Reactions of Cyclotron-produced [^{18}F]Fluoride with Diaryliodonium Salts—a Novel Single-step Route to No-carrier-added [^{18}]Fluoroarenes

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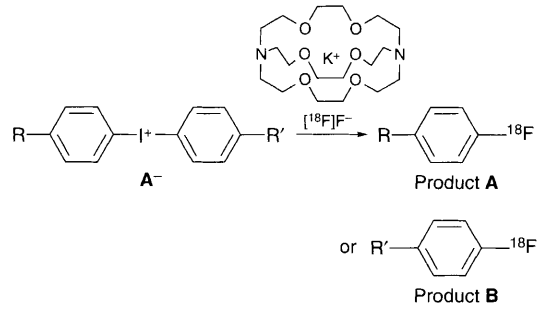
Treatment of diaryliodonium salts with cyclotron-produced [^{18}]fluoride in the presence of potassium carbonate–aminopolyether 2.2.2 constitutes a new single-step route to no-carrier-added [^{18}F)fluoroarenes.

Methods for the facile introduction of the short-lived positron-emitter, fluorine-18 ($t_{\frac{1}{2}}$ = 109.6 min), are increasingly needed to provide radiotracers for clinical research with the important non-invasive imaging technique of positron emission tomography (PET).[1] Fluorine-18 is generally produced with a cyclotron, either as molecular [^{18}F]fluorine or as [^{18}F]fluoride.[2] Any application of fluorine-18 in PET therefore demands rapid and efficient radiochemistry to introduce the fluorine-18 into the tracer of interest. [^{18}F]Fluoride is the preferred precursor because this can be produced in higher radioactivity and in higher specific radioactivity (by several orders of magnitude) than molecular [^{18}F]fluorine; moreover, all of the [^{18}F]fluoride is potentially available for incorporation into a labelled compound whereas only half the radioactivity of molecular [^{18}F]fluorine can be utilised for mono-radiofluorination of an organic compound. Methods for labelling aryl rings that bear no electron-withdrawing substituents, using no-carrier-added (NCA) [^{18}F]fluoride as the source of fluorine-18, are lacking; the only described methods are the decomposition of triazenes in the presence of [^{18}F]fluoride[3] and the well-known Balz–Schiemann procedure and its recent modification,[4] based on the decomposition of a suitable diazonium salt in the presence of [^{18}F]fluoride. The triazene method has not generally provided high radiochemical yields in the labelling of complex substrates and is now little used while the maximum radiochemical yield obtainable from the Balz–Schiemann procedures is 25%.[4]

Diaryliodonium salts ($Ar_2I^+X^-$) are becoming highly popular reagents for efficient arylation.[5] They are known to react with a wide range of nucleophiles, such as methoxide, cyanide and halides, to give the substituted arene (plus iodoarene as byproduct). A reaction of diphenyliodonium fluoroborate with potassium fluoride in the presence of a crown ether has been shown to produce fluorobenzene in high yield.[6] This suggested to us that the treatment of diaryliodonium salts with NCA [^{18}F]fluoride might provide a novel single step-procedure for the rapid radiosynthesis of [^{18}F]fluoroarenes, as depicted in Scheme 1. Here we report results from initial studies of such reactions (Table 1).

A selection of known diaryliodonium salts, with various substituents and counter-anions, were purchased or otherwise prepared by treating substituted benzenes with (diacetoxy)iodobenzene,[7] iodosyl benzene[8] or iodine trifluoroacetate.[9] Radiochemistry was performed using the powerfully nucleophilic radiofluorinating agent, [^{18}F]fluoride K$^+$–APE 2.2.2 (K$^+$–4,17,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane), prepared from cyclotron-produced NCA [^{18}F]fluoride as described previously.[2,10] This reagent was treated with a diaryliodonium salt (*ca.* 30 mg) in acetonitrile at 85 or 110 °C under nitrogen pressure (20 p.s.i.) for 40 or 35 min, respectively. The reaction solution was analysed for radiochemical products and yields by reverse phase HPLC.

Reactions of NCA [^{18}F]fluoride with diphenyliodonium chloride or triflate provided the first truly single-step method for the radiosynthesis of [^{18}F]fluorobenzene in high radiochemical yield. Radiochemical yields from the chloride were especially impressive, though variable (31–78%). The reasons for the variation in radiochemical yield from experiment to experiment are not yet understood, but may be related to the 'quality' of the cyclotron-produced [^{18}F]fluoride with respect to low level contaminants. The reaction conditions have yet to be optimised.



Scheme 1 Investigated route to NCA [^{18}F]fluoroarenes—the reaction of [^{18}F]fluoride with diaryliodonium salts

Table 1 Radiochemical yields of [^{18}F]fluoroarenes from reactions of diaryliodonium salts with NCA [^{18}F]fluoride according to Scheme 1

Precursor iodonium salt			Radiochemical yield of [^{18}F]fluoroarenes[a] (%)	Loss of initial radioactivity as volatile products[b] (%)	Distribution of radioactivity between aryl products	
R	R′	A$^-$			**A** (%)	**B** (%)
H	H	Cl^-	31	26	100	
H	H	Cl^-	78	6	100	
H	H	$CF_3SO_3^-$	7.5	9	100	
H	H	$CF_3SO_3^-$	15	13	100	
H	Me	$CF_3SO_3^-$	10	6.5	72	28
H	Me	$CF_3SO_3^-$	68*	2	60	40
H	Cl	$CF_3SO_3^-$	10	20	32	68
H	Cl	$CF_3SO_3^-$	14	10	40	60
H	OMe	Br^-	35	17	100	0
H	OMe	Br^-	88*	6	100	0
OMe	OMe	$CF_3CO_2^-$	36	14	100	
OMe	OMe	$CF_3CO_2^-$	73*	4	100	

[a] Radiochemical yields (decay-corrected) are based on the total radioactivity of [^{18}F]fluoroarenes (products **A** and **B**) in solution as a percentage of the initial radioactivity, measured by HPLC. Yields are for reactions carried out at 110 °C for 35 min, except yields that are asterisked which are from reactions carried out at 85 °C for 40 min. [b] The losses of radioactivity have not been identified chemically, but may represent volatile [^{18}F]fluoroarenes.

Reactions of [^{18}F]fluoride with 4-chloro-diphenyliodonium triflate gave substantial yields of radiofluorinated arenes, with the formation of 4-[^{18}F]fluoro-chlorobenzene dominating over the formation of [^{18}F]fluorobenzene. By contrast, in reactions of [^{18}F]fluoride with 4-methyl-diphenyliodonium triflate the formation of [^{18}F]fluorobenzene dominated over that of the alternative product, 4-[^{18}F]fluorotoluene. Reactions of [^{18}F]fluoride with 4-methoxy-diphenyliodonium bromide gave high radiochemical yields (88% at 85 °C) of [^{18}F]fluorobenzene and no detectable 4-[^{18}F]fluoroanisole. However, reactions of 4,4′-dimethoxydiphenyliodonium trifluoroacetate gave impressive yields of 4-[^{18}F]fluoroanisole (73% at 85 °C). No positional isomers of [^{18}F]fluoroanisole were detected.

In all these reactions a small proportion [< 26% at 110 °C and < 6% at 85 °C) of the initial radioactivity was lost by volatilisation; this radioactivity loss has not been identified chemically in any single case, but may also be in the form of one or more [^{18}F]fluoroarenes. For all the reactions of [^{18}F]fluoride on the tested unsymmetrical diaryliodonium salts, iodobenzene was detected as a major non-radioactive product.

The described single-step radiosyntheses of NCA [^{18}F]fluorobenzene, 4-[^{18}]fluorochlorobenzene, 4-[^{18}F]fluorotoluene and 4-[^{18}F]fluoroanisole from cyclotron-produced [^{18}F]fluoride in useful radiochemical yields are remarkable. These results show that diaryliodonium salts are precursors that enable arenes, including those without electron-withdrawing substitutents, to be labelled in a single step using NCA [^{18}F]fluoride. We have also found that reactions can be performed with macroscopic quantities of potassium fluoride in the presence of a slight excess of APE 2.2.2 to give non-radioactive fluoroarenes. At present the mechanisms of these reactions are matters for conjecture. Studies are now planned to investigate mechanistic aspects, the influence of the pattern of substituents in the iodonium salts on reactivity with [^{18}F]fluoride and on product spectrum, and the preparation of more complex iodonium salts as possible precursors to PET radiopharmaceuticals. In particular, there is considerable potential to prepare structurally complex iodonium salts, whether symmetric or asymmetric, by reactions at aryl–H or aryl–I centres as substrates for the surrogate *ipso* substitution of aryl–H or aryl–I by NCA [^{18}F]fluoride. This potential is a further attractive feature of this new approach to the labelling of arenes with fluorine-18 at high specific radioactivity.

The authors are grateful to Mr Colin J. Steel for the production of [^{18}F]fluoride and to Dr Smruti Waiker for assistance in the preparation of iodonium salts for these studies.

Received, 14th July 1995; Com. 5/04628I

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