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Efficient regioselective labelling of the CFC alternative 1,1,1,2-tetrafluoroethane (HFC-134a) with fluorine-18

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Abstract

Efficient chemistry is described for the regioselective labelling of the CFC alternative 1,1,1,2-tetrafluoroethane with cyclotron-produced positron-emitting fluorine-18 ($t_{1/2}$ = 109.7 min). [1-^{18}F]1,1,1,2-Tetrafluoroethane was prepared by nucleophilic addition of no-carrier-added [^{18}F]fluoride to trifluoroethylene and [2-^{18}F]1,1,1,2-tetrafluoroethane by nucleophilic displacement of tosylate with [^{18}F]fluoride in 2,2,2-trifluoroethyl *p*-toluenesulphonate. Each reaction was mediated by a potassium cation–Kryptofix® 2.2.2 complex, with or without acetonitrile as solvent, in a sealed glassy carbon vessel. The selectivities were 97.2 ± 0.4% for labelling in the 1-position by nucleophilic addition and 91.2 ± 1.2% for labelling in the 2-position by nucleophilic substitution. GC separation afforded each labelled tetrafluoroethane in high radiochemical purity (> 99.995%) and high chemical purity (> 99.6%). Specific radioactivities of about 37 MBq (1 mCi) per μmol were obtained. Each synthesis was fully automated to cope safely with the high initial radioactivity and delivered purified product within one physical half-life of the fluorine-18. The products are suitable for pharmacokinetic studies in man.

Keywords: Regioselective labelling; 1,1,1,2-Tetrafluoroethane; Fluorine-18; Nucleophilic addition; Nucleophilic substitution; Mass spectrometry

1. Introduction

1,1,1,2-Tetrafluoroethane (HFC-134a) is now produced on a large scale as the main halogenated replacement for ozone-depleting chlorofluorocarbons (CFCs) as refrigerants and coolants [1–3]. 1,1,1,2-Tetrafluoroethane also has potential application as a propellant in metered dose inhalers for administering therapeutics to patients. This leads to a requirement to study the absorption, retention and distribution of 1,1,1,2-tetrafluoroethane in man. It was considered that these parameters might be studied by using 1,1,1,2-tetrafluoroethane labelled with fluorine-18, a short-lived ($t_{1/2}$ = 109.7 min) positron-emitting (β^+ = 96.9%) isotope. Compounds labelled with positron-emitting isotopes are externally detectable in vivo, for example by using simple whole-body counting using sensitive sodium iodide detectors [4] or high-resolution positron emission tomography (PET) [5]. Importantly, by using regioselective labelling techniques, the metabolism of a labelled compound as well as its pharmacokinetics and biodistribution in man may be elucidated.

Fluorine-18 can be produced with a cyclotron by the ^{18}O(p,n)^{18}F reaction on ^{18}O-enriched water as aqueous [^{18}F]fluoride in high radioactivity (37 GBq; ca. 1 Ci) and in high specific radioactivity (370 MBq μmol^{-1}; 10 Ci μmol^{-1}) (for a recent review see Ref. [6]). Here we report on the efficient use of [^{18}F]fluoride for preparing [1-^{18}F]1,1,1,2-tetrafluoroethane and [2-^{18}F]1,1,1,2-tetrafluoroethane in high radiochemical and chemical purity, ready for pharmacokinetic studies in man. The radiochemistry was performed in lead-shielded apparatus by remote control to allow high radioactivities to be produced safely.

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2. Experimental and results

2.1. Chemicals

2-Chloro-1,1,1,2-tetrafluoroethane (HFC-124), 1,1,2,2-tetrafluoroethane (HFC-134) and trifluoroethylene (HFC-1123) were obtained from Fluorochem Ltd. 1,1,1,2-Tetrafluoroethane (HFC-134a) was obtained as a gift from ICI Chemicals and Polymers Ltd or purchased from Fluorochem Ltd. 2,2,2-Trifluoroethyl *p*-toluenesulphonate (2,2,2-trifluoroethyl tosylate), lithium aluminium hydride (1 M in tetrahydrofuran; LAH), 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix® 2.2.2; aminopolyether 2.2.2; APE 2.2.2), anhydrous potassium fluoride, anhydrous potassium carbonate and acetonitrile-d_3 were obtained from Aldrich Chemical Co. Ltd.

2.2. Gas chromatography

Gas chromatography (GC) was performed on either a dual column (Carlo Erba 8340; Fisons Instruments PLC) or single column instrument (Shimadzu 14 ABPST; Dyson 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 a 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 FI and sodium iodide detectors in parallel (split ratio 1) and a PLOT fused silica (Al_2O_3/KCl) capillary column (50 mm × 0.32 mm i.d.; Chrompack Ltd.), was operated with helium (5 ml min^{-1}; 30 p.s.i.) and the following oven programme: hold 60 °C for 5 min; raise 10 °C min^{-1} to 75 °C; hold 8 min; raise 20 °C min^{-1} to 200 °C; hold 10 min. Retention times: trifluoroethylene (6.8 min), 1,1,1,2-tetrafluoroethane (15.5 min), 2-chloro-1,1,1,2-tetrafluoroethane (18.5 min), 1,1,2,2-tetrafluoroethane (21.6 min). From their known empirical ECNs (effective carbon numbers), these compounds are calculated to give a similar relative response per unit weight in FI detection (within ±10% of the response for 1,1,1,2-tetrafluoroethane) [7–9].

Method 2: Conditions were as in Method 1, except that the oven was run isothermally (120 °C). Retention times: trifluoroethylene (5.0 min), 1,1,1,2-tetrafluoroethane (6.8 min), 2-chloro-1,1,1,2-tetrafluoroethane (8.7 min), 1,1,2,2-tetrafluoroethane (11.7 min).

Method 3: The Carlo Erba instrument, equipped with TC and sodium iodide detectors in series and with a 60/80 Carbopack™ B/5% Fluorcol™ SP alloy column (10 ft. × 1/8 in. o.d.; Supelco Ltd.), was operated with helium (30 ml min^{-1}; 30 p.s.i.) and the following oven programme: hold 25 °C for 10 min; raise 10 °C min^{-1} to 120 °C; hold 20 min. Retention times: trifluoroethylene (1.7 min), 1,1,1,2-tetrafluoroethane (2.8 min).

The TC detector was calibrated regularly for 1,1,1,2-tetrafluoroethane as follows. Responses (peak area: μV s) were obtained for known volumes of air (at room temperature and pressure) injected from a calibrated gas-tight syringe (100 μl; Hamilton). Response was linear up to 100 μl. A 10 ml syringe was repeatedly filled with 1,1,1,2-tetrafluoroethane from a stock cylinder. This syringe was then sampled through a luer-fit septum (Braun) into a gas-tight syringe (100 μl; open needle Hamilton) for GC. Responses for 1,1,1,2-tetrafluoroethane (10–100 μl at room temperature and pressure, including any ingress of air) were then obtained. For each sample the true amount of 1,1,1,2-tetrafluoroethane injected into the instrument was calculated (assuming ideal gas behaviour) as follows:

1,1,1,2-Tetrafluoroethane (μmol)

$$= 0.0416[(\text{injection vol., } \mu\text{l}) - (\text{air detected, } \mu\text{l})]$$

Response (ca. 1.86 × nV s per μmol at each calibration) was linear over the measured range (0.416–4.16 μmol). Response for trifluoroethylene was nearly identical.

Method 4: The Shimadzu instrument, equipped with TC and plastic scintillant PM-tube detectors in series and a Carboxen-1000 stainless-steel column (3.05 m × 1/8 in. o.d.; Supelco Ltd.), was operated isothermally (150 °C) with helium (60 ml min^{-1}, 60 p.s.i.). Retention times: trifluoroethylene (15.6 min), 1,1,1,2-tetrafluoroethane (30.6 min), 1,1,2,2-tetrafluoroethane (40.0 min).

2.3. GC–MS

A Varian gas chromatograph 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 (EI) mode. Spectral data were collected using either a PDP 11/23 (Digital Computers) with Sidar software programs (Nermag) for analysis or a 486 microprocessor with the ONYX software program (P2A Systems).

Method 1: A PLOT fused silica (Al_2O_3/KCl) column (50 m × 0.32 mm i.d.; Chrompack Ltd.) was operated isothermally (120 °C) with helium (15 p.s.i.). Injections (20 μl) were made from a Valco gas valve. Retention time: 1,1,1,2-tetrafluoroethane (5.0 min).

Method 2: A B.P. 1 column (5 μm thick dimethyl siloxane, 25 m × 0.33 mm i.d.; SGE Ltd.) was operated isothermally (25 °C) with helium (5 p.s.i.). Injections (50 μl) were made from a heated (40 °C) Valco gas valve. Retention times: trifluoroethylene (46 s), 1,1,1,2-

tetrafluoroethane (49 s). Though these compounds elute rapidly, they are completely separated.

2.4. Production of fluorine-18 as n.c.a. [^{18}F]fluoride

No carrier added (n.c.a.) aqueous [^{18}F]fluoride was produced on the Scanditronix MC 40 Mk II cyclotron at the MRC Clinical Sciences Centre by the $^{18}O(p,n)^{18}F$ reaction on ^{18}O-enriched water (20 atom%), essentially as described previously [6]. [^{18}F]Fluoride (ca. 1.85 GBq, 50 mCi) was separated from the ^{18}O-enriched water and low levels of cationic radionuclidic impurities by adsorption on to a column (28 mm×3 mm i.d.) of anion-exchange resin (100–200 mesh Dowex AG 1X 8 in the carbonate form; 90 mg) and subsequent elution with potassium carbonate solution (4.6 mg ml^{-1}, 0.0333 M; 0.5 ml) [6,10]. Generally, for labelling experiments, a portion of this solution was added to a solution of APE 2.2.2 [2.6 mg (6.9 μmol) per 100 μl of [^{18}F]fluoride potassium carbonate solution) in acetonitrile (0.5 ml) and boiled to dryness in an open glassy carbon vessel (Sigridur™) under a stream of nitrogen. Acetonitrile (0.5 ml) was twice added and evaporated to leave a residue of dry K^+–APE 2.2.2–[^{18}F]fluoride.

2.5. Reaction of 1,1,1,2-tetrafluoroethane with K^+–APE 2.2.2–[^{18}F]fluoride

Method A: A glassy carbon vessel containing n.c.a. [^{18}F]fluoride (ca. 370 MBq, ca. 10 mCi), APE 2.2.2 (13 mg, 34.5 μmol), potassium carbonate (2.3 mg, 16.6 μmol) and dry acetonitrile (0.3 ml) was pressurized to 2.8 bar (40 p.s.i.) with 1,1,1,2-tetrafluoroethane (ca. 50 mg, ca. 0.5 mmol) and then sealed and heated at 95 °C for 20 min. The vessel was then allowed to cool to room temperature and vented to an all-polypropylene syringe. GC analysis of the collected gas (Method 1) revealed the presence of 99.7% 1,1,1,2-tetrafluoroethane and 0.2% trifluoroethylene by weight of organic compounds (remainder unknowns), plus 70% [^{18}F]1,1,1,2-tetrafluoroethane and 30% [^{18}F]trifluoroethylene by radioactivity. The two radioactive products contained 7.5% of the initial radioactivity (decay-corrected).

Method B: The above reaction was repeated without acetonitrile. GC analysis (Method 1) revealed the gaseous product (4% of the initial radioactivity, decay-corrected) to have a similar chemical and radiochemical composition to the product obtained in the presence of solvent.

2.6. Synthesis of 1,1,1,2-tetrafluoroethane from 2-chloro-1,1,1,2-tetrafluoroethane

2-Chloro-1,1,1,2-tetrafluoroethane (50 ml at room temperature and pressure, 2.2 mmol) was bubbled into a solution of LAH (30 ml, 1.0 M) at room temperature. The effluent was then passed through a stainless-steel trap cooled to −78 °C. GC–MS (Methods 1 and 2) of the trapped product revealed 1,1,1,2-tetrafluoroethane: *m/z* 102 ($[M]^+$, 2%); 83 ($[M-F]^+$, 85); 69 ($[CF_3]^+$, 100); 63 ($[M-HF-F]^+$, 15); 51 ($[CF_2H]^+$, 28); 50 ($[CF_2]^+$ 10); 33 ($[CH_2F]^+$, 20); 31 ($[CF]^+$, 45).

2.7. Radiosynthesis of [^{18}F]2-chloro-1,1,1,2-tetrafluoroethane

Method A: A glassy carbon vessel containing n.c.a. [^{18}F]fluoride (ca. 370 MBq, ca. 10 mCi), APE 2.2.2 (13 mg, 34.5 μmol), potassium carbonate (2.3 mg, 16.6 μmol) and dry acetonitrile (0.3 ml) was pressurized (2.8 bar, 40 p.s.i.) with 2-chloro-1,1,1,2-tetrafluoroethane (ca. 60 mg, ca. 0.44 mmol), sealed and heated at 95 °C for 20 min. The vessel was then allowed to cool to room temperature and vented to a syringe. GC analysis of the collected gas (Methods 1 and 2) revealed the only radioactive product to be [^{18}F]2-chloro-1,1,1,2-tetrafluoroethane (decay-corrected radiochemical yield, 40%).

Method B: Method A was repeated without acetonitrile. GC analysis of the collected gas (Methods 1 and 2) revealed the only radioactive product to be[^{18}F]2-chloro-1,1,1,2-tetrafluoroethane (decay-corrected radiochemical yield, 32%).

2.8. Reactions of trifluoroethylene with K^+–APE 2.2.2–[^{18}F]fluoride

Reaction A: A glassy carbon vessel containing dry n.c.a. [^{18}F]fluoride (ca. 110 MBq, ca. 3 mCi), APE 2.2.2 (34.5 μmol, 13 mg), potassium carbonate (16.6 μmol, 2.3 mg) and dry acetonitrile (0.3 ml) was pressurized to 3.5 bar (50 p.s.i.) with trifluoroethylene (ca. 60 mg, ca. 0.73 mmol), sealed and heated at 95 °C for 25 min. The vessel was then allowed to cool to 75 °C and vented to a polypropylene syringe. GC analyses of products from several reactions (Methods 1–3) revealed approximately 99.5% trifluoroethylene and 0.5% 1,1,1,2-tetrafluoroethane by weight of organic compounds plus 2%–30% [^{18}F]trifluoroethylene, 70%–98% [^{18}F]1,1,1,2-tetrafluoroethane and 0%–10% of an unknown (retention time, 12.5 min in Method 2) by radioactivity. GC–MS (Method 1) confirmed the identity of the major non-radioactive products. The three radioactive products contained 80%–90% of the initial radioactivity (decay-corrected). (The use of temperatures up to 115 °C and pressures up to 78 p.s.i. also gave high incorporations of [^{18}F]fluoride.)

Reaction B: The above reaction was repeated using acetonitrile-d_3 as the solvent. Analysis by GC (Methods 1–3) and GC–MS (Method 2) revealed the product to have the following composition by weight of organic compounds: $CF_2{=}CDF + CF_2{=}CHF$ [96.2%; *m/z* 83

($[CF_2=CDF]^+$, 35%); 82 ($[CF_2=CHF]^+$, 10); 64 ($[CF_2=CDF-F]^+$, 55); 63 ($[CF_2=CHF-F]^+$, 15); 52 ($[CF_2D]^+$, 20); 51 ($[CF_2H]^+$, 5); 45 (10); 33 ($[CH_2F]^+$, 25); 31 ($[CF]^+$, 100)] and CF_3CD_2F, $CF_3CDHF + CF_3CH_2F$ [3.8%; *m/z* 85 ($[CF_3CD_2F-F]^+$, 60%); 84 ($[CF_3CHD-F]^+$, 30); 83 ($[CF_3CH_2F-F]^+$, 5); 69 ($[CF_3]^+$, 90); 52 ($[CF_2D]^+$, 15); 45 (10); 35 ($[CD_2F]^+$, 100); 34 ($[CDHF]^+$, 60); 33 ($[CH_2F]^+$, 20); 31 ($[CF]^+$, 45)]. The composition by radioactivity was found to be deuterated [^{18}F]trifluoroethylene (42%), deuterated [^{18}F]1,1,1,2-tetrafluoroethane (32%) and unknown (26%). (Since the carrier (stable) trifluorethylene and 1,1,1,2-tetrafluoroethane are found to be deuterated, the ^{18}F-labelled trifluoroethylene and 1,1,1,2-tetrafluoroethane must also be deuterated.) Of the original radioactivity, 80% was incorporated into gases (decay-corrected).

Reaction C: Reaction A was repeated without acetonitrile but with heating of the reaction vessel to 150 °C for 30 min. Analytical GC (Methods 1 and 2) confirmed that the same radioactive products were obtained, namely [^{18}F]trifluoroethylene (25%), [^{18}F]1,1,1,2-tetrafluoroethane (65%) and unknown (10%). Of the total radioactivity, 62% (decay-corrected) was incorporated into radioactive gases.

2.9. Synthesis of 1,1,1,2-tetrafluoroethane from 2,2,2-trifluoroethyl tosylate

To a glassy carbon vessel containing anhydrous potassium fluoride (8.4 mg, 145 μmol), APE 2.2.2 (67 mg, 178 μmol) and anhydrous potassium carbonate (2.3 mg, 16.6 μmol) was added a solution of 2,2,2-trifluoroethyl tosylate (30 mg, 120 μmol) in acetonitrile (0.4 ml). The vessel was capped, pressurized with nitrogen (1.4 bar, 20 p.s.i.), sealed and then heated at 115 °C for 25 min. The vessel was then allowed to cool to 75 °C and vented to a polypropylene syringe (20 ml). GC analysis of the collected gas (Methods 1 and 2) revealed only 1,1,1,2-tetrafluoroethane (yield estimated as ca. 50% from fluoride).

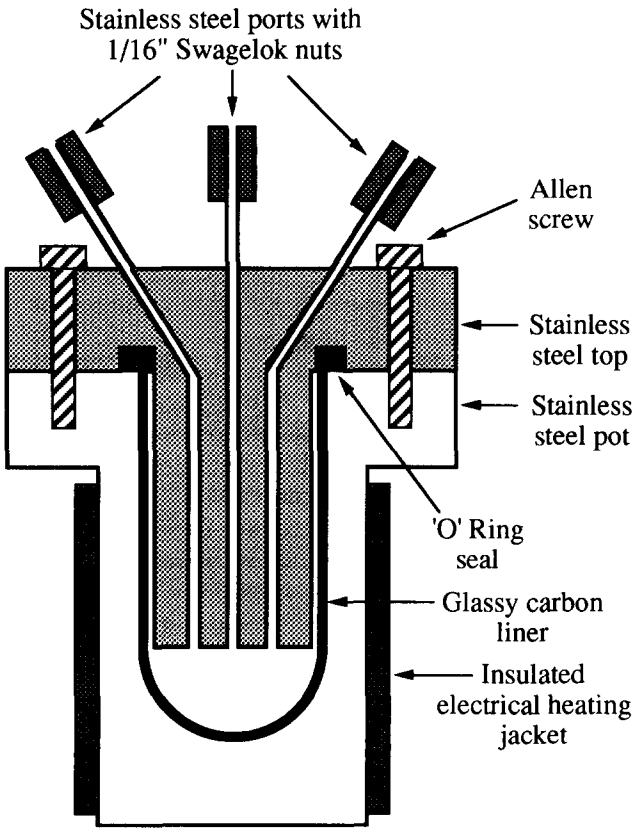
2.10. Radiosynthesis of [2-^{18}F]1,1,1,2-tetrafluoroethane

To a glassy carbon vessel (internal volume, 6 ml) containing n.c.a. [^{18}F]fluoride (ca. 110 MBq, ca. 3 mCi), APE 2.2.2 (13 mg, 34.5 μmol), potassium carbonate (2.3 mg, 16.6 μmol) and dry acetonitrile (0.1 ml) was added a solution of 2,2,2-trifluoroethyl tosylate (30 mg, 0.12 mmol) in dry acetonitrile (0.3 ml). The vessel was pressurized with nitrogen (1.4 bar, 20 p.s.i.), sealed and heated at 115 °C for 25 min. The vessel was then allowed to cool to 75 °C and vented to a polypropylene syringe (20 ml). GC analysis of the collected gas (Methods 1 and 2) revealed the only radioactive product to be [2-^{18}F]1,1,1,2-tetrafluoroethane (70 MBq, 1.87 mCi; decay-corrected radiochemical yield, 58%; specific radioactivity 46 MBq μmol^{-1} (1.24 mCi μmol^{-1}) at the end of synthesis). GC–MS (Methods 1 and 2) confirmed that the carrier in the radioactive product was 1,1,1,2-tetrafluoroethane. The selectivity of labelling for the 2-position versus the 1-position was found to be 91.2±1.2% by an 'isotope separator' technique [11].

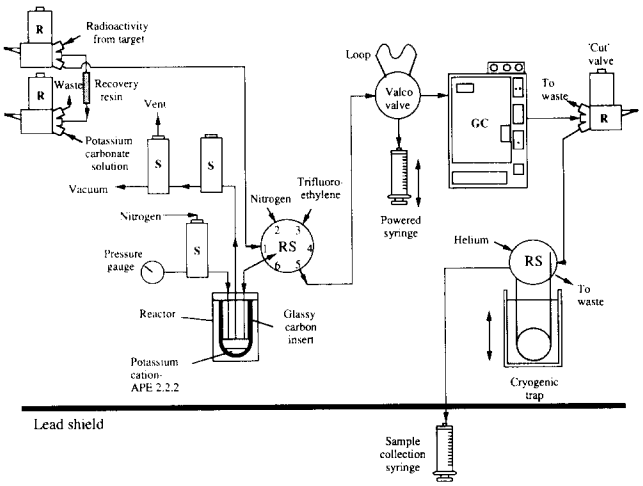
2.11. Remotely-controlled radiosynthesis of high purity [1-^{18}F]1,1,1,2-tetrafluoroethane

The preparation was performed in a glassy carbon vessel (6 ml Sigridur™, fitted with a stainless-steel spacer to reduce the internal volume to ca. 2.5 ml) with facility for heating and cooling (Scheme 1). This reactor was built into a remotely controlled apparatus, including preparative GC (Scheme 2).

N.c.a. [^{18}F]fluoride was produced and trapped on ion-exchange resin, as described above, within the remotely controlled apparatus (Scheme 2). The [^{18}F]fluoride (ca. 185 MBq, ca. 50 mCi) was eluted from the resin with potassium carbonate solution (0.4 ml, 0.3 M) into the gassy carbon reaction vessel containing a solution of APE 2.2.2 (10.4 mg, 27.6 μmol) in acetonitrile (0.2 ml). The solution was heated to dryness while the vessel was simultaneously evacuated to a reduced pressure and purged with a slow flow of



Scheme 1. Sectional view of the reactor used for the remotely-controlled preparation of ^{18}F-labelled 1,1,1,2-tetrafluoroethanes.



Scheme 2. Representation of the apparatus constructed for the remotely-controlled production of [^{18}F]1,1,1,2-tetrafluoroethanes. The apparatus is shown in the configuration for producing [1-^{18}F]1,1,1,2-tetrafluoroethane. For the production of [2-^{18}F]1,1,1,2-tetrafluoroethane, the pneumatically-controlled rotary valve (RS) is reconfigured as follows: port 2, acetonitrile inlet; port 3, nitrogen inlet; port 4, 2,2,2-trifluoroethyl tosylate inlet; port 5, closed; port 6 outlet to GC. R and S are pneumatically-operated Rheodyne and solenoid valves, respectively. The apparatus is housed within a lead-shielded 'hot-cell' and controlled externally.

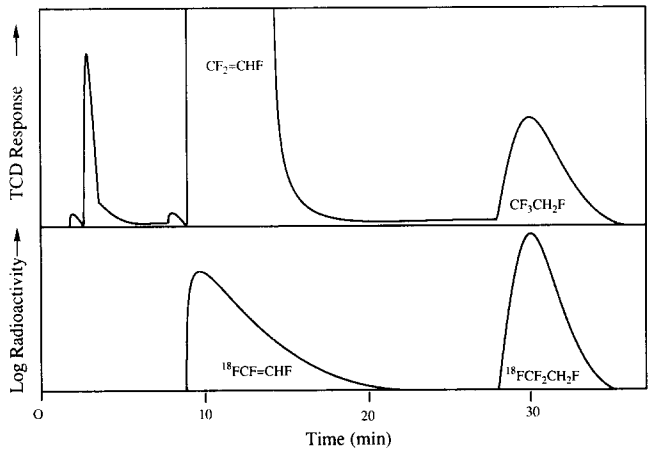


Fig. 1. Chromatogram of the preparative GC of [1-^{18}F]1,1,1,2-tetrafluoroethane on a Carboxen 1000 column. For elution details see Experimental details for GC Method 4.

nitrogen. The vessel was then pressurized to 2.8 bar (40 p.s.i.) with trifluoroethylene (ca. 0.5 mmol) sealed and heated at 115 °C for 30 min. The vessel was then vented into the loop (3.5 ml) of a pneumatically-controlled Valco GC valve (a motorized syringe linked to the valve was used to maximize the radioactivity in the loop). The radioactivity was then injected on to preparative GC (Method 4). The radioactive output between 28.6 and 35 min after injection (Fig. 1) was switched into a stainless-steel tube cooled with liquid nitrogen (−178 °C). The trapped radioactivity was then collected into a polypropylene syringe (20 ml) by automatically raising the trap into air and switching a flow of helium through the trap. The preparation required 80 min.

Radio-analytical GC (Method 2; Fig. 2) confirmed that the trapped radioactivity (110–185 MBq, 3–5 mCi) was [1-^{18}F]1,1,1,2-tetrafluoroethane. [GC–MS (Method 2) also confirmed that the carrier was 1,1,1,2-tetrafluoroethane.] The chemical purity exceeded 99.6%. Trifluoroethylene was identified as the trace impurity. [^{18}F]Trifluoroethylene was also present. Radio-analytical GC (Method 2) of the crude product before purification was used to estimate the relative specific radioactivities of [^{18}F]trifluoroethylene and of [1-^{18}F]1,1,1,2-tetrafluoroethane (Fig. 2). From these values and the GC analysis of chemical purity, the contamination of [1-^{18}F]1,1,1,2-tetrafluoroethane by [^{18}F]trifluoroethylene was calculated to be <0.005%. No other radiochemical impurities were detected. High levels of chemical and radiochemical purity were routinely achievable for [1-^{18}F]1,1,1,2-tetrafluoroethane. The selectivity for labelling in the 1-position versus the 2-position was determined to be 97.2±0.4% by an 'isotope separator' technique [11].

2.12. *Remotely-controlled radiosynthesis of high-purity [2-^{18}F]1,1,1,2-tetrafluoroethane*

The preparation was performed in the remotely-controlled apparatus already described with minor reconfiguration of the rotary valve to allow 2,2,2-trifluoroethyl tosylate to be introduced as a solution in acetonitrile after drying of the [^{18}F]fluoride (Scheme 2). The preparation required 100 min.

Analytical GC (Method, 2; Fig. 3) confirmed that the trapped radioactivity (110–185 MBq, 3–5 mCi) was [2-^{18}F]1,1,1,2-tetrafluoroethane (>99% radiochemically pure, >99% chemical purity). (GC–MS (Method 2) confirmed that the carrier was 1,1,1,2-tetrafluoroethane.) No chemical or radiochemical impurities were detected in the chromatogram. Thus, the minimal level of radiochemical purity was estimated as follows. The background level of radioactivity recorded was determined from the early region of the chromatogram in which no compounds eluted. This background was then subtracted from the integrated radioactivity corresponding to [2-^{18}F]1,1,1,2-tetrafluoroethane (over a peak width of ca. 2 min) to give the corrected radioactivity of product (P). This process was repeated for 10 other regions of the chromatogram with the same width (five each side of the main peak) and summed to give total radioactive impurity (I). The radiochemical purity was then expressed as $100P/(P+I)\%$.

3. Discussion

Previously, fluorine-18 labelled 1,1,1,2-tetrafluoroethane has only been produced in extremely low amounts

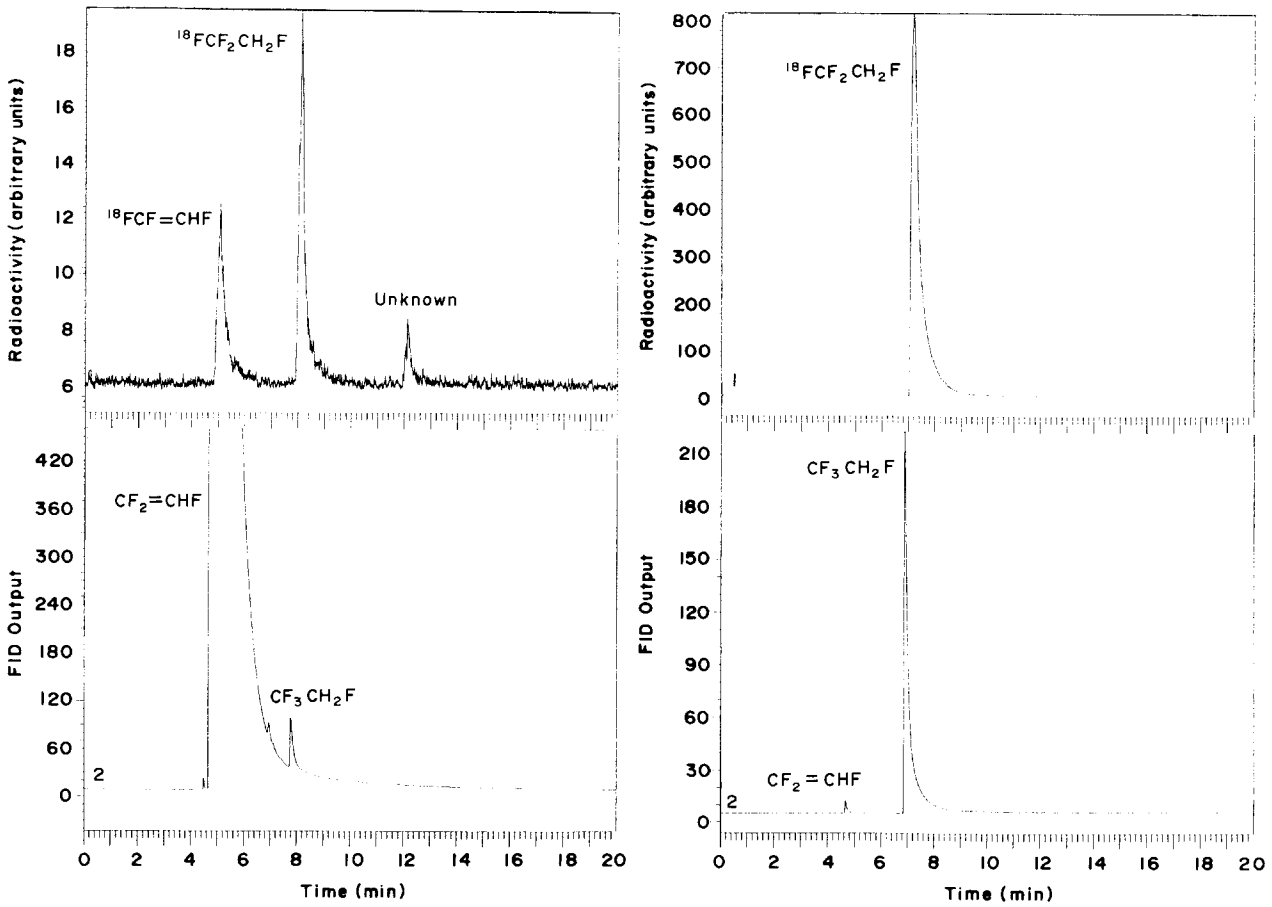


Fig. 2. GC analysis of crude [1-^{18}F]1,1,1,2-tetrafluoroethane (left-hand panel) and purified [1-^{18}F]1,1,1,2-tetrafluoroethane (right-hand panel). For elution details see Experimental details for GC Method 2.

as a low radiochemical yield product (ca. 0.3%) from recoil reactions during the irradiation of 1,1,2,2-tetrafluoroethane with low currents (2 nA) of 52 MeV protons [12,13]. The fluorine-18 arises from the $^{19}F(p, pn)^{18}F$ nuclear reaction. Fluorine-18 is usually prepared with a cyclotron, either as [^{18}F]fluorine from the $^{20}Ne(d, \alpha)^{18}F$ reaction on neon gas or as [^{18}F]fluoride from the $^{18}O(p,n)^{18}F$ reaction on ^{18}O-enriched water [6]. The latter route is highly attractive because it is high-yielding (up to 37 GBq or 1 Ci may be produced), the radioisotope is produced at high specific radioactivity and all of the radioactivity is potentially useful for labelling. Monofluorinations with [^{18}F]fluorine or derived agents, such as [^{18}F]acetyl hypofluorite, inevitably waste half of the initial radioactivity. We therefore sought methods of labelling 1,1,1,2-tetrafluoroethane based on the use of no-carrier-added [^{18}F]fluoride.

Many methods exist for converting the unreactive aqueous [^{18}F]fluoride from the $^{18}O(p,n)^{18}F$ reaction into anhydrous or 'naked' [^{18}F]fluoride, a powerful nucleophile when in a suitable organic solvent. In this study, this conversion was achieved by first passing the irradiated water into an ion-exchange resin in the carbonate form [10] (see Scheme 2). This resin absorbed the [^{18}F]fluoride from the valuable ^{18}O-enriched water, which was then recovered for further irradiations. [^{18}F]Fluoride was then eluted from the resin with potassium carbonate solution into a glassy carbon vessel. This solution was evaporated to dryness. The radioactive residue was solubilized in a solution of the cryptand (Kryptofix®; aminopolyether 2.2.2) in acetonitrile, and further dried by repeated addition and evaporation of acetonitrile. Finally, the radioactive residue was resolubilized in acetonitrile. This gave a powerful [^{18}F]fluoride reagent for aliphatic nucleophilic substitution reactions [14]. Glassy carbon vessels were used throughout this study because they permit efficient resolubilization of the dry [^{18}F]fluoride.

Three main approaches were considered for preparing [1-^{18}F]1,1,1,2-tetrafluoroethane from [^{18}F]fluoride (Scheme 3), namely fluorine exchange (*A*), fluorine exchange in 2-chloro-1,1,1,2-tetrafluoroethane followed by hydrodechlorination (*B*) and nucleophilic addition to trifluoroethylene (*C*).

We found that the exchange of [^{18}F]fluoride in 1,1,1,2-tetrafluoroethane, mediated by K^+–aminopolyether 2.2.2, gives a low radiochemical yield, whether the reaction is performed with acetonitrile as solvent (ca. 5% decay-corrected) or without (3% decay-corrected). Exchange in other 1,1,1-trifluoro-2-haloethanes

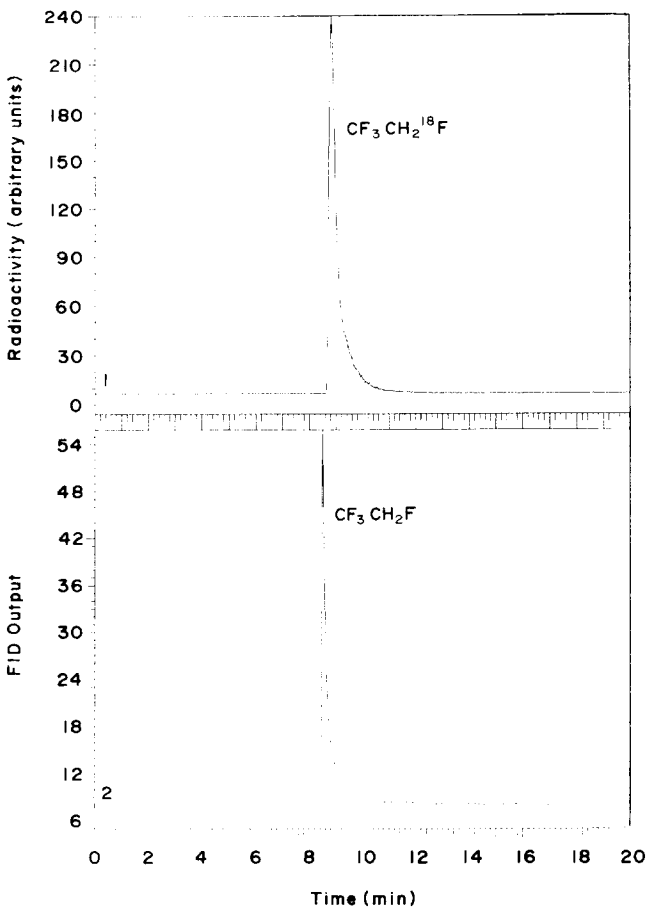


Fig. 3. GC analysis of purified [2-^{18}F]1,1,1,2-tetrafluoroethane. For elution details see Experimental details for GC Method 2.

A. Exchange

$$CF_3{-}CH_2F \xrightleftharpoons{^{18}F^-} {}^{18}FCF_2{-}CH_2F$$

B. Exchange followed by dechlorination

$$CF_3{-}CHClF \xrightleftharpoons{^{18}F^-} {}^{18}FCF_2{-}CHClF \xrightarrow{LAH} {}^{18}FCF_2{-}CH_2F$$

C. Nucleophilic addition

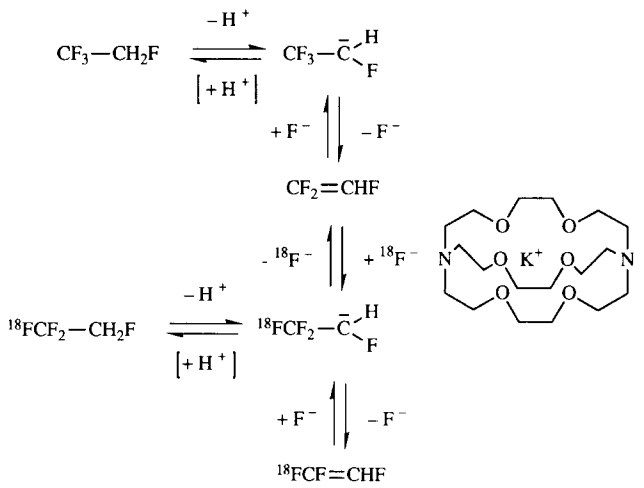
$$CF_2{=}CHF \xrightarrow{^{18}F^-} {}^{18}FCF_2{-}\bar{C}HF \xrightarrow{[H^+]} {}^{18}FCF_2{-}CH_2F$$

D. Nucleophilic substitution

$$CF_3{-}CH_2OTs \xrightarrow{^{18}F^-} CF_3{-}CH_2{}^{18}F$$

Scheme 3. Routes examined for labelling 1,1,1,2-tetrafluoroethane with fluorine-18, using cyclotron-produced [^{18}F]fluoride as labelling agent.

(CF_3CH_2Br, CF_3CH_2I) in acetonitrile under similar conditions gives high radiochemical yields [15]. The mechanism of these exchange reactions is presumed to involve reversible deprotonation to an intermediate carbanion which may reversibly lose fluoride (Scheme 4). The low radiochemical yield for exchange in 1,1,1,2-tetrafluoroethane, as for the lack of exchange observed



Scheme 4. The exchange of [^{18}F]fluoride with 1,1,1,2-tetrafluoroethane via a carbanion intermediate.

in desflurane ($CF_3CHFOCF_2H$) [15], is rationalized on the basis that the 2-fluoro-substituent lacks a d-orbital capable of stabilizing the intermediate carbanion (Scheme 4). The observation of [^{18}F]trifluoroethylene and non-radioactive trifluoroethylene as by-products in the poor exchange of [^{18}F]fluoride with 1,1,1,2-tetrafluoroethane is however consistent with the proposed mechanism (Scheme 4). A further disadvantage of exchange labelling is the very low specific radioactivity that is inevitably obtained. A more efficient labelling procedure capable of delivering higher specific radioactivity was therefore sought.

Efficient reductive dechlorination of hydrochlorofluorocarbons can be achieved with LAH [16]. Thus, exchange of [^{18}F]fluoride in 1,1,1-trifluoro-2-chloro-2-fluoroethane followed by hydro for chloro exchange seemed attractive as a route to [1-^{18}F]1,1,1,2-tetrafluoroethane. Initially, 2-chloro-1,1,1,2-tetrafluoroethane was shown to be efficiently and cleanly dechlorinated by LAH. The K^+–aminopolyether 2.2.2-mediated fluorine exchange with [^{18}F]fluoride was found to proceed in good radiochemical yield (40% with solvent and 32% without). As expected, the 2-chloro-substituent clearly provided effective stabilization of the intermediate carbanion. [^{18}F]2-Chloro-1,1,2-trifluoroethylene was not observed in GC as a by-product. These results showed the potential of exchange followed by dechlorination for the preparation of [1-^{18}F]1,1,1,2-tetrafluoroethane, though clearly an approach involving only a single stage would still be more desirable.

Exchange of [^{18}F]fluoride with a 1,1,1-trifluoro-2-haloethane is assumed to occur via a carbanion intermediate (Scheme 4) [15]. Vicinal difluoroalkenes are known to be susceptible to nucleophilic addition [17]. We therefore considered nucleophilic addition of [^{18}F]fluoride to trifluoroethylene (*C*, Scheme 3) as a route to [1-^{18}F]1,1,1,2-tetrafluoroethane. The K^+–aminopolyether 2.2.2.-mediated addition of

[^{18}F]fluoride to trifluoroethylene in acetonitrile at 95 °C for 25 min was found to give a high radiochemical yield of [1-^{18}F]1,1,1,2-tetrafluoroethylane (>56%). GC revealed [^{18}F]trifluoroethylene to be the major radioactive by-product. When the reaction was performed in acetonitrile-d_3, mono- and di-deuterated [1-^{18}F]1,1,1,2-tetrafluoroethane were obtained as the major radioactive products. Stable and radioactive monodeuterated trifluroethylene were also observed as by-products. These findings demonstrate that the solvent acts as a source of protons and supports the notion that the reaction proceeds through a carbanion intermediate (Scheme 4).

It was found that the reaction could also be carried out at a higher temperature without added solvent. A reaction at 150 °C for 30 min gave a 40% radiochemical yield of [1-^{18}F]1,1,1,2-tetrafluoroethane and a similar distribution of radioactive products (Fig. 2). In this reaction the source of protons is uncertain but may include the cryptand or starting material, in view of the strong basicity expected for the intermediate α-fluorocarbanion (cf. Ref. [18]).

Preparative GC (Fig. 1) gave a product with very high radiochemical and chemical purity (Fig. 2). By using an isotope separator, we have measured the selectivity for labelling in the 1-position to be $97.2 \pm 0.4\%$ [11]. This demonstrates that direct exchange of [^{18}F]fluoride for fluoro in the 2-position of trifluoroethylene or 1,1,1,2-tetrafluoroethane is a very minor process. The specific radioactivity of the prepared [1-^{18}F]1,1,1,2-tetrafluoroethane is 2–3 orders of magnitude lower than that expected for the specific radioactivity of the cyclotron-produced no-carrier-added [^{18}F]fluoride [6]. This implies that free fluoride is generated in the reaction in accord with the proposed mechanism (Scheme 4)

This reaction is the first demonstration of the efficient addition of [^{18}F]fluoride to a fluoro-olefin. It achieves the equivalent of the addition of hydrogen [^{18}F]fluoride, a difficult reagent to produce and manage. Because of the simplicity and high radiochemical yield of the reaction it is the preferred route to [1-^{18}F]1,1,1,2-tetrafluoroethane.

We considered that the labelling of 1,1,1,2-tetrafluoroethane in the 2-position might be achieved by nucleophilic substitution with [^{18}F]fluoride on a substrate having a good leaving group. As noted above, the 1,1,1-trifluoro-2-haloethanes (halo: iodo or bromo) when reacted with [^{18}F]fluoride in the presence of K^+–aminopolyether 2.2.2 in acetonitrile, undergo exchange in the 1-position in preference to substitution in the 2-position [15]. However, 1,1,1,2-tetrafluoroethane has been prepared in 35% yield by the reaction of potassium fluoride with 2,2,2-trifluoroethyl tosylate, though under quite harsh reaction conditions (8 h, 500 mmHg pressure, 210–240 °C) [19]. We found that the reaction between 2,2,2-trifluoroethyl tosylate and fluoride, mediated by K^+–aminopolyether 2.2.2 in acetonitrile at 115 °C, gave a 50% yield of 1,1,1,2-tetrafluoroethane after only 25 min. Furthermore, we obtained an excellent radiochemical yield (58%, decay-corrected) of [2-^{18}F]1,1,1,2-tetrafluoroethane by the reaction of n.c.a. [^{18}F]fluoride with 2,2,2-trifluoroethyl tosylate (*D*, Scheme 3) under identical reaction conditions. Since 2,2,2-trifluoroethyl tosylate is a solid at room temperature, the [2-^{18}F]1,1,1,2-tetrafluoroethane was simply collected from the headspace of the reaction mixture. GC analysis demonstrated that the crude product is radiochemically pure and also of high chemical purity. Preparative GC gave [2-^{18}F]1,1,1,2-tetrafluoroethane in very high radiochemical and chemical purity, as assessed by GC analysis (Fig. 3).

Using an isotope separator [11], it was found that the selectivity for labelling in the 2-position was $91.2 \pm 1.2\%$. Thus, some exchange of [^{18}F]fluoride with the trifluoromethyl group occurs. Some of the lack of specificity for labelling in the 2-position in the reaction of 2,2,2-trifluoroethyl tosylate with [^{18}F]fluoride might be accounted for by exchange at the 1-position in the product. By analogy with the reactions of other 1,1,1-trifluoro-2-halo compounds with [^{18}F]fluoride [15], similar exchange may occur in the tosylate, and to a greater extent before substitution at the 2-position by non-radioactive fluoride. The specific radioactivity of the prepared [2-^{18}F]1,1,1,2-tetrafluoroethane is 2–3 orders of magnitude lower than that expected for the specific radioactivity of the cyclotron-produced [^{18}F]fluoride [6]. This implies that stable fluoride is generated from the tosylate and is consistent with some exchange in the trifluoromethyl group.

The reaction between trifluoroethylene and solid K^+–aminopolyether 2.2.2–[^{18}F]fluoride was especially simple to automate for routine productions of [1-^{18}F]1,1,1,2-tetrafluoroethane. The same automated apparatus was easily reconfigured for the production of [2-^{18}F]1,1,1,2-tetrafluoroethane by nucleophilic substitution with [^{18}F]fluoride in 2,2,2-trifluoroethyl tosylate. The automated apparatus included preparative GC, which in each case delivers radioactive product in very high radiochemical and chemical purity as assessed by analytical GC (Figs. 2 and 3). Each process could be carried out within one half-life of fluorine-18.

In conclusion, K^+–aminopolyether 2.2.2 has been shown to be highly effective at promoting nucleophilic substitution in 2,2,2-trifluoroethyl tosylate and nucleophilic addition to trifluoroethylene, enabling efficient automated procedures to be devised for producing radiochemically and chemically pure [2-^{18}F]1,1,1,2-tetrafluoroethane and [1-^{18}F]1,1,1,2-tetrafluoroethane, respectively. The use of these tracers to study the

pharmacokinetics of 1,1,1,2-tetrafluoroethane in humans will be reported elsewhere.

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