclo-[8.8.8]hexacosane (aminopolyether 2.2.2; Kryptofix® 2.2.2; APE 2.2.2) and acetonitrile were purchased from Aldrich Chemical Co. Ltd.

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### 2.2. Gas chromatography

Gas chromatography (GC) was performed on either a dual column (Carlo Erba 8340; Fisons Instruments plc) or a single column instrument (Shimadzu 14 ABPST; Dysons Instruments). Radioactivity was detected in analytical GC by a sodium iodide crystal detector (20 mm diameter; Bioscan™; Lablogic Ltd.) and in preparative GC by a plastic scintillant PM-tube detector with scaler ratemeter (Mini-instruments Ltd.). Data were acquired and analyzed from analytical GC with a Turbochrom™ 3 system (Perkin-Elmer Ltd.) and acquired from preparative GC with a dual-pen chart recorder.

*Method 1*

The Carlo Erba instrument, equipped with a 60/80 Carbopack B/5% Fluorcol SP alloy column (10 ft × 1/8 in o.d.; Supelco Ltd.) plus TC and radioactivity (sodium iodide) detectors in series, was operated with helium (30 ml $min^{-1}$; 30 p.s.i.) and the following oven programme: hold 15 °C for 10 min; raise 5 °C $min^{-1}$ to 100 °C; hold 30 min. Retention times: hexafluoropropene, 7.7 min; HFC 227ea, 10.9 min; perfluoro-isohex-2-ene, 29.6 min; 1-iodo-2*H*-hexafluoropropane, 35 min. The TC detector was calibrated for mass of HFC 227ea.

*Method 2*

The Shimadzu instrument, equipped with a Carboxen-1000 stainless-steel column (3.05 m × 1/8 in o.d.; Supelco Ltd.) plus TC and plastic scintillant-PM tube detectors in series, was operated isothermally at 225 °C with helium (60 ml $min^{-1}$; 60 p.s.i.),. Retention times; hexafluoropropene, 14.3 min; HFC 227ea, 24.8 min.

### 2.3. GC–MS

A Varian gas chromatograph, equipped with a BP 1 column (5 mm thick dimethyl siloxane, 25 mm × 0.33 mm i.d.; SGE Ltd.) and coupled to a quadrupole mass spectrometer (Nermag R10/10C), was used. The mass spectrometer was calibrated conventionally using perfluorobutylamine and run in the electron impact mode. Spectral data were collected using either a PDB 11/23 (Digital computers) with Sidar software program (NERMAG) for analysis or a 486 microprocessor with the ONYX software program (P2A systems).

### 2.4. Production of no-carrier-added $K^+$-APE 2.2.2-[$^{18}$F]fluoride

No-carrier-added (NCA) [$^{18}$F]fluoride (typical specific radioactivity > 1 Ci $\mu mol^{-1}$) was produced on the cyclotron at the MRC Clinical Sciences Centre by the $^{18}O(p,n)^{18}F$ reaction on $^{18}O$-enriched water [7]. As described previously [10,11], this [$^{18}$F]fluoride was converted within a glassy carbon vessel into dry $K^+$-APE 2.2.2-[$^{18}$F]fluoride using, unless otherwise stated, APE 2.2.2 (13 mg, 0.035 mmol) and anhydrous potassium carbonate (2.3 mg, 0.017 mmol).

### 2.5. Reaction of 2H-hexafluoroisopropyl tosylate with $K^+$-APE 2.2.2-[$^{18}$F]fluoride

To the glassy-carbon vessel containing dry $K^+$-APE 2.2.2-[$^{18}$F]fluoride (ca. 3 mCi) was added a solution of 2*H*-hexafluoroisopropyl tosylate (30 mg, 0.093 mmol) in acetonitrile (400 μl). The vessel was sealed, pressurized to 30 p.s.i. with nitrogen and heated for 30 min at 100 °C. The vessel was then allowed to cool to 50 °C. A gas sample was obtained by venting the headspace into a syringe. The radioactivity lost from the fully vented reaction vessel as volatile compounds was 14% (decay-corrected). Analysis of the sample by GC (Method 1) revealed that this collected radioactivity was distributed between [$^{18}$F]HFC 227ea (14%) and three other unidentified products, with retention times of 7.9, 10.4 and 31.1 min, respectively.

### 2.6. Reaction of 1-iodo-2H-hexafluoropropane with $K^+$-APE 2.2.2-[$^{18}$F]fluoride

To the glassy-carbon vessel containing dry $K^+$-APE 2.2.2-[$^{18}$F]fluoride (ca. 3 mCi) was added a solution of 1-iodo-2*H*-hexafluoropropane (0.2 ml) in acetonitrile (400 μl). The vessel was sealed, pressurized to 50 p.s.i. with nitrogen and heated for 30 min at 50 °C. The vessel was allowed to cool to 30 °C. A gas sample was obtained by venting the headspace into a syringe; 50% (decay-corrected) of the radioactivity was lost as volatile products from the fully vented reaction vessel. Radio-GC (Method 1) analysis revealed all the radioactivity in the sample to be [1-$^{18}$F]HFC 227ea with a specific radioactivity of 7 mCi $\mu mol^{-1}$ (Fig. 1). Hexafluoropropene and 1,1,2-trifluoropropene were also observed (Fig. 1); however, these compounds were present as trace impurities in the starting material and not formed in the reaction. GC–MS confirmed the presence of non-radioactive HFC 227ea; $m/z$ = 151 ($[M-F]^+$, 10%); 82 ($[M-CF_4]^+$, 15); 69 ($[CF_3]^+$, 100); 51 ($[CHF_2]^+$, 18); 31 ($[CF]^+$, 15).

### 2.7. Reaction of hexafluoropropene with $K^+$-APE 2.2.2-fluoride

The glassy carbon vessel was loaded with potassium fluoride (4.1 mg, 0.071 mmol), APE 2.2.2 (13 mg, 0.035 mmol), anhydrous potassium carbonate (2.3 mg, 0.017 mmol) and dry acetonitrile (400 μl), pressurized with hexafluoropropene (65 p.s.i.; ca. 160 mg), sealed and then heated at 95 °C for 30 min. The vessel was then allowed to cool to room temperature. A gas sample was taken by venting the headspace into a syringe. GC analysis (Method 1) of this sample revealed the following composition: hexafluoropropene (60% of TC detector response); HFC 227ea (8% of TC detector response); perfluoro-isohex-2-ene (32% of TC detector response) (the *cis* and *trans* isomers of perfluoro-isohex-2-ene were not discriminated in the analysis).

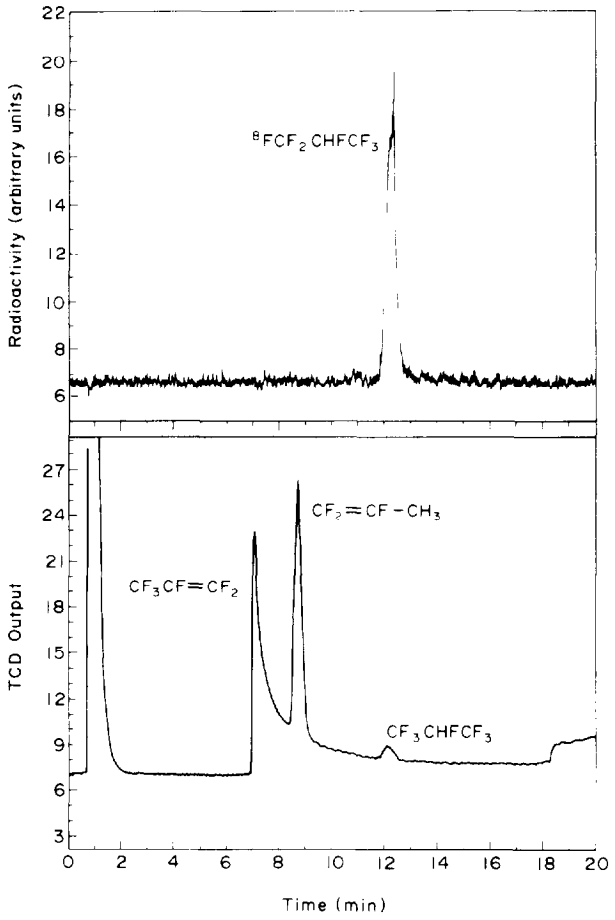



Fig. 1. Radio-GC analysis (Method 1; see text) of the volatile products from the reaction of $K^+$-APE 2.2.2-[$^{18}$F]fluoride with 1-iodo-2*H*-hexafluoropropane.

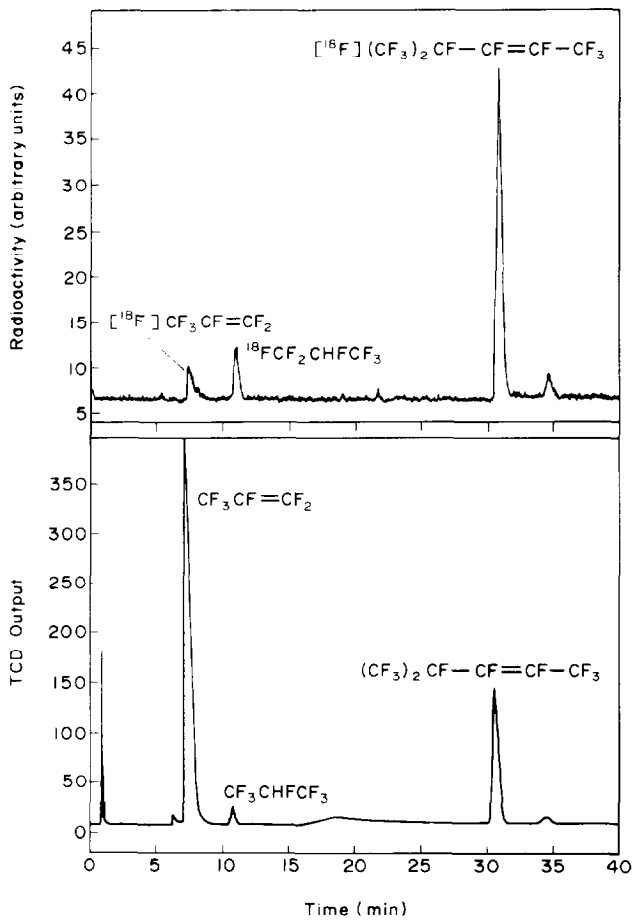



Fig. 2. Radio-GC analysis (Method 1; see text) of the volatile products from the reaction of $K^+$-APE 2.2.2-[$^{18}$F]fluoride with hexafluoropropene.

### 2.8. Reaction of hexafluoropropene with $K^+$-APE 2.2.2-[$^{18}$F]fluoride

The glassy carbon vessel, containing dry $K^+$-APE 2.2.2-[$^{18}$F]fluoride (ca. 3 mCi) in dry acetonitrile (400 μl), was pressurized with hexafluoropropene (65 p.s.i.; ca. 160 mg), sealed and then heated at 95 °C for 30 min. The vessel was allowed to cool to room temperature. A gas sample was taken by venting the headspace into a syringe; 80.6% (decay-corrected) of the radioactivity was lost from the fully vented reaction vessel as volatile products. The sample was analysed by GC (Method 1) and GC–MS analysis. The following pairs of radioactive and non-radioactive compounds were found (Fig. 2).

[$^{18}$F]Hexafluoropropene (28% of radioactivity) and hexafluoropropene {72.5% of TC detector response; $m/z$ = 150 ($[M]^+$, 20%); 131 ($[M-F]^+$, 50); 100 ($[M-CF_2]^+$, 30); 93 ($[M-3F]^+$, 10); 81 ($[M-CF_3]^+$, 15); 69 ($[CF_3]^+$, 95); 50 ($[CF_2]^+$, 15); 31 ($[CF]^+$, 100)}.

[$^{18}$F]HFC 227ea (10% of radioactivity) and HFC 227ea (2% of TC detector response; mass spectrum as given under Section 2.6).

[$^{18}$F]Perfluoro-isohex-2-ene (76% of radioactivity) and perfluoro-isohex-2-ene {24% of TC detector response: $m/z$ = 300 ($[M]^+$, 5%); 281 ($[M-F]^+$, 5); 231 ($[M-CF_3]^+$, 5); 212 ($[M-CF_4]^+$, 3); 181 ($[M-CF_3-CF_2]^+$, 15); 131 ($[M-2CF_3-CF]^+$, 10); 93 ($[M-3CF_3]^+$, 12); 69 ($[CF_3]^+$, 100); 31 ($[CF]^+$, 10)}.

Radioactive unknown (6% of radioactivity) and co-eluting non-radioactive compound {1.5% of TC detector response: $m/z$ = 304 (6); 293 (5); 280 (3); 256; 245; 209 (5); 174 (5); 162 (15); 150 (5); 93 (12); 69 (100); 29 (24).

### 2.9. Reaction of HFC 227ea with $K^+$-APE 2.2.2-[$^{18}$F]fluoride

*Reaction A*

The glassy carbon vessel, containing dry $K^+$-APE 2.2.2-[$^{18}$F]fluoride (ca. 3 mCi) in dry acetonitrile (500 μl), was pressurized with HFC 227ea (40 p.s.i.; ca. 110 mg), sealed and heated at 100 °C for 30 min. The vessel was allowed to cool to room temperature. A gas sample was obtained by venting the headspace into a syringe; 81% (decay-corrected) of the radioactivity was lost from the fully vented reaction vessel as volatile products. The sample was found by GC analysis (Method 1) to consist of [$^{18}$F]HFC 227ea (>99% of radioactivity), HFC 227ea (98.9% of TC detector

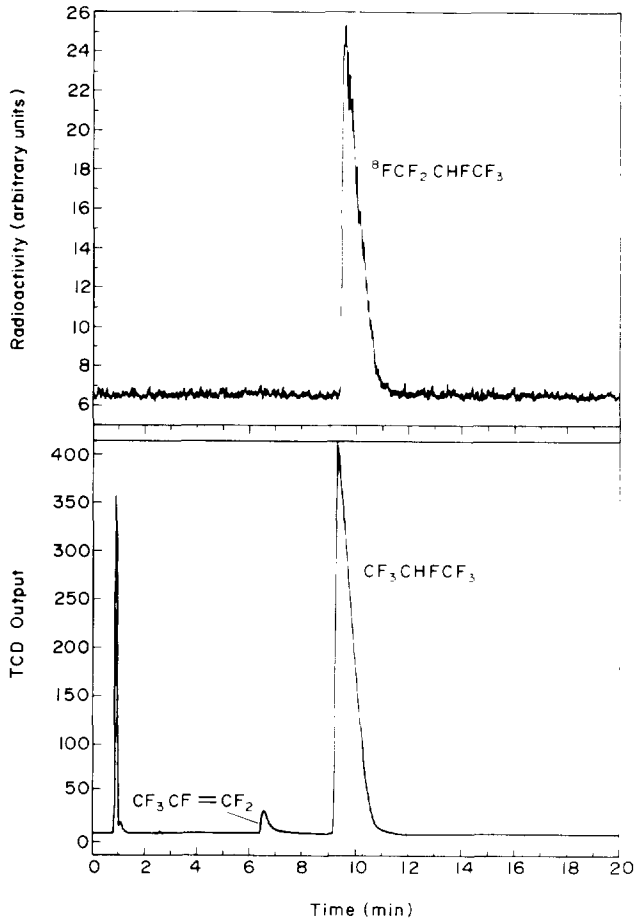



Fig. 3. Radio-GC analysis (Method 1; see text) of the volatile products from the reaction of $K^+$-APE 2.2.2-[$^{18}$F]fluoride with HFC 227ea.

response) and hexafluoropropene (1.1% of TC detector response) (Fig. 3).

*Reaction B*

The above reaction was repeated without acetonitrile. GC analysis (Method 1) revealed the gaseous product to have radiochemical and chemical compositions that were similar to that obtained in the presence of solvent. The total incorporation of radioactivity into volatile fluorocarbons was 80% (decay-corrected).

### 2.10. Automated synthesis of [1-$^{18}$F]HFC 227ea

A fully lead-shielded and automated apparatus was used to produce pure [1-$^{18}$F]HFC 227ea in high radioactivities. The apparatus has been described in detail previously [11]. It features a sealable glassy carbon reaction vessel coupled to a preparative gas chromatograph. NCA [$^{18}$F]fluoride in $^{18}$O-enriched water (20 atom%) was transferred from the proton-irradiated production target and passed through an anion-exchange resin in the carbonate form [8]. The adsorbed [$^{18}$F]fluoride [ca. 1.85 GBq (ca. 25 mCi)] was eluted from the resin with potassium carbonate solution (0.6 ml; 0.3 M) [8] into the glassy-carbon reaction vessel containing a solution of APE 2.2.2 (15.6 mg) in acetonitrile (0.2 ml). The solution was then heated to dryness under reduced pressure with a slow purge of nitrogen. The vessel was pressurized to 45 p.s.i. with HFC 227ea (ca. 0.5 mmol), sealed, heated at 150 °C for 25 min and then vented into a Valco GC injection valve (loop size, 3 ml) for separation of the volatile products by GC (Method 2). The effluent of the gas chromatograph eluting between 23.5 and 26 min was passed through a stainless-steel cold trap (−178 °C) to collect the [1-$^{18}$F]HFC 227ea. The cold trap was allowed to warm to room temperature and then purged with helium into a 10 ml syringe. This product was then analysed by GC (Method 1) and GC–MS and shown to consist of [$^{18}$F]HFC 227ea [110 MBq; 3 mCi; >99% of radioactivity] and HFC 227ea {98.4% of TC detector response; $m/z$=151 ([M−F]$^+$, 10%); 100 ([M−$CHF_3$]$^+$, 1); 82 ([M−$CF_4$]$^+$, 15); 69 ([$CF_3$]$^+$, 100); 51 ([$CF_2^+$], 18)} and an unknown {1.1% of TC detector response; $m/z$=82 ([$C_2HF_3$]$^+$, 10%); 69 ([$CF_3$]$^+$, 100); 51 ([$CHF_2$]$^+$, 15)}.

## 3. Discussion

Nucleophilic substitution of a good leaving group, such as iodo or tosyl [12] by no-carrier-added [$^{18}$F]fluoride is often used to introduce fluorine-18 at aliphatic carbons. Generally, these are rapid and high-yielding reactions, especially if performed in polar aprotic solvents, such as acetonitrile, with $K^+$-APE 2.2.2 as counterion [12]. Thus, [$^{18}$F]fluoride reacts with 2-iodopropane in acetonitrile to give 2-[$^{18}$F]-fluoropropane in good radiochemical yield [13]. Also, $K^+$-APE 2.2.2-[$^{18}$F]fluoride reacts with 2,2,2-trifluoroethyl tosylate in acetonitrile to give [2-$^{18}$F]1,1,1,2-tetrafluoroethane in high radiochemical yield [11]. However, an initial attempt to prepare [2-$^{18}$F]HFC 227ea by substitution in commercially available 2*H*-hexafluoroisopropyl tosylate with $K^+$-APE 2.2.2-[$^{18}$F]fluoride in acetonitrile gave the desired [$^{18}$F]HFC 227ea in less than 2% radiochemical yield (decay-corrected) and three other unidentified volatile radioactive products, which accounted for only 12% of the initial radioactivity (Scheme 1). This result discouraged pursuit of nucleophilic substitution as a route to high radioactivities of [2-$^{18}$F]HFA 227ea. However, we considered that HFA 227ea might be labelled efficiently in the 1-position by a nucleophilic substitution in a suitable precursor with [$^{18}$F]fluoride.

$$K^+\text{-APE 2.2.2-}{}^{18}F^- \xrightarrow{(CF_3)_2CHOTs} \underset{(2\%)}{(CF_3)_2CH^{18}F} + \underset{(12\%)}{\text{other radioactive products}}$$

Scheme 1. Reaction of $K^+$-APE 2.2.2-[$^{18}$F]fluoride with 2*H*-hexafluoroisopropyl tosylate.

Reaction of commercially available 1-iodo-2*H*-hexafluoropropane with $K^+$-APE 2.2.2-[$^{18}$F]fluoride in acetonitrile under mild conditions (50 °C for 30 min) gave a 50% radiochemical yield (decay-corrected) of $^{18}$F-labelled HFC

227ea. No other volatile radioactive product was observed (Scheme 2). (Non-radioactive alkenes were detected but these were present as trace impurities in the starting material.) [$^{18}$F]1-Fluoropropane has been prepared in 44% radiochemical yield by the reaction of silver-supported [$^{18}$F]fluoride with gaseous 1-iodopropane at 200 °C [13] and in greater than 75% radiochemical yield by the silver(I)-catalysed reaction of [$^{18}$F]tetraethylammonium fluoride with iodopropane in acetonitrile at 120 °C for 30 min [14]. Thus, it seems, as would be predicted, that the electron-withdrawing 2*H*-hexafluoropropyl group encourages [$^{18}$F]fluoro for iodo exchange more strongly than the propyl group.

$$K^+\text{-APE 2.2.2-}{}^{18}F^- \xrightarrow{CF_3CHFCF_2I} \underset{(50\%)}{CF_3CHFCF_2{}^{18}F}$$

Scheme 2. Reaction of K$^+$-APE 2.2.2-[$^{18}$F]fluoride with 1-iodo-2*H*-hexafluoropropane.

The reactions of hexafluoropropene with (i) potassium fluoride/formamide at 65 °C for 6 h and (ii) potassium fluoride in water/dioxan for 7 d at room temperature are known to give HFC 227ea in 21% and 84% yield, respectively [15]. Furthermore, we have recently shown that the reaction of K$^+$-APE 2.2.2-[$^{18}$]fluoride with trifluoroethylene is tantamount to the addition of anhydrous hydrogen [$^{18}$F]fluoride and produces [1-$^{18}$F]1,1,1,2-tetrafluoroethane in high radiochemical yield [10]. On this basis, we considered that [1-$^{18}$F]HFC 227ea might also be obtained by the reaction of hexafluoropropene with K$^+$-APE 2.2.2-[$^{18}$F]fluoride, with the reservation that fluoride is known to induce the ready dimerisation of hexafluoropropene and that even trimerisation is possible under certain conditions [16–19].

Initially, the reaction of hexafluoropropene with potassium fluoride in acetonitrile in the presence of a molar excess of APE 2.2.2 was studied. GC–MS analysis demonstrated that HFC 227ea was produced (8% of TC detector response), but that the major product was a dimer, perfluoro-isohex-2-ene (32% of TC detector response). Starting material was the only other compound detected in the analysis. These products are almost certainly formed through addition of fluoride to hexafluoropropene, thus giving an intermediate carbanion which may then abstract a proton from the reaction milieu or react with another molecule of hexafluoropropene to give the dimeric olefin (Scheme 3) [16–19].

$$CF_3CF{=}CF_2 \underset{-F^-}{\overset{K^+\text{-APE 2.2.2-}F}{\rightleftharpoons}}$$

$$[CF_3\bar{C}FCF_3] \xrightarrow{H^+} \underset{(8\%)}{CF_3CHFCF_3}$$

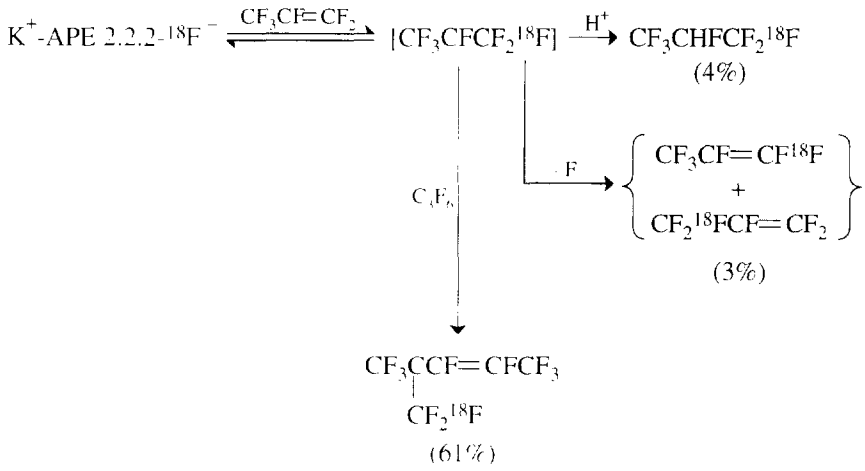
$$[CF_3\bar{C}FCF_3] \xrightarrow{C_3F_6} \underset{(32\%)}{(CF_3)_2CCF{=}CFCF_3}$$

Scheme 3. Reaction of K$^+$-APE 2.2.2-fluoride with hexafluoropropene.

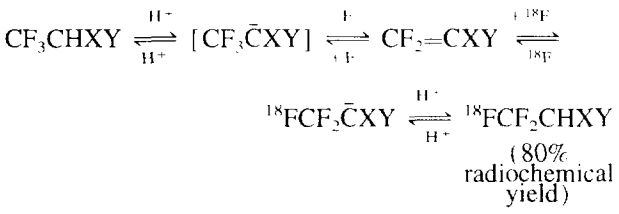
The reaction of K$^+$-APE 2.2.2-[$^{18}$F]fluoride with hexafluoropropene in acetonitrile incorporated 80.6% of the radioactivity into four main radioactive products, namely the desired [1-$^{18}$F]HFC 227ea, [$^{18}$F]hexafluoropropene [1], the dimer [$^{18}$F]perfluoro-isohex-2-ene and an unknown, in the molar ratio of 5:4:38:3, respectively. These results are broadly consistent with those from the non-radioactive reaction. The specific radioactivity of the labelled HFC 227ea (7 mCi mmol$^{-1}$) was found to be much less than that of the cyclotron-produced NCA [$^{18}$F]fluoride (>100 mCi $\mu$mol$^{-1}$), showing that carrier fluoride is generated in the reaction. This observation and the noted incorporation of fluorine-18 into the starting material are consistent with the existence of an equilibrium between hexafluoropropene and the carbanion formed by addition of [$^{18}$F]fluoride (Scheme 4). Due to the modest radiochemical yield of [1-$^{18}$F]HFC 227ea and the formation of radioactive byproducts, this approach was not considered further.

[$^{18}$F]Fluoride has been incorporated into several 1,1,1-trifluoroalkanes by exchange with K$^+$-APE 2.2.2-[$^{18}$F]fluoride [11,21,22]. Much evidence [21,22] suggests that the mechanism of exchange involves deprotonation of the hydrofluorocarbon followed by fluoride loss from the trifluoromethyl group of the generated carbanion (an E1cB mechanism), with the reverse sequence resulting in the incorporation of [$^{18}$F]fluoride (Scheme 5). Exchange is favoured when the intermediate carbanion is stabilised [21] and able to extract a proton from the reaction milieu; protons are readily abstracted from solvents such as acetonitrile [11,21]. The trifluoromethyl group is highly electron-withdrawing and itself stabilises the intermediate carbanion [23]. Stabilisation increases with the number of trifluoromethyl or other electron-withdrawing substituents bonded to the carbon bearing the formal negative charge [21–23]. Thus, sevoflurane [$(CF_3)_2CHOCF_2H$] and 2-chloro-2*H*-hexafluoropropane readily exchange fluorine with [$^{18}$F]fluoride in the presence of K$^+$-APE 2.2.2 in acetonitrile at 125 °C. Radiochemical yields are greater than 90% [21]. Exceptionally, the strongly electronegative fluoro group is weakly effective at stabilising an intermediate carbanion because of its opposing mesomeric effect [22,24]. Thus, 1,1,1-trifluoro-2-iodoethane exchanges fluoro for [$^{18}$F]fluoro much more readily than 1,1,1,2-tetrafluoroethane [10,11,20]. Thus, it was of interest to test whether HFC 227ea, which has two trifluoromethyl and one fluoro group bonded to a single carbon atom, could be labelled efficiently with fluorine-18 by an exchange reaction. HFC 227ea was treated with K$^+$-APE-2.2.2-[$^{18}$F]fluoride in the presence and in the absence of acetonitrile as solvent. Each reaction produced carrier-added [$^{18}$F]HFC 227ea in high radiochemical yield (ca. 80%) and in high radiochemical purity (>99%).

[1] It should be noted that exchange of fluorine between hexafluoropropene and rubidium [$^{18}$F]fluoride has been reported previously [20].




Scheme 4. The reaction of K$^+$-APE 2.2.2-[$^{18}$F]fluoride with hexafluoropropene.




Scheme 5. Reaction of K$^+$-APE-2.2.2-[$^{18}$F]fluoride with 1,1,1-trifluoroalkanes.

The supposed mechanism of this exchange reaction (Scheme 5: X = $CF_3$, Y = F) implies that labelling is mainly in the 1-position. A recent study of the labelling of 1,1,1,2-tetrafluoroethane by nucleophilic substitution and addition reactions of [$^{18}$F]fluoride warns against assuming regiospecificity on the basis of the formal reaction mechanism [25]. Thus, it is conceivable that in the exchange labelling of HFC 227ea some label will appear in the 2-position as a result of direct exchange by nucleophilic substitution. However, the reaction of K$^+$-APE-2.2.2-[$^{18}$F]fluoride with 2-chloro-2*H*-hexafluoropropane in acetonitrile clearly favours exchange over any substitution [21]. Moreover, here we obtained only a low radiochemical yield (2%) of [$^{18}$F]HFC 227ea from the reaction of K$^+$-APE-2.2.2-[$^{18}$F]fluoride with 2*H*-hexafluoropropyl tosylate. Thus, direct substitution in the 2-position is probably a very minor process in the exchange labelling of HFC 227ea. On the same basis, efficient exchange of fluoro with [$^{18}$F]fluoro in the reaction of K$^+$-APE-2.2.2-[$^{18}$F]fluoride with 2*H*-hexafluoropropyl tosylate (i.e. Scheme 3; X = H, Y = OTs) probably accounts for the very low radiochemical yield of [2-$^{18}$F]HFC 227ea.

The exchange reaction without solvent was chosen for its simplicity and high radiochemical yield for the synthesis of high radioactivities of pure [1-$^{18}$F]HFC 227ea. In order to ensure radiation safety for personnel, a fully lead-shielded and automated apparatus including preparative GC, previously developed for the synthesis of [1-$^{18}$F]HFC 1,1,1,2-tetrafluoroethane [11], was modified with respect to GC conditions for the production of high radioactivities of [1-$^{18}$F]HFC 227ea. [1-$^{18}$F]HFC 227ea (3 mCi) was produced in 80 min with a radiochemical purity of greater than 99% and a chemical purity of 98.4%. This product is suitable for the study of the disposition of HFA 227ea in vivo by whole body γ-counting. Exchange reactions necessarily give low specific radioactivity. The same apparatus could be used to produce pure no-carrier-added product by the reaction of [$^{18}$F]fluoride with 1-iodo-2*H*-hexafluoropropane.

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