Displacement of a Nitro-group by [^{18}F]Fluoride Ion. A New Route to Aryl Fluorides of High Specific Activity

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Nucleophilic displacement of activated nitro-groups by [^{18}F]fluoride ion is an efficient route to ^{18}F-labelled aromatics; these compounds can be in the no-fluorine-carrier-added state if required.

The expanding role of ^{18}F-labelled radiopharmaceuticals in positron emission tomography[1] calls for efficient synthetic routes to a variety of ^{18}F-labelled organic molecules. Such syntheses must be rapid, give acceptable yields, and most importantly, lead to products whose specific activity is appropriate for the use to which these compounds are to be put. Among the available labelled fluorinating reagents, [^{18}F]fluoride ion is the only one that can be conveniently prepared in high yields without the addition of carriers, and therefore represents the precursor of choice in the synthesis of ^{18}F-labelled aromatics which are, in theory at least, carrier free.†

We have previously shown that the isotopic exchange of activated aryl fluorides with $^{18}F^-$ in dimethyl sulphoxide (DMSO) is an effective labelling technique.[2] However, it suffers from the problem, inherent in isotopic exchange reactions, that the label is diluted by the stable isotope undergoing the exchange. Based on the leaving group order typical of nucleophilic aromatic substitutions,[3] the displacement of activated nitro-groups by $^{18}F^-$ appeared to be the most promising approach to no-carrier-added [^{18}F]fluoroaromatics, an expectation borne out by the present results.

In fact, reaction of Rb^{18}F either in the no-carrier-added state or diluted with inactive fluoride (typically, 2×10^{-3} M) in dry DMSO at moderate temperatures with substituted nitrobenzenes (*ca.* 3×10^{-2} M), rapidly gave satisfactory yields of the corresponding [^{18}F]fluorodenitration products (Table 1). Reaction times of 20 min or less were used. That acceptable yields for labelling purposes may be obtained even at relatively low temperatures is a distinct advantage when heat-sensitive organic substrates are being used. Thus, in a typical preparative run, 10 mg of 1,4-dinitrobenzene and 35 mCi of $^{18}F^-$ in the no-carrier-added state gave 23.4 mCi of [4-^{18}F]fluoronitrobenzene in a reaction time of 20 min at 85 °C, a radiochemical yield of 67%.

Comparison of appropriate pairs of substrates of the general formula $NO_2C_6H_4X$ led to the following approximate order of nucleofugality of the leaving group X in the reaction with $^{18}F^-$ carried out at 150 °C: *p*-NO_2 > *o*-CN > *o*-NO_2 = *ca.* *p*-CN = *ca.* *o*-F > *p*-F ≫ *p*-Cl, Br, I.

From these results, fluorodenitration appears to result in more rapid ^{18}F incorporation[2] than in the previously

† Any ^{18}F-labelled compound, where *all* the fluorine atoms are the fluorine-18 isotope, would have a specific activity of 1.7×10^9 Ci/mol if there were one fluorine ligand per molecule. While syntheses with added carrier, *i.e.* fluorine-19, the stable isotope, are experimentally less demanding (a synthesis at the carrier-free mCi level of ^{18}F would involve only 3.5×10^{11} molecules or 0.58 picomol) the need for ultra-high specific activity neuroreceptor ligand molecules for the *in vivo* study of neuroreceptor biochemistry makes the need for 'carrier-free' compounds mandatory.

Table 1. Labelled aryl fluorides from the displacement of a nitro-group by $^{18}F^-$.

Substrate[a]	T/°C	Product[b]	Yield,[c] %
1,4-$(NO_2)_2C_6H_4$	110	[4-^{18}F]$C_6H_4NO_2$	87
	90		62
2-$NO_2C_6H_4CN$	150	[2-^{18}F]C_6H_4CN	85
	110		41
2-Cl-6-$NO_2C_6H_3CN$	150	2-Cl-[6-^{18}F]C_6H_3CN	55
		6-NO_2-[2-^{18}F]C_6H_3CN	17
1,2-$(NO_2)_2C_6H_4$	150	[2-^{18}F]$C_6H_4NO_2$	58
4-$NO_2C_6H_4CO_2Me$	150	[4-^{18}F]$C_6H_4CO_2Me$	34
$NO_2C_6Cl_5$	150	[^{18}F]C_6Cl_5	11
		[^{18}F]$C_6Cl_4NO_2$	29[d]

[a] Reactions carried out for 20 min, with an organic substrate concentration of *ca.* 3×10^{-2} M. [b] Identified by comparison of their retention volumes, in both radio g.l.c. and h.p.l.c., with those of authentic samples. [c] Standard deviation *ca.* 10%. [d] Mixture of isomers.

studied isotopic exchange of $^{18}F^-$ with fluorinated aromatics.[4] The method thus constitutes an efficient labelling procedure, suitable for the direct preparation of ^{18}F-labelled radiopharmaceuticals, an obvious example being the synthesis of [^{18}F]-spiroperidol[5] from its inactive nitro-analogue, or for the preparation of synthetically useful labelled intermediates. In the latter case, one can exploit the versatile reactivity of any activating nitro-groups present in the substrate which can be rapidly and efficiently converted into the NH_2 and N_2^+ functions, which can, in turn, be rapidly converted into a variety of other synthetically useful groups, such as CN, OH, OR, H, or the halogens.

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