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Xenon Difluoride Exchanges Fluoride under Mild Conditions: A Simple Preparation of [^{18}F]Xenon Difluoride for PET and Mechanistic Studies

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Xenon difluoride (XeF_2) has a rich chemistry for the introduction of "electrophilic" fluorine into a wide variety of organic compounds.[1] Thus, XeF_2, labeled with positron-emitting ^{18}F ($t_{1/2}$ = 110 min), could be valuable in the preparation of tracers for use with positron emission tomography (PET),[2] an important biomedical imaging technique. [^{18}F]XeF_2 has been prepared by reaction of cyclotron-produced [^{18}F]F_2 with xenon.[3] However, the method requires high pressure and is low-yielding. [^{18}F]Fluoride is available from moderate-energy cyclotrons in very high quantities (multi-Ci) by the ^{18}O(p,n)^{18}F nuclear reaction on [^{18}O]-H_2O.[4] Hence, a simple method for preparing [^{18}F]XeF_2 from [^{18}F]fluoride, rather than [^{18}F]F_2, would be highly attractive. Schrobilgen et al. prepared [^{18}F]XeF_2 by treating sulfuryl chloride fluoride solutions of XeF_2 in fluorinated ethylene propylene (FEP) vessels with Brønsted or Lewis acids ([^{18}F]HF, [^{18}F]SiF_4, or [^{18}F]AsF_5) that had themselves been prepared from [^{18}F]fluoride.[5] However, this method is too hazardous or unwieldy for widespread use. [^{18}F]Fluoride does not exchange with XeF_2 in an FEP vessel in the absence of the Brønsted or Lewis acid.[5] Similarly, there is no direct exchange in CH_2Cl_2 [6] and very low (<1%) and slow exchange in H_2O.[7]

The critical dependence of the reactivity of XeF_2 on reaction vessel, solvent, and catalysts is now better understood.[8] Also the cryptand, Kryptofix 222, has gained wide use for solvating metal counterions (K^+ or Cs^+) and for promoting the reactions of [^{18}F]fluoride in polar aprotic organic solvents.[9] For these reasons, we reexamined the potential for [^{18}F]fluoride to exchange with XeF_2. We now report (i) a mild and practical method for preparing [^{18}F]XeF_2, (ii) a demonstration of its use as an electrophilic radiofluorinating agent, and (iii) isotope distribution evidence to support the proposed reaction mechanism.

Fluoride exchange with XeF_2 is expected to require at least partial ionization (i.e., $XeF_2 + A \rightarrow FXe^{\delta+}\cdots FA^{\delta-}$, where A is a Lewis acid). We have shown[8] that Pyrex glass (13% B_2O_3) catalyzes ionization of XeF_2 and its reaction as the electrophile, FXe^+,[10] or a closely related species: no reaction occurs in identical quartz or soda glass flasks. This catalysis is inhibited if the solvent is MeCN, which presumably occupies all of the Lewis acid sites on the glass surface. In the absence of a catalyst, XeF_2 remains un-ionized and reacts by single-electron transfer (SET).[8] Other non-protic, non-hydroxylic materials, such as platinum and glassy carbon, are generally preferred to Pyrex glass as vessels for the preparation and reactions of [^{18}F]fluoride.[11] Here we show that Cs^+−Kryptofix 222 complex is a convenient alternative to Pyrex glass as a catalyst for the ionization of XeF_2 in chlorinated solvents (CH_2Cl_2, $CHCl_3$) and that this catalyst is also inhibited by MeCN.

XeF_2 is adequately stable in CH_2Cl_2 and $CHCl_3$ for performing short reactions.[12] Indeed CH_2Cl_2 is often used for this purpose.[8a] We have found that the absorbance spectrum of XeF_2[8c] in MeCN, H_2O, or MeCN−H_2O mixtures has λ_{max} at 245 nm (ϵ = 56) and is essentially invariant, thus confirming the good stability of XeF_2 in these media.[12c] Hence, these media were selected for the separation, analysis, and reactions of [^{18}F]XeF_2.

In a typical isotope-exchange experiment, [^{18}F]fluoride in [^{18}O]-H_2O was collected in a glassy carbon vessel.[13] Cs_2CO_3 (0.5 mg; 1.53 μmol) in H_2O (0.1 mL) and Kryptofix 222 (2 mg; 5.31 μmol) in MeCN (0.1 mL) were added, and the solution was taken to dryness under N_2. Twice more MeCN was added and evaporated under N_2. XeF_2 (50 mg, 99.99%, Aldrich Ltd) was added in CH_2Cl_2 (1 mL) and the solution kept under N_2 in the covered vessel at room temperature for 50 min. Analysis of the reaction mixture by HPLC on a Primesphere C18 column (25 × 0.46 cm o.d.; Phenomenex Ltd.) eluted with MeCN−H_2O (3: 2 v/v) at 1 mL/min, with eluate monitored for radioactivity and absorbance at 255 nm (system A), revealed [^{18}F]XeF_2, unchanged [^{18}F]fluoride, and unchanged XeF_2 (identified by its UV absorbance, MS, and ^{19}F NMR spectra; Figure 1, panels A and B). The reaction mixture was loaded onto a silica Sep-Pak (preactivated with MeCN, followed by CH_2Cl_2) and then eluted with MeCN (2.5 mL). HPLC analysis (system A) of the MeCN eluate revealed [^{18}F]XeF_2 as the predominant radioactive component (Figure 1, panel C). Part of the radioactivity loaded onto the Sep-Pak was recovered as [^{18}F]XeF_2 (37−84% (mean 60%, n = 14)). Exchange experiments with $CHCl_3$ as solvent and K^+−Kryptofix 222 as catalyst incorporated ≤90% of the radioactivity into XeF_2, but yields were highly variable. Significantly, no exchange was observed when MeCN was used as solvent. We propose that this solvent inhibits catalysis by competing with XeF_2 for Lewis acid binding sites on the surface of the Cs^+−Kryptofix 222 complex.

The decay-corrected yield of [^{18}F]XeF_2 from the exchange reaction in CH_2Cl_2 increased with reaction time and amount of XeF_2; almost complete incorporation of [^{18}F]fluoride was achievable (Figure 2). The specific radioactivity of the [^{18}F]XeF_2 is fixed

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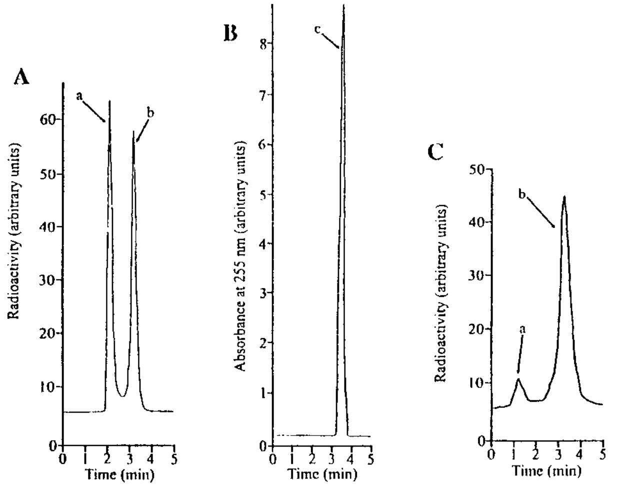


Figure 1. HPLC analysis of [^{18}F]XeF$_2$, prepared by exchange, before (panels A and B) and after (panel C) purification. Key: (a) [^{18}F]fluoride; (b) [^{18}F]XeF$_2$; (c) XeF$_2$.

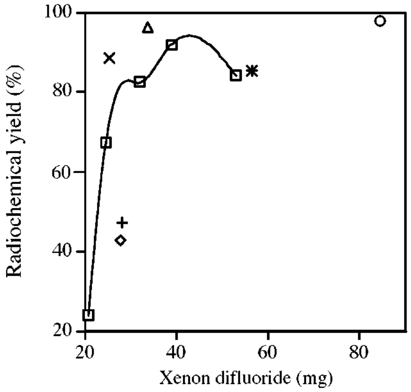


Figure 2. Dependence of the decay-corrected radiochemical yield of [^{18}F]XeF$_2$ on amount of XeF$_2$ treated with [^{18}F]fluoride, for different reaction times (×, 30 min; ◇, 35 min; △, 40 min; □, 45 min; +, 50 min; ∗, 53 min; ○, 110 min). The curve is drawn through the 45 min data.

by the ratio of incorporated radioactivity to the amount of XeF$_2$ and has not yet been optimized.

The use of [^{18}F]XeF$_2$ as a mechanistic probe for the modes of reaction of XeF$_2$ is of some interest. We have reported that XeF$_2$ reacts cleanly with 1-((trimethylsilyl)oxy)cyclo-hexene **1** in MeCN in a glass vessel to give 2-fluorocyclohexanone **2** in high yield, and we have proposed an SET mechanism for this process (Scheme 1).[8] A MeCN solution of **1** was treated with [^{18}F]XeF$_2$ in a glass vessel for 16 min at room temperature. HPLC analysis of the reaction mixture on System A eluted with MeCN−H$_2$O (3: 1 v/v) at 1.5 mL/min revealed 33% decay-corrected radiochemical yield of [^{18}F]**2** (Figure 3), identified by MS and ^{19}F NMR of coeluting carrier ($m/z = 117$ [M + H]$^+$; δ 187 ppm (doublet), $^2J_{HF} = 52.9$ Hz) and co-migration with reference **2**. Unchanged [^{18}F]XeF$_2$ and XeF$_2$ were also observed. In some reactions a more strongly retained radioactive product (retention time, 3.75 min) was also detected in similar yield to [^{18}F]**2**, and this is presumed to be volatile [^{18}F]trimethylsilylfluoride **3**. These findings affirm the identity and reactivity of the prepared [^{18}F]XeF$_2$.

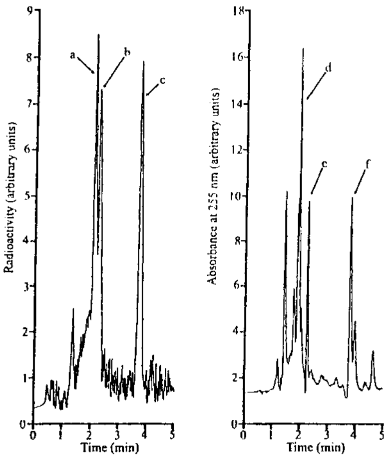
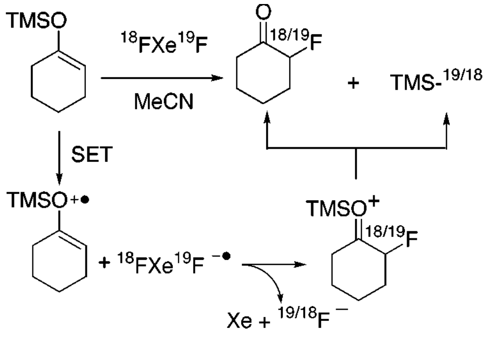


Figure 3. HPLC analysis of products from the reaction of **1** with [^{18}F]XeF$_2$. Key: (a) [^{18}F]XeF$_2$; (b) [^{18}F]**2**; (c) putative [^{18}F]Me$_3$SiF; (d) XeF$_2$; (e) **2**; (f) putative Me$_3$SiF.

Scheme 1. Reaction of 1-((Trimethylsilyl)oxy)cyclohexene 1 with [^{18}F]XeF$_2$ According to an SET Mechanism



XeF$_2$ can promote the reaction of [^{18}F]fluoride with certain substrates, such as aliphatic carboxylic acids[6,14] and thioethers.[15] Treatment of **1** with [^{18}F]fluoride and XeF$_2$ in MeCN failed to produce any [^{18}F]**2**. Hence, our findings are fully consistent with the SET mechanism proposed for the reaction of XeF$_2$ with **1** (Scheme 1) and show that in this reaction the fluorine is not introduced via fluoride.

In conclusion, Cs$^+$−Kryptofix 222 is able to catalyze the efficient exchange of [^{18}F]fluoride with XeF$_2$ in CH$_2$Cl$_2$ under mild conditions. Consequently, [^{18}F]XeF$_2$ should now find wider use for the preparation of tracers for PET. This study of [^{18}F]XeF$_2$ provides further evidence for two discrete mechanisms of reaction of XeF$_2$ that are influenced by solvent, reaction vessel, and catalyst. Pyrex or Cs$^+$−Kryptofix 222 complex acts as a Lewis acid catalyst leading to reactions, including fluoride exchange, via an ionic mechanism. In the absence of these catalysts, or in solutions of the weak Lewis base MeCN, XeF$_2$ remains un-ionized and reacts by SET.

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