

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]SiF₄, and [^{18}F]AsF₅ 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 fluoro-dopa† by direct fluorination with XeF_2 .² Fluoro-dopa, labelled with the positron-emitting isotope ^{18}F ($t_{1/2}$ 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 $[\text{}^{18}\text{F}]\text{XeF}_2$ by exchange labelling from reactor-produced $^{18}\text{F}^-$.

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 $\text{Bu}_4\text{N}^+\text{OH}^-$ and evaporated to dryness *in vacuo* at 50 °C. The residue of $\text{Bu}_4\text{N}^{18}\text{F}$ and $(\text{Bu}_4\text{N})_2\text{SO}_4$ 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 $[\text{}^{18}\text{F}]\text{HF}$ 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 $\text{Bu}_4\text{N}^+\text{F}^-$. The exchange between XeF_2 and $[\text{}^{18}\text{F}]\text{HF}$ 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 $[\text{}^{18}\text{F}]\text{XeF}_2$ 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 $[\text{}^{18}\text{F}]\text{HF}$, was absorbed on to NaF as $[\text{}^{18}\text{F}]\text{Na}^+\text{HF}_2^-$. 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.

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

‡ FEP = a copolymer of perfluoropolyethylene and perfluoropolypropylene.

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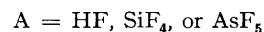
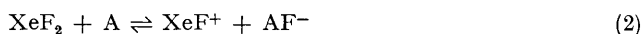
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⁷ E. H. Appleman, *Inorg. Chem.*, 1967, **6**, 1268.

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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 inter-



mediate xenon species, XeF^+ and Xe_2F_3^+ , has been well established both in solution⁵ 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

Analogous exchanges were found to occur when we used SiF_4 or AsF_5 in place of HF. While stable adducts possessing the formulations $\text{XeF}^+\text{AsF}_6^-$ and $\text{Xe}_2\text{F}_3^+\text{AsF}_6^-$ 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, $\text{XeF}_6\cdot\text{GeF}_4$ ($\text{XeF}_5^+\text{GeF}_5^-$).⁸

We found that no exchange occurs between $^{18}\text{F}^-$ 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 $^{18}\text{F}^-$ with XeF_2 and, possibly, other xenon fluorides.

We expect that $[\text{}^{18}\text{F}]\text{XeF}_2$ 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-glucose⁹ and fluoro-dopa.²

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