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On The Preparation of Fluorine-18 Labelled XeF_2 and Chemical Exchange between Fluoride Ion and XeF_2

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Abstract: A recent report claims to have prepared $[^{18}F]XeF_2$ by exchange between a large stoichiometric excess of XeF_2 and no-carrier-added $^{18}F^-$, as salts of the [2,2,2-crypt-M^+] (M = K or Cs) cations, in CH_2Cl_2 or $CHCl_3$ solvents at room temperature. Attempts to repeat this work have proven unsuccessful and have led to a critical reinvestigation of chemical exchange between fluoride ion, in the form of anhydrous $[N(CH_3)_4][F]$ and [2,2,2-crypt-K][F], and XeF_2 in dry CH_2Cl_2 and CH_3CN solvents. It was shown, by use of ^{19}F and ^1H NMR spectroscopies, that [2,2,2-crypt-K][F] rapidly reacts with CH_3CN solvent to form HF_2^-, and with CH_2Cl_2 solvent to form HF_2^-, CH_2ClF, and CH_2F_2 at room temperature. Moreover, XeF_2 rapidly oxidizes 2,2,2-crypt in CH_2Cl_2 solvent at room temperature to form HF and HF_2^-. Thus, the exchange between XeF_2 and no-carrier-added $^{18}F^-$ reported in the prior work arises from exchange between XeF_2 and HF/HF_2^-, and does not involve fluoride ion. However, naked fluoride ion has been shown to undergo exchange with XeF_2 under rigorously anhydrous and HF-free conditions. A two-dimensional $^{19}F-^{19}F$ EXSY NMR study demonstrated that $[N(CH_3)_4][F]$ exchanges with XeF_2 in CH_3CN solvent, but exchange of HF_2^- with either XeF_2 or F^- is not detectable under these conditions. The exchange between XeF_2 and F^- is postulated to proceed by the formation of XeF_3^- as the exchange intermediate.

Introduction

Xenon difluoride has been extensively used as a fluorinating agent for a wide variety of inorganic and organic compounds.[1] Fluorine-18 (^{18}F, 97% β^+, $t_{1/2} = 109.7$ min, $E_{max} = 0.635$ MeV) labelled XeF_2 has been synthesized[2,3] and used to prepare positron emitting medical imaging agents such as [^{18}F]2-fluoro-2-deoxy-D-glucose[4] and [^{18}F]6-fluoro-L-DOPA.[5] Fluorine-18 labelled XeF_2 was first prepared in our laboratories[2] by treating SO_2ClF solutions of XeF_2 with $[^{18}F]HF$, $[^{18}F]SiF_4$, or $[^{18}F]AsF_5$. The exchanges are attributed to the Lewis acid properties of the labelled fluorides (eqs 1 and 2).

$$A^{18}F + XeF_2 \rightarrow FA^{18}F^- + XeF^+ \qquad (1)$$

$$FA^{18}F^- + XeF^+ \rightarrow FXe^{18}F + AF \qquad (2)$$

$$A = H,\ SiF_3,\ \text{or}\ AsF_4$$

We have since shown that $[^{18}F]XeF_2$ can also be synthesized by the thermochemical reaction of carrier-added $[^{18}F]F_2$ and Xe.[3] Appelman[6] has also shown that very slow fluorine exchange occurs between XeF_2 and aqueous $H^{18}F$ (ca. 0.8% after 2 h at 0 °C).

A recent study in this journal by Pike et al.[7] reports that no-carrier-added (nca) ^{18}F-labelled KF and CsF, sequestered by 2,2,2-crypt (1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]-hexacosane), undergo fluorine exchange with XeF_2 at room temperature in CH_2Cl_2 and $CHCl_3$ solvents. The study also reports that the exchange was inhibited in CH_3CN solvent. It was claimed that the 2,2,2-crypt-M^+ cation (M = K or Cs) catalyzes ionization of XeF_2 in chlorinated solvents. Exchange experiments conducted in CH_2Cl_2 solutions required a large molar excess of XeF_2 relative to the cryptand (molar ratio of XeF_2:2,2,2-crypt:Cs_2CO_3 used in a typical exchange experiment was 56:1:0.29) for "efficient" exchange of nca $^{18}F^-$ ion. When 2,2,2-crypt-K^+ and $CHCl_3$ solvents were used, ≤90% of the radioactivity was incorporated into XeF_2; however, yields were reported to be highly variable. This work is at apparent odds with earlier ^{18}F-labelling experiments which have shown that fluoride ion, in the form of $[N(n\text{-}Bu)_4][^{18}F]$, does not exchange with XeF_2 in CH_2Cl_2 solvent after 30 min at room temperature.[8]

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(1) Brel, V. K.; Pirkuliev, N. Sh.; Zefirov, N. S. *Russ. Chem. Rev.* **2001**, *70*, 231.

(2) Schrobilgen, G.; Firnau, G.; Chirakal, R.; Garnett, E. S. *J. Chem. Soc., Chem. Commun.* **1981**, 198.

(3) Chirakal, R.; Firnau, G.; Schrobilgen G. J.; McKay, J.; Garnett, S. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 401.

(4) Sood, S.; Firnau, G.; Garnett, E. S. *Int. J. Appl. Radiat. Isot.* **1983**, *34*, 743.

(5) Firnau, G.; Chirakal, R.; Sood, S.; Garnett, E. S. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 7.

(6) Appelman, E. H. *Inorg. Chem.* **1967**, *6*, 1268.

(7) Constantinou, M.; Aigbirhio, F. I.; Smith, R. G.; Ramsden, C. A.; Pike, V. W. *J. Am. Chem. Soc.* **2001**, *123*, 1780.

(8) Patrick, T. B.; Johri, K. K.; White, D. H.; Bertrand, W. S.; Mokhtar, R.; Kilbourn, M. R.; Welch, M. J. *Can. J. Chem.* **1986**, *64*, 138.

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Fluoride ion and XeF_2 are known to react with a number of organic solvents. Christe and Wilson[9] have demonstrated, by ^1H and ^{19}F NMR spectroscopies, that anhydrous $[N(CH_3)_4][F]$, so-called "naked fluoride", reacts with CH_3CN, CH_2Cl_2, and $CHCl_3$ solvents at room temperature. These authors have shown that fluoride ion reacts relatively slowly with CH_3CN to form HF_2^- and CH_2CN^- anions, according to eqs 3 and 4.

$$F^- + CH_3CN \rightarrow HF + CH_2CN^- \quad (3)$$

$$HF + F^- \rightarrow HF_2^- \quad (4)$$

Fluoride ion was also reported to react slowly with CH_2Cl_2, forming CH_2ClF as the only reported fluorination product, but rapidly with $CHCl_3$, resulting in all three possible halogen exchange products, $CHCl_2F$, $CHClF_2$, and CHF_3 in a 2:3:1 molar ratio. Holloway et al.[10] showed, using ^1H and ^{19}F NMR spectroscopies, that XeF_2 reacts with CH_2Cl_2 and $CHCl_3$ over a period of 2 days at room temperature. The reaction of XeF_2 with CH_2Cl_2 yielded predominantly CH_2ClF, $CHCl_2F$, and HF, with CH_2F_2, $CHClF_2$, CCl_2F_2, and $CFCl_3$ as minor (<0.5%) products, and that with $CHCl_3$ yielded $CHCl_2F$, $CHClF_2$, $CHCl_3$, and HF. Based on these findings, the authors suggested CH_3CN or chlorofluorocarbons might be more appropriate solvents for XeF_2 when the kinetics of the desired fluorination reactions are slow.

The aforementioned work and failed attempts in our laboratories to repeat the work of Pike et al.[7] have led us to critically reassess the interaction of [2,2,2-crypt-K][F], and other fluoride ion sources, with XeF_2 in CH_2Cl_2 and CH_3CN solvents under rigorously anhydrous conditions by use of one- and two-dimensional NMR techniques. The previous work[7] has shown that radiochemical yields in $CHCl_3$ were highly variable. This is not surprising because fluoride ion has been shown to rapidly react with $CHCl_3$ to form all three possible solvent exchange products, $CHCl_2F$, $CHClF_2$, and CHF_3,[9] and because XeF_2 has been shown to react with $CHCl_3$ to form $CHFCl_2$, CHF_2Cl, $CFCl_3$, and HF.[10] Consequently, the role of $CHCl_3$ as a fluoride ion exchange medium was not reinvestigated in the present study.

Results and Discussion

Reaction of XeF_2 with 2,2,2-crypt and KF in CH_2Cl_2 Solvent. We have found that equimolar mixtures of XeF_2, KF, and 2,2,2-crypt in CH_2Cl_2 solvent detonate, under rigorously anhydrous conditions, when rapidly warmed from −196 °C to room temperature. The heat of reaction was, however, effectively dissipated in experiments where [2,2,2-crypt-K][F] was initially dissolved in CH_2Cl_2, followed by XeF_2 addition at ca. −140 °C to the frozen mixture and slow warming to room temperature over a period of ca. 1 h. The reaction mixture slowly changed from a colorless to a brown solution. The ^{19}F NMR spectrum of this sample was complex, and several fluorination products were observed. The absence of characteristic ^{19}F signals for XeF_2,[11] HF,[12] or HF_2^- [9] in the ^{19}F NMR spectrum indicated that chemical exchange may occur between two or more of these species, and/or all of the XeF_2 had reacted with the 2,2,2-crypt-K^+ to form HF and HF_2^-, which underwent rapid fluorine exchange. The dominant ^{19}F resonance was a broad singlet at −162.8 ppm ($\Delta\nu_{1/2}$, 46 Hz). Christe and Wilson[13] have observed broad, exchange-averaged resonances for $F^-/HF_2^-/HF$ mixtures in mixed water (10%)/CH_3CN solutions ranging from −118 to −170 ppm ($\Delta\nu_{1/2}$, 80 Hz), which have chemical shifts that are dependent upon the mole ratios of the components. Very weak triplets arising from CH_2F_2 at −142.1 ppm ($^2J_{HF}$, 49 Hz), and CH_2ClF at −168.9 ($^2J_{HF}$, 48 Hz) were also observed. In addition, a series of weak, equally intense pairs of ^{19}F NMR resonances appears at −79.9, −80.2 and −85.5, −86.2 ppm, which have chemical shifts that are similar to those of the CF_2 resonances in perfluoro-2,2,2-crypt (OCF_2CF_2O, −81.4 ppm, s; OCF_2, −87.0 ppm, t, $^3J_{FF} \sim 1$ Hz; NCF_2, −88.5 ppm, t, $^3J_{FF} \sim 1$ Hz).[14] It is therefore likely that partially fluorinated 2,2,2-cryptands result from oxidative fluorination of 2,2,2-crypt by XeF_2. A second series of weak and equally intense ^{19}F resonances also appeared at −126.9, −127.2 and −131.7, −131.9 ppm. Although the detailed characterization of all fluorination products was beyond the scope of the present work, these findings clearly demonstrate that alkali metal (K^+ and Cs^+) 2,2,2-cryptands are not inert in these reactions and therefore do not function as "catalysts", as previously claimed.[7]

Stability of XeF_2 and 2,2,2-crypt in CH_2Cl_2 Solvent. The reactivity of XeF_2 with 2,2,2-crypt in the absence of KF was also investigated in CH_2Cl_2 solvent. Samples of XeF_2 and 2,2,2-crypt were prepared in an equimolar ratio in CH_2Cl_2 solvent and warmed from −196 °C to room temperature over a period of ca. 1 h. A brown-colored solution resulted, similar to that arising from the reaction of [2,2,2-crypt-K][F] and XeF_2 in CH_2Cl_2 (vide supra). The ^{19}F NMR spectrum revealed several fluorination products, among which was an intense, broad singlet at −162.6 ppm ($\Delta\nu_{1/2}$, 35 Hz) that is attributable to HF_2^-/HF exchange. The corresponding ^1H resonance was observed as a broad singlet at 12.65 ppm ($\Delta\nu_{1/2}$, 40 Hz) and is intermediate with respect to those of HF (7.00 ppm)[12] and HF_2^- (16.20 ppm) in CH_2Cl_2 (this work; see Reactions of [2,2,2-crypt-K][F] with CH_3CN and CH_2Cl_2 Solvents). Two series of weak and equally intense pairs of ^{19}F NMR resonances (−78.7, −79.2; −86.3, −87.0; −87.4, −87.9; −93.7, −94.4 ppm; and −127.3, −127.5; −127.8, −128.1; −132.6, −132.8; and −142.3, −142.6 ppm) that are similar to those observed for the XeF_2/2,2,2-crypt/KF system described above were observed, which are indicative of cryptand fluorination by XeF_2. The ^1H NMR spectrum of this sample revealed, in addition to CH_2Cl_2 (5.34 ppm) solvent, unreacted 2,2,2-crypt (OCH_2CH_2O, 3.58 ppm, s; OCH_2, 3.66 ppm, t, $^3J_{HH} = 5$ Hz; NCH_2, 3.00 ppm, t, $^3J_{HH} = 5$ Hz) and a broad line (12.72 ppm, $\Delta\nu_{1/2}$, 56 Hz) that is assigned to HF and HF_2^- undergoing rapid proton exchange. It is reasonable to assume that protonated nitrogen centers of the fluorination products and unreacted 2,2,2-crypt may serve as the countercations; however, the NH protons can be expected to undergo chemical exchange with HF/HF_2^- and therefore may also be represented by the resonance at 12.72 ppm. Several very weak, broad features were also observed in the ^1H NMR spectrum between 6 and 10 ppm.

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(9) Christe, K. O.; Wilson, W. W. *J. Fluorine Chem.* **1990**, *47*, 117.
(10) Dukat, W. W.; Holloway, J. H.; Hope, E. G.; Townson, P. J.; Powell, R. L. *J. Fluorine Chem.* **1993**, *62*, 293.
(11) Gerken, M.; Schrobilgen, G. J. *Coord. Chem. Rev.* **2000**, *197*, 335.
(12) The ^1H and ^{19}F chemical shifts of anhydrous HF in dry CH_2Cl_2 are 7.00 and −191.3 ppm, respectively, at 15 °C; this work.
(13) Christe, K. O.; Wilson, W. W. *J. Fluorine Chem.* **1990**, *46*, 339.
(14) Clark, W. D.; Lin, T. Y.; Maleknia, S. D.; Lagow, R. J. *J. Org. Chem.* **1990**, *55*, 5933.

A sample containing a 33:1 molar ratio of XeF_2 to 2,2,2-crypt was warmed from −196 °C to room temperature over a period of 1 h and produced a two-phase mixture with a clear lower density layer and a minor yellow, higher density layer. Unlike the equimolar sample of XeF_2 and 2,2,2-crypt, the ^{19}F NMR spectrum of the 33:1 molar ratio of XeF_2 to 2,2,2-crypt revealed the presence of XeF_2 (−175.1 ppm; $^1J(^{129}Xe-^{19}F)$, 5605 Hz), and a second weaker XeF_2 resonance in the second phase (−178.4 ppm; $^1J(^{129}Xe-^{19}F)$, 5630 Hz), as well as a doublet arising from $CHCl_2F$ (−81.0 ppm; $^2J_{HF}$, 53 Hz), and triplets arising from CH_2F_2 (−142.9 ppm; $^2J_{HF}$, 49 Hz) and CH_2ClF (−170.4; $^2J_{HF}$, 48 Hz). The ^{19}F NMR spectrum also showed intense resonances at −176.4 and −181.2 ppm with line widths of 220 and 200 Hz, respectively, that are assigned to HF and HF_2^- undergoing rapid fluorine exchange in their respective phases. The corresponding ^1H resonances were observed at 11.64 and 11.27 ppm and had line widths of 64 and 22 Hz, respectively. Although the ^1H NMR spectrum of this sample was complicated by the presence of a second phase, it is noteworthy that 2,2,2-crypt was not observed, as in the equimolar sample, confirming that 2,2,2-crypt had fully reacted when a 33:1 molar excess of XeF_2 in CH_2Cl_2 solvent had been allowed to react at room temperature for 1 h. These findings clearly contradict the previous study,[7] which claims that a 56:1 molar ratio of XeF_2 to 2,2,2-crypt is required to achieve "efficient" exchange with $^{18}F^-$ ion in CH_2Cl_2, and further confirms that 2,2,2-crypt is not inert under these reaction conditions. The NMR spectra show large amounts of HF and HF_2^- corresponding to the fluorination of the CH_2 groups of 2,2,2-crypt and the solvent by XeF_2. The fluorination products that result from the reaction of XeF_2 with 2,2,2-crypt are likely contained in the second, higher density phase. Scale up of the reaction for the purpose of characterizing the 2,2,2-crypt fluorination products was not attempted because of the exothermicity of the reaction in CH_2Cl_2. In view of the 56:1 molar ratio of XeF_2:2,2,2-crypt in the previous report,[7] and the 33:1 molar ratio of XeF_2:2,2,2-crypt in the present study, it is clear that a significant amount of XeF_2 survives in the presence of HF generated in these reactions. Hydrogen fluoride has already been shown in our earlier ^{18}F studies to promote fluorine exchange by acting as a weak fluoride ion acceptor toward XeF_2 (eqs 1 and 2).[2] Therefore, the exchange reported in the previous work[7] cannot possibly arise from exchange of free F^- ion with XeF_2, but must arise from HF/HF_2^- exchange with XeF_2, where HF is in very large excess relative to HF_2^- in these nca ^{18}F exchange studies.

Reaction of [N(CH$_3$)$_4$][F] and XeF$_2$ in CH$_2$Cl$_2$ Solvent. Christe and co-workers[15] reported the synthesis of the "naked fluoride ion" source, anhydrous $[N(CH_3)_4][F]$. They demonstrated that $[N(CH_3)_4][F]$ reacts with CH_3CN and chlorinated solvents.[9] In the present study, an equimolar sample of $[N(CH_3)_4][F]$ and XeF_2 in CH_2Cl_2 solvent was prepared to investigate the role of fluoride ion in chemical exchange with XeF_2 in the absence of 2,2,2-crypt. Reaction took place over a period of 1 day at room temperature without color change. The ^{19}F NMR spectrum revealed the presence of CH_2F_2, $CHCl_2F$, and CH_2ClF, in addition to XeF_2 and fluoride ion, and further confirmed that the fluorination of 2,2,2-crypt-M^+ by XeF_2 was responsible for the vigorous reactions that occurred in equimolar mixtures of XeF_2 and [2,2,2-crypt-K][F] in CH_2Cl_2 solvent at room temperature (see Reaction of XeF_2 with 2,2,2-crypt and KF in CH_2Cl_2 Solvent). To verify that [2,2,2-crypt-K][F] demonstrates a reactivity similar to that of $[N(CH_3)_4][F]$ in CH_3CN and CH_2Cl_2 solvents, [2,2,2-crypt-K][F] was studied in these solvents by ^1H and ^{19}F NMR spectroscopies.

Reactions of [2,2,2-crypt-K][F] with CH$_3$CN and CH$_2$Cl$_2$ Solvents. The ^{19}F NMR spectrum of [2,2,2-crypt-K][F] in CH_3CN, after 1 h at room temperature, showed two signals, a weak singlet (−75 ppm; $\Delta\nu_{1/2}$, 167 Hz) corresponding to F^- and an intense doublet (−147.1 ppm; $^1J_{HF}$, 121 Hz) assigned to HF_2^-.[9] The ^1H NMR spectrum showed, in addition to the solvent line (CH_3CN, 1.96 ppm) and 2,2,2-crypt (OCH_2CH_2O, 3.57 ppm, s; OCH_2, 3.52 ppm, t, $^3J_{HH} = 5.5$ Hz; NCH_2, 2.55 ppm, t, $^3J_{HH} = 5.5$ Hz), a triplet at 16.33 ppm ($^1J_{HF}$, 121 Hz) characteristic of HF_2^-.[9] Using saturated solutions of anhydrous $[N(CH_3)_4][F]$ as the fluoride ion source, CH_2CN^- has been previously detected as a broad singlet (line width not reported) at 9.1 ppm in the ^1H NMR spectrum, which was found to increase in intensity with time (up to several days).[9] In the present study, CH_2CN^- was not observed when [2,2,2-crypt-K][F] was allowed to react in CH_3CN at room temperature over a 1 h period, likely because of the lower concentration of fluoride ion and shorter reaction time used when compared with the previous study,[9] and the expected breadth of the resonance. This study confirms previous work which showed that the major product resulting from the reaction of fluoride ion with CH_3CN is HF_2^- when either $[N(CH_3)_4][F]$[9] or [2,2,2-crypt-K][F][16] is used as the fluoride ion source.

The ^{19}F NMR spectrum of [2,2,2-crypt-K][F] in CH_2Cl_2, after 1 h at room temperature, showed a weak singlet (−115 ppm; $\Delta\nu_{1/2}$, 242 Hz) for F^- and a triplet (−169.7 ppm; $^1J_{HF}$, 48.0 Hz), characteristic of CH_2ClF. The ^1H NMR spectrum of the same sample showed CH_2ClF (5.92 ppm, d, $^2J_{HF}$, 48.0 Hz), in addition to the solvent line (CH_2Cl_2, 5.34 ppm), and 2,2,2-crypt (OCH_2CH_2O, 3.57 ppm, s; OCH_2, 3.49 ppm, t, $^3J_{HH} = 5.5$ Hz; NCH_2, 2.53 ppm, t, $^3J_{HH} = 5.5$ Hz). A triplet was also observed in the present work in the ^{19}F NMR spectrum (−142.8 ppm; $^2J_{HF}$, 49.9 Hz) that is characteristic of CH_2F_2.[17] The triplet expected for CH_2F_2 in the ^1H NMR spectrum was not observed because it was masked by the CH_2Cl_2 solvent signal (the ^1H chemical shift of CH_2F_2 is reported at 5.62 ppm[18]). The ^{19}F NMR spectrum of the HF_2^- anion was observed as a doublet (−156.3 ppm; $^1J_{HF}$, 122 Hz) and showed a triplet (16.20 ppm; $^1J_{HF}$, 122 Hz) in the ^1H NMR spectrum. Christe and Wilson[9] showed that CH_2Cl_2 undergoes slow halogen exchange with $[N(CH_3)_4][F]$ at room temperature, giving CH_2ClF as the main reaction product, but did not report the presence of CH_2F_2. However, it was shown in the present study, using ^{19}F NMR spectroscopy, that a sample of $[N(CH_3)_4][F]$ in CH_2Cl_2, after 1 h at room temperature, resulted in the formation of CH_2F_2 as the major product, with CH_2ClF as the minor product (the molar ratio of F^-:CH_2F_2:CH_2ClF was 2.2:6.8:1.0). The formation of CH_2F_2 as a major product in this reaction is not surprising and is consistent with previously reported halogen exchange reactions between CH_2Cl_2 and alkali metal fluorides. Fukui and

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(15) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. *J. Am. Chem. Soc.* **1990**, *112*, 7619.

(16) Chirakal, R.; McCarry, B.; Lonergan, M.; Firnau, G.; Garnett, S. *Appl. Radiat. Isot.* **1995**, *46*, 149.

(17) Hudlický, M. *Organic Fluorine Chemistry*; Plenum Press: New York, 1971; p 48.

(18) Lazeretti, P.; Taddei, F. *Org. Magn. Reson.* **1971**, *3*, 113.

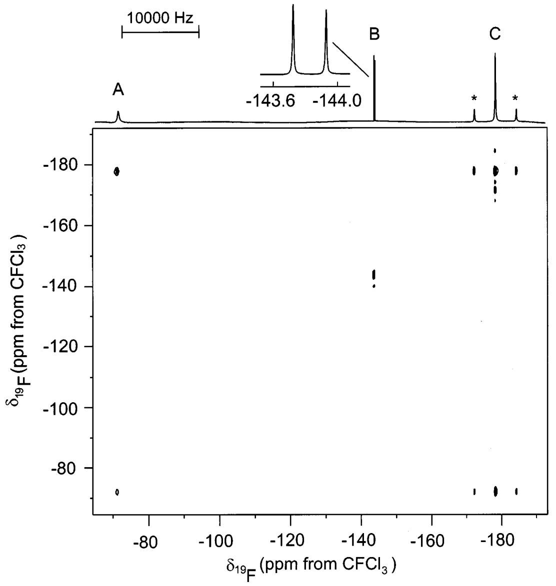

Figure 1. The 2-D $^{19}F-^{19}F$ EXSY spectrum of an equimolar sample of XeF_2 and $[N(CH_3)_4][F]$ in CH_3CN solvent, acquired at 15 °C using a mixing time of 400 ms. The labels A, B, and C refer to F^-, HF_2^-, and XeF_2, respectively, and asterisks (*) denote natural-abundance ^{129}Xe satellites ($^1J(^{129}Xe-^{19}F)$, 5657 Hz).

Kitano[19] synthesized CH_2ClF and CH_2F_2 in 19% and 17% yields, respectively, by passing CH_2Cl_2 through a mixture of NaF and KF in $HO(CH_2)_2OH$ at 180−200 °C, and Verbeek and Sundermeyer[20] synthesized CH_2F_2 in 82% yield (34% conversion) by reaction of CH_2Cl_2 with a KF−HF melt at 300 °C. In agreement with the work of Christe and Wilson,[9] HF_2^- was not observed in the present work when $[N(CH_3)_4][F]$ was allowed to react with CH_2Cl_2 for 1 h, whereas reaction of [2,2,2-crypt-K][F] in CH_2Cl_2 resulted in the formation of HF_2^- after 1 h at room temperature. These findings further demonstrate that the previously reported[7] exchange reaction between XeF_2 and [2,2,2-crypt-K][^{18}F] was not catalyzed by 2,2,2-crypt, but rather resulted from exchange among HF, HF_2^-, and XeF_2, as described above (see Stability of XeF_2 and 2,2,2-crypt in CH_2Cl_2 Solvent) and in our earlier study.[2]

Fluoride Ion Exchange with XeF_2. A two-dimensional (2-D) $^{19}F-^{19}F$ EXSY experiment demonstrates that fluoride ion exchanges with XeF_2 in CH_3CN solvent. The off-diagonal correlations (Figure 1) confirm exchange between an initially equimolar mixture of $[N(CH_3)_4][F]$, −71.5 ppm ($\Delta\nu_{1/2} = 267$ Hz), and XeF_2, −178.2 ppm; $^1J(^{129}Xe-^{19}F)$, 5657 Hz. It was also shown that HF_2^- (−143.8 ppm; $^1J_{HF}$, 120 Hz) does not exchange with XeF_2 or fluoride ion on the NMR time scale under the experimental conditions used in this study. The HF_2^- anion present in these samples was derived from fluoride attack on the solvent (eqs 3 and 4), as previously reported.[9] The ^{19}F exchange is postulated to proceed through the formation of trifluoroxenate(II), XeF_3^-, anion as the exchange intermediate (eq 5). The exchange of XeF_2 with HF was also studied by

$$XeF_2 + F^- \rightleftharpoons XeF_3^- \qquad (5)$$

variable-temperature ^{19}F and ^{129}Xe NMR spectroscopy of XeF_2 in anhydrous HF solvent and will be discussed in subsequent publications along with electron structure calculations and energy-minimized geometry of the novel XeF_3^- anion.[21]

Influence of Solvent and Vessel upon the Reactions of XeF_2 with Organic Substrates. It has been assumed that F^- ion exchange with XeF_2 proceeds by a dissociative mechanism. A report in this journal[22] claims that Pyrex glass surfaces catalyze the ionization of XeF_2 in CH_2Cl_2, $CHCl_3$, $CFCl_3$, and C_6F_6 solvents to presumably form the strong electrophile XeF^+ (estimated electron affinity, 10.9 eV[23]). There are numerous examples of stable XeF^+ salts,[24,25] and it is well recognized in the field of noble-gas chemistry that the XeF^+ cation is only stable in a very limited number of inorganic solvent media which are not susceptible to oxidative attack by this cation, such as anhydrous HF and BrF_5; thus the formation of the strong electrophile, XeF^+, as a reactive intermediate in organic solvents is unlikely and unfounded. A more likely scenario involves an HF-assisted exchange in which HF hydrogen bonds to and polarizes XeF_2, followed by nucleophilic attack at xenon by the fluorine of HF. Moreover, these authors[22] also claimed that F^- ion exchange with XeF_2 does not occur under certain conditions, such as in an FEP vessel or in CH_3CN solvent, and it was suggested that CH_3CN inhibits the exchange of XeF_2 with [2,2,2-crypt-M][^{18}F].[7] Contrary to these claims, a 2-D $^{19}F-^{19}F$ EXSY experiment in this study has demonstrated that fluoride ion exchanges with XeF_2 in CH_3CN solvent contained in an FEP vessel (see Fluoride Ion Exchange with XeF_2).

Ramsden and Smith[22] have also claimed that the catalytic effects of glass surfaces in electrophilic fluorination reactions using XeF_2 in dry CH_2Cl_2 circumvent the need for HF in reactions described as requiring HF catalysis. The alleged surface catalysis of XeF_2/F^- exchange is more likely attributable to HF attack of the glass surface. The origin of HF, as pointed out previously, may arise from occlusion of HF by XeF_2,[26] as well as from solvent attack by XeF_2, as described above, and from a lack of truly anhydrous conditions (eq 6). Attack of glass

$$XeF_2 + H_2O \rightarrow Xe + \frac{1}{2}O_2 + 2HF \qquad (6)$$

by HF is a cyclic process, producing water which further reacts with and reduces XeF_2 to produce HF (eq 6). Moreover, the H_2O/HF/glass system is repeatedly emphasized in the literature of fluorine chemistry to introduce a variety of species, including boron- and silicon-containing Lewis acids,[27] which may also serve as fluorine exchange catalysts.[2]

Synthesis of [^{18}F]XeF_2 by $^{18}F^-$ Exchange with XeF_2 in CH_2Cl_2. There are also several major concerns relating to exchange of ^{18}F-labelled fluoride ion with XeF_2 as previously reported.[7] Among these are the large molar excess of XeF_2 relative to 2,2,2-crypt (56:1) and the high concentration (0.285

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(19) Fukui, K.; Kitano, N. Japanese Patent 7761, 1957; *Chem. Abstr.* **1958**, *52*, 13773.
(20) Verbeek, W.; Sundermeyer, W. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 314; *Angew. Chem.* **1966**, *78*, 307.
(21) Vasdev, N.; Schrobilgen, G. J.; Chirakal, R.; Suontamo, R. J., to be submitted.
(22) Ramsden, C. A.; Smith, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 6842.
(23) Schrobilgen, G. J. In *Synthetic Fluorine Chemistry*; Chambers, R. D., Olah, G. A., Prakash, G. K. S., Eds.; Wiley and Sons: New York, 1992; Chapter 1, pp 1−30.
(24) Selig, H.; Holloway, J. H. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: Berlin, 1984; Vol. 124, pp 33−90.
(25) Lehmann, J. F.; Mercier, H. P. A.; Schrobilgen, G. J. *Coord. Chem. Rev.*, in press.
(26) Shellhamer, D. F.; Chua Chiaco, M.; Gallego, K. M.; Low, W. S. C.; Carter, B.; Heasley, V. L.; Chapman, R. D. *J. Fluorine Chem.* **1995**, *72*, 83.
(27) Janzen, A. F. *Coord. Chem. Rev.* **1994**, *130*, 355.

M) of XeF_2 in CH_2Cl_2 that was required to effect exchange with nca $^{18}F^-$ ion in 1 mL of CH_2Cl_2. Attempts to repeat the previous work[7] and to exchange 10 mCi of nca $^{18}F^-$ ion (5.8×10^{-10} mol), in the form of [2,2,2-crypt-K][^{18}F], with XeF_2 in 1 mL of CH_2Cl_2 solvent at room temperature were unsuccessful in the present study. Separate HPLC experiments (Phenomenex, Hypersil C18, 5 μm, 25 × 0.46 cm, eluted with 60% CH_3CN/H_2O, using a flow rate of 1.0 mL/min) were run for nca $^{18}F^-$ and XeF_2 to establish their retention times. Sharp peaks corresponding to $^{18}F^-$ (3.1 min) and XeF_2 (UV, $\lambda = 254$ nm, 3.8 min) were obtained. The chromatograms acquired for the reaction of [2,2,2-crypt-K][^{18}F] with XeF_2 in CH_2Cl_2 solvent at room temperature after 1 h were not reproducible. The UV trace showed a sharp peak with a retention time corresponding to XeF_2 (3.8 min); however, the radiochromatogram showed one broad, tailing ^{18}F-containing peak that eluted from 4 to 6 min which was not identified. The broad peak is consistent with the coelution of several species, but no discrete $^{18}F^-$ ion peak was observed. "Cold" experiments, described in previous sections, demonstrate that the system is complex and leads to several fluorinated products. The ^{18}F exchange experiments described previously and here employed carbonate[7] or bicarbonate, respectively. Both anions are known to accelerate the decomposition of XeF_2 in aqueous media.[28] The inability to separate $^{18}F^-$ from [^{18}F]XeF_2 in the radiochromatogram results because the ^{18}F activity is distributed among XeF_2, F^-, HF, and HF_2^-, as well as the products of solvent fluorination (vide supra).

Fluorine-18 exchange experiments between XeF_2 and ^{18}F-labelled fluoride ion, in the form of a tetraalkylammonium salt, were not attempted because it is difficult to obtain rigorously anhydrous ^{18}F-labelled fluoride salts. Consequently, the formation of fluoride ion hydrates, $F^-(H_2O)_n$ ($n = 1-6$),[29] in ^{18}F-labelling experiments is expected to greatly attenuate the degree of fluoride ion "nakedness" in these studies, and the reaction of XeF_2 with coordinated water and trace amounts of other adventitious water is expected to lead to HF (eq 6) and HF_2^- (eq 4). Furthermore, the reaction of XeF_2 with CH_2Cl_2 is known to produce CH_2ClF, $CHCl_2F$, and HF, with CH_2F_2, $CHClF_2$, CCl_2F_2, and $CFCl_3$ as minor (<0.5%) products.[10] These factors could also account for the failure of [N(n-Bu$_4$)$_4$][^{18}F] to undergo exchange with XeF_2 in CH_2Cl_2.[8]

Because multiple fluorination products have been shown to form in reactions of "cold" fluoride ion and XeF_2 with CH_3CN and CH_2Cl_2 solvents at room temperature after 1 h, these methods are also not practical routes for the preparation of [^{18}F]-XeF_2 from nca $^{18}F^-$ ion. Moreover, the resulting hydrochlorofluorocarbons can be highly toxic, i.e., CH_2ClF is a known carcinogen,[30] and thus pose problems for medicinal use if the toxins cannot be reliably separated.

Conclusions

The present work has demonstrated, by EXSY NMR studies, that XeF_2 exchanges with fluoride ion when a countercation, such as $N(CH_3)_4^+$, which is oxidatively resistant to XeF_2, is employed. The exchange is postulated to proceed through the XeF_3^- anion as the intermediate. Moreover, this study shows that a 33:1 molar ratio of XeF_2 to 2,2,2-crypt in CH_2Cl_2 solvent leads to fluorination of 2,2,2-crypt and CH_2Cl_2, producing $CHCl_2F$, CH_2F_2, CH_2ClF, and large amounts of HF and HF_2^-. These findings establish that the previously claimed[7] catalytic behavior of 2,2,2-crypt-M^+ (and its implied inertness) in the ionization of XeF_2 and in fluoride ion exchange with XeF_2 are erroneous. Reactions of [2,2,2-crypt-K][^{18}F] with XeF_2 in CH_2Cl_2 solvent in the present study were not reproducible and were complicated by fluorinated side products, including large amounts of HF, that result from fluorination of 2,2,2-crypt and the solvent. The exchange observed in previous work[7] is attributable to HF formation, in accord with earlier ^{18}F-exchange studies which have shown that HF undergoes fluorine exchange with XeF_2 by acting as a weak fluoride ion acceptor toward XeF_2 (eqs 1 and 2).[2] It must also be concluded that exchange reactions between nca [2,2,2-crypt-M][^{18}F] salts and XeF_2 in CH_2Cl_2 at room temperature are not viable routes to [^{18}F]XeF_2 for use in clinical work.

Experimental Section

CAUTION: We recommend that precautionary measures be established prior to repeating aspects of this work, particularly when $^{18}F^-$ is employed. Rapid outgassing and/or detonation can result from the oxidation of 2,2,2-crypt by XeF_2 in CH_2Cl_2 if the reaction temperature is not properly moderated. Before beginning work with anhydrous HF, first-aid treatment procedures[31−33] should be available and known to all laboratory personnel. Disposal of samples containing XeF_2 or HF were carried out by freezing the heat-sealed FEP sample tube in liquid nitrogen, followed by cutting off the tube top and inverting the open tube end in a mixture of ice and aqueous base solution inside a fumehood.

Nonlabelled Experiments. (a) Materials. Fluorine (Air Products) was used without further purification. Anhydrous hydrogen fluoride (Harshaw Chemical Co.) was purified as described previously[34] and stored in a Kel-F storage vessel equipped with a Kel-F valve until used. Hydrogen fluoride was transferred into reaction vessels by vacuum distillation on a stainless steel vacuum line through a submanifold fabricated from FEP and Kel-F. Literature methods were used for the synthesis of xenon difluoride,[35] the naked fluoride ion source, anhydrous [$N(CH_3)_4$][F],[15] for the drying of anhydrous potassium fluoride (J. T. Baker Chemical Company, 99.6%)[36] and 2,2,2-crypt (1,10-diaza-4,7,-13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane) (Merck, 99%).[37]

Acetonitrile (HPLC grade, Caledon) was purified to electrochemical standards according to the literature procedure.[38] Dichloromethane (reagent grade, Caledon) was dried over CaH_2 powder (BDH Chemicals, 99.5%) for several days and vacuum distilled onto Davison Type 3A molecular sieves (Fisher Scientific) and stored in a dry glass bulb equipped with a 4-mm glass J. Young glass stopcock equipped with a PTFE barrel until used. Molecular sieves were dried under dynamic vacuum for 24 h at ca. 250 °C prior to use as a drying agent. Dried CH_2Cl_2 (^{1}H chemical shift 5.34 ppm) did not show water in the ^{1}H NMR spectrum under high gain conditions (the ^{1}H chemical shift of water in CH_2Cl_2 was determined from a spiked sample to be 1.58 ppm).

(b) Standard Techniques. The compounds used in this study were moisture-sensitive; consequently, all manipulations were carried out

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(28) Beck, M. T.; Dózsa, L. *J. Am. Chem. Soc.* **1967**, *89*, 5713.

(29) Gerken, M.; Boatz, J. A.; Kornath, A.; Haiges, R.; Schneider, S.; Schroer, T.; Christe, K. O. *J. Fluorine Chem.* **2002**, *116*, 49.

(30) Lewis, R. J., Sr. *Hazardous Chemicals Desk Reference*, 4th ed.; John Wiley and Sons: New York, 1997; p 267.

(31) Reinhardt, C. F.; Hume, W. G.; Linch, A. L.; Wetherhold, J. M. *J. Chem. Educ.* **1969**, *46*, A171.

(32) Peters, D.; Miethchen, R. *J. Fluorine Chem.* **1996**, *79*, 161.

(33) Segal, E. B. *Chem. Health Saf.* **2000**, *7*, 18.

(34) Emara, A. A. A.; Schrobilgen, G. J. *Inorg. Chem.* **1992**, *31*, 1323.

(35) Mercier, H. P. A.; Sanders, J. C. P.; Schrobilgen, G. J.; Tsai, S. S. *Inorg. Chem.* **1993**, *32*, 386.

(36) Christe, K. O.; Curtis, E. C.; Dixon, D. A.; Mercier, H. P.; Sanders, J. C. P.; Schrobilgen, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 3351.

(37) Campbell, J.; Mercier, H. P. A.; Santry, D. P.; Suontamo, R.; Borrmann, H.; Schrobilgen, G. J. *Inorg. Chem.* **2001**, *40*, 233.

(38) Winfield, J. M. *J. Fluorine Chem.* **1984**, *25*, 91.

on glass and metal vacuum line systems or in the moisture-free (<0.1%) nitrogen atmosphere of a Vacuum Atmospheres Model DLX drybox as previously described.[39] In instances where low-temperature sample preparations were required, samples were cooled inside the drybox by placing the FEP sample tubes inside a metal Dewar filled with 4.5 mm copper plated steel spheres previously cooled to ca. −140 °C inside the glass cryowell of the drybox.

Anhydrous CH_3CN and CH_2Cl_2 solvents were manipulated using a Pyrex glass vacuum line equipped with grease-free 6-mm J. Young glass stopcocks equipped with PTFE barrels. Pressures inside the vacuum manifold were monitored using a mercury manometer. Fluorine and anhydrous HF were handled on a metal vacuum line constructed from nickel and 316 stainless steel, and equipped with 316 stainless steel valves and fittings (Autoclave Engineers, Inc.). Vessels were attached to vacuum lines through thick-walled FEP tubing and $^1/_4$-in. PTFE Swagelok connectors by means of PTFE compression fittings or $^1/_4$-in. stainless steel Cajon Ultra-Torr connectors fitted with Viton rubber O-rings. Pressures were measured at ambient temperature using an MKS Model PDR-5B power supply and digital readout in conjunction with pressure transducers (effective range 0−1000 Torr) having inert wetted surfaces constructed of Inconel.

All preparative work was carried out in 4-mm-o.d. FEP tubes. One end of the tube was heat sealed by pushing it into the end of a 5-mm-o.d. glass NMR tube previously heated in a Bunsen flame. The other end was fused to ca. 5 cm of $^1/_4$-in.-o.d. FEP tubing, which was heat flared and fitted with a Kel-F valve. The FEP sample tubes were dried under dynamic vacuum for ca. 12 h on a glass vacuum line prior to transfer to a metal vacuum line where they were passivated with ca. 1 atm of F_2 for ca. 12 h. Samples were prepared in the drybox prior to addition of solvent (ca. 0.5 mL) and contained ca. 0.2 mmol of $[N(CH_3)_4][F]$, KF, and/or 2,2,2-crypt, and the molar ratio of XeF_2 to the aforementioned reagent was adjusted. The sample containing a 33-fold molar excess of XeF_2 to 2,2,2-crypt contained 0.942 and 0.0289 mmol, respectively.

The sample tubes used for recording the NMR spectra were heat sealed under dynamic vacuum at −196 °C using a miniature Nichrome wire resistance furnace. The sealed samples were stored submerged in liquid nitrogen. For NMR measurements, the 4-mm FEP tube was inserted into standard 5-mm precision Wilmad NMR tube before insertion into the NMR probe.

Fluorine-18 Labelling Experiments. (a) Materials. Anhydrous CH_3CN (Aldrich, 99.8%), anhydrous CH_2Cl_2 (Aldrich, 99.8%), Kryptofix 222 (Aldrich, 98%), $KHCO_3$ (British Drug Houses, 99.5%), and $[^{18}O]H_2O$ (Isotec, 98 atom %) were used without further purification. Xenon difluoride was prepared as described previously (vide supra).

(b) Standard Techniques. No-carrier-added ^{18}F-fluoride was produced using a Siemens 11 MeV proton-only cyclotron (RDS 112) and by means of the nuclear reaction $^{18}O(p,n)^{18}F$. The $[^{18}O]H_2O$ was separated from the $^{18}F^-$ by passing the bolus through an anion exchange column (Bio-Rad, AG 11 A8 resin, 50−100 mesh, converted to HCO_3^- form). The $^{18}F^-$ was subsequently eluted from the column using 1 mL of CH_3CN/H_2O (95/5) solution containing 8 mg of 2,2,2-crypt and 2 mg of $KHCO_3$ and the CH_3CN/H_2O was evaporated at 120 °C. The residue was redissolved in 1 mL of anhydrous CH_3CN and redried.

The dry ^{18}F-containing residue was redissolved in anhydrous CH_3CN or anhydrous CH_2Cl_2 diluted to 10 mCi/mL, and 1 mL was transferred to a covered Teflon or glass vessel containing 10−50 mg of XeF_2 (XeF_2 had been transferred in a glovebag purged with dry nitrogen). Aliquots of the resulting reaction mixtures were analyzed at various time intervals between 5 and 90 min on a reverse phase HPLC column (Phenomenex, Hypersil C18, 5 μm, 25 × 0.46 cm) eluted with 60% CH_3CN (HPLC grade, Caledon) in water, at a flow rate of 1.0 mL/min. The eluates from the column were passed through a Waters 490E programmable multiwavelength detector (255 nm) and a Beckman radioisotope detector (Model 170). Both detectors were connected to a Waters Millenium Chromatography Manager.

Nuclear Magnetic Resonance Spectroscopy. Proton and ^{19}F NMR spectra were referenced to external TMS and $CFCl_3$, respectively, at 30 °C. All spectra in this study were recorded unlocked without spinning the samples.

Proton and ^{19}F NMR spectra of samples containing reaction mixtures of [2,2,2-crypt-K][F] with CH_3CN and CH_2Cl_2 were recorded on a Bruker AV-200 spectrometer. Proton and ^{19}F spectra were acquired at 200.200 and 188.376 MHz, respectively. Proton spectra were obtained in eight scans, in 16 K memories over a 4.1 kHz spectral width corresponding to an acquisition time of 2.02 s and a data point resolution of 0.25 Hz/point. Fluorine-19 spectra were obtained in 300 scans, in 32 K memories over a 47.1 kHz spectral width corresponding to an acquisition time of 0.347 s and a data point resolution of 1.44 Hz/point. Proton and ^{19}F NMR spectra of samples prepared for investigation of the interaction of XeF_2 with fluoride ion were recorded on a Bruker AV-300 spectrometer and referenced to external TMS and $CFCl_3$, respectively, at 30 °C. Proton and ^{19}F spectra were acquired at 300.130 and 282.404 MHz, respectively. Proton spectra were obtained in eight scans, in 32 K memories over a 4.5 kHz spectral width corresponding to an acquisition time of 3.645 s and a data point resolution of 0.14 Hz/point. Fluorine-19 spectra were obtained in 1000 scans and in 32 K memories over a 33.8 kHz spectral width corresponding to an acquisition time of 0.131 s and a data point resolution of 1.03 Hz/point.

Two-dimensional $^{19}F-^{19}F$ EXSY spectra were acquired at 470.55 MHz using a Bruker Avance DRX-500 spectrometer. Spectra were recorded in the phase sensitive mode, using the pulse sequence $90°-t_1-90°-t_m-90°-ACQ$. A temperature of 15 °C was used in order to slow the formation of HF_2^- while maintaining solubility. 256 FIDs were recorded in the F1 dimension, with each FID acquired in 48 scans over a 60 kHz spectral width. Mixing times of 400 and 800 ms were employed.

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(39) Casteel, W. J., Jr.; Kolb, P.; LeBlond, N.; Mercier, H. P. A.; Schrobilgen, G. J. *Inorg. Chem.* **1996**, *35*, 929.