Efficient and Selective Labelling of the CFC Alternative, 1,1,1,2-Tetrafluoroethane, with ^{18}F in the 1-Position

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Treatment of trifluoroethylene with cyclotron-produced [^{18}F]fluoride, in the presence of potassium carbonate–aminopolyether 2.2.2, labels 1,1,1,2-tetrafluoroethane efficiently and selectively in the 1-position.

1,1,1,2-Tetrafluoroethane (HFA 134a) is now produced on a large scale as the main replacement for ozone-depleting chlorofluorocarbons (CFCs) in their many applications, including their use as refrigerants and coolants.[1–3] It also has potential application as a propellant in metered dose inhalers used to administer drugs to patients. This potential application leads to a requirement to study the biological fate of HFA 134a in man. This information might be gained by using HFA 134a labelled with ^{18}F.

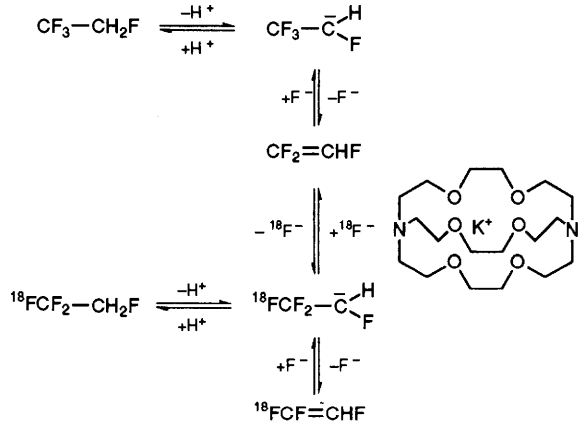
^{18}F is a short-lived ($t_{\frac{1}{2}}$ = 109.6 min) positron-emitting (β^+ = 96.9%) isotope, which can be produced with a cyclotron by the $^{18}O(p,n)^{18}F$ reaction on ^{18}O-enriched water as aqueous [^{18}F]fluoride in high activity (*ca.* 1 Ci) and in high specific radioactivity (10 Ci μmol^{-1}).[4] Compounds labelled with positron-emitting radioisotopes are externally detectable *in vivo* by, *e.g.*, simple whole-body counting using sensitive sodium iodide detectors[5] or by sophisticated high resolution positron emission tomography.[6] By using regioselective labelling techniques the metabolism of a labelled compound as well as its pharmacokinetics and biodistribution in man may be elucidated. Here we report on the use of [^{18}F]fluoride for labelling 1,1,1,2-tetrafluoroethane efficiently and selectively in the 1-position.

The exchange of ^{18}F in 2-substituted 1,1,1-trifluoroalkanes has been studied previously.[7,8] Successful exchange was observed only in those compounds having a 2-substituent capable of stabilising an intermediate carbanion **1** by a strong inductive effect. Exceptionally, exchange was not observed when the 2-substituent is fluoro.[7] This was rationalised[7] on the basis that the fluorine atom has no d-orbital to accommodate extra electrons in the carbanion structure. Our attempts at direct exchange in 1,1,1,2-tetrafluoroethane with [^{18}F]fluoride gave low but measurable radiochemical yields (*ca.* 5%). It is supposed that the exchange mechanism involves a carbanion intermediate in a complex equilibrium (*cf.* Scheme 1). Assuming this mechanism to operate, and noting the previously reported nucleophilic additions of fluoride to vicinal difluoroethylenes,[9] we considered that higher radiochemical yields of [1-^{18}F]1,1,1,2-tetrafluoroethane might be obtained by [^{18}F]fluoride addition to trifluoroethylene (Scheme 1). This was confirmed experimentally as follows.

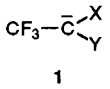
Cyclotron-produced 'no-carrier-added' [^{18}F]fluoride in ^{18}O-enriched water (20%) was adsorbed onto an anion exchange resin and eluted with potassium carbonate solution (0.3 mol dm^{-3}).[4,10] A portion of this solution (0.2 ml; *ca.* 4 mCi) was added to a solution of aminopolyether 2.2.2 (5.2 mg) in acetonitrile (0.2 ml) in a glassy carbon vessel and heated to dryness. Acetonitrile (0.2 ml) was again added and taken to dryness. The residue was taken up in acetonitrile (0.2 ml), the vessel was capped and filled with trifluoroethylene to a pressure of 50 psi (1 psi ≈ 6.89 × 10^3 Pa) at ambient temperature. The vessel was sealed, heated to 95 °C for 25 min, cooled and finally vented to a syringe. The collected radioactive product was found by GC and by GC-MS to contain [^{18}F]1,1,1,2-tetrafluoroethane (*ca.* 98% by radioactivity) and [^{18}F]trifluoroethylene† (*ca.* 2%). [^{18}F]1,1,1,2-Tetrafluoroethane (in an overall radiochemical yield of 78% decay-corrected at 80 min from radioisotope production) could be separated by GC on various columns. Carbon–carbon bond scission in an 'isotope separator' gave [$^{18}FCF_2$]$^+$ (m/z = 68) and [$CH_2{}^{18}F$]$^+$ (m/z = 32) fragments in the ratio of 35 : 1, demonstrating 97.2 ± 1.6% selectivity for labelling in the 1-position.[11] A reaction performed in [$^2H_3$]acetonitrile produced mono-deteuriated [1-^{18}F]1,1,1,2-tetrafluoroethane, proving that the solvent acts as a proton source.

This is the first demonstration of the use of the powerfully nucleophilic [^{18}F]fluoride-K$^+$-aminopolyether 2.2.2‡ system[12] to achieve the equivalent of the addition of anhydrous hydrogen [^{18}F]fluoride, which is a far less accessible and less manageable reagent.[4] Hence, the scope of the reaction is being explored further for radiofluorination.

We have also shown that 1,1,1,2-tetrafluorethane can be labelled selectively and efficiently (58% radiochemical yield, decay-corrected) in the 2-position by nucleophilic substitution in 2,2,2-trifluoroethyltoluene-*p*-sulfonate with [^{18}F]fluoride. The easy availability of selectively radiofluorinated 1,1,1,2-tetrafluoroethanes now enables the biodistribution and metabolism of this CFC alternative to be studied in man. The results of these studies will be published elsewhere. Feasibly, these radiotracers could be applied to other investigations including the catalytic synthesis of HFA 134a[13] and its behaviour in industrial applications.[14]



Scheme 1



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† The incorporation of ^{18}F into the starting material, trifluoroethylene, demonstrates that stable fluoride is generated in this reaction system, as implied in Scheme 1. Thus, the amount of carrier 1,1,1,2-tetrafluorethane co-produced (400 nmol; 40 μg) with the [^{18}F]1,1,1,2-tetrafluoroethane is therefore larger than would be expected in the absence of any carrier dilution of the cyclotron-produced [^{18}F]fluoride.

‡ 4,7,13,16,21,24-Hexaoxa-1,10-diazabicylo[8.8.8]hexacosane.

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