Synthesis of [^{18}F]XeF_2, a Novel Agent for the Preparation of ^{18}F-Radiopharmaceuticals

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Summary [^{18}F]XeF_2 was synthesised by isotopic exchange between XeF_2 and anhydrous reactor-produced [^{18}F]HF, [^{18}F]SiF_4, and [^{18}F]AsF_5 with a radiochemical yield of 30%; [^{18}F]XeF_2 may facilitate the direct radiofluorination of organic tracer molecules for positron emission tomography.

XENON DIFLUORIDE, XeF_2, has been shown to fluorinate a variety of organic compounds mildly and rapidly.[1] Recently, we have synthesised the L-stereoisomer of fluorodopa† by direct fluorination with XeF_2.[2] Fluoro-dopa, labelled with the positron-emitting isotope ^{18}F ($t_{\frac{1}{2}}$ 110 min), is used to measure, *in vivo* and atraumatically, the cerebral metabolism of the neurotransmitter dopamine.[3] Before

the XeF_2 method can be applied to radiofluorinations of biomolecules, such as fluoro-dopa, labelled XeF_2 must be made available. Therefore, we report the synthesis of $[^{18}F]XeF_2$ by exchange labelling from reactor-produced $^{18}F^-$.

In a typical experiment, Li_2CO_3 (95% enriched in ^6Li) was irradiated with thermal neutrons in the McMaster 5-megawatt nuclear reactor for 3 h.[4] The irradiated Li_2CO_3 was dissolved in 4 M H_2SO_4. The acid mixture was heated and water containing carrier-free $H^{18}F$ and traces of H_2SO_4 was distilled off. It was then neutralised with an aqueous solution of Bu^n_4NOH and evaporated to dryness *in vacuo* at 50 °C. The residue of $Bu^n_4N^{18}F$ and $(Bu^n_4N)_2SO_4$ was dissolved in dry MeCN and transferred to an FEP vessel.‡ The mixture was evaporated to dryness at 40 °C *in vacuo*. Sulphuryl chloride fluoride was chosen as solvent for the exchange reaction because of its resistance to oxidative fluorination by XeF_2. Spectroscopic grade SO_2ClF was condensed on to the dried residue at −196 °C, followed by condensation of anhydrous HF (0·3 mmol). The solution was warmed to, and maintained at, 40 °C for 20 min.

Both SO_2ClF and $[^{18}F]HF$ were vacuum-distilled into an FEP vessel that contained XeF_2 (0·67 mmol) at −196 °C. Thus, 90% of the ^{18}F-activity was freed from the Bu^n_4NF. The exchange between XeF_2 and $[^{18}F]HF$ was allowed to proceed for 20 min at 40 °C. After removal of the SO_2ClF and HF under dynamic vacuum at −48 °C, dry crystalline $[^{18}F]XeF_2$ remained (0·59 mmol, 88% chemical yield; 31% radiochemical yield). The identity and purity of the labelled XeF_2 were established by laser Raman spectroscopy on the solid at −196 °C. The activity remaining in the solvent, presumably $[^{18}F]HF$, was absorbed on to NaF as $[^{18}F]Na^+HF_2^-$. When the solvent, SO_2ClF, was distilled off, ^{18}F was completely absorbed on NaF. Thus, the fluorine of the solvent, SO_2ClF, is shown to be non-labile.

Hydrogen fluoride presumably acts as a weak fluoride acceptor towards XeF_2, promoting exchange according to equilibria (1) and (2). The existence of the proposed intermediate xenon species, XeF^+ and $Xe_2F_3^+$, has been well established both in solution[5] and in the solid state.[6] It is noteworthy that no significant exchange between XeF_2 and $H^{18}F$ was observed to occur in water.[7]

$$XeF_2 + XeF^+ \rightleftharpoons Xe_2F_3^+ \quad (1)$$

$$XeF_2 + A \rightleftharpoons XeF^+ + AF^- \quad (2)$$

$$A = HF, SiF_4, \text{ or } AsF_5$$

Analogous exchanges were found to occur when we used SiF_4 or AsF_5 in place of HF. While stable adducts possessing the formulations $XeF^+AsF_6^-$ and $Xe_2F_3^+AsF_6^-$ are known,[6] silicon tetrafluoride, a weak fluoride acceptor, is not known to form stable adducts with any of the binary xenon fluorides. However, the weak fluoride acceptor GeF_4 and the strong xenon fluoride base, XeF_6, form the stable adduct, $XeF_6{\cdot}GeF_4$ ($XeF_5^+GeF_5^-$).[8]

We found that no exchange occurs between $^{18}F^-$ and XeF_2 in the absence of HF, SiF_4, or AsF_5. We propose that the mechanism represented by equilibria (1) and (2) is also responsible for these isotopic exchanges. Weak fluoride acceptors, in general, provide a means to exchange anhydrous $^{18}F^-$ with XeF_2 and, possibly, other xenon fluorides.

We expect that $[^{18}F]XeF_2$ will become a highly useful intermediate for the radiofluorination of a wide variety of medically important ^{18}F-tracers, such as 2-deoxy-2-fluoro-glucose[9] and fluoro-dopa.[2]

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† Fluoro-dopa = L-3,4-dihydroxy-6-fluorophenylalanine.

‡ FEP = a copolymer of perfluoropolyethylene and perfluoropolypropylene.

[1] R. Filler, *Isr. J. Chem.*, 1978, **17**, 71.
[2] G. Firnau, R. Chirakal, S. Sood, and E. S. Garnett, *Can. J. Chem.*, 1980, **58**, 1449.
[3] E. S. Garnett, G. Firnau, C. Nahmias, S. Sood, and L. Belbeck, *Am. J. Physiol.*, 1980, **238**, R318.
[4] P. K. H. Chan, G. Firnau, and E. S. Garnett, *Radiochem. Radioanal. Lett.*, 1974, **19**, 237.
[5] R. J. Gillespie, A. Netzer, and G. J. Schrobilgen, *Inorg. Chem.*, 1974, **13**, 1455.
[6] N. Bartlett and F. O. Sladky, 'Comprehensive Inorganic Chemistry,' ed. A. F. Trotman-Dickenson, Pergamon Press, Oxford, 1973, Vol. 1, pp. 275—279.
[7] E. H. Appleman, *Inorg. Chem.*, 1967, **6**, 1268.
[8] K. E. Pullen and G. H. Cady, *Inorg. Chem.*, 1967, **6**, 1300.
[9] W. Korytnyk and S. Valentekovic-Horvat, *Tetrahedron Lett.*, 1980, **21**, 1493.