FLUORINE-18 TRACER STUDIES OF ELECTROPHILIC FLUORINE SOURCES
Fluorine-18 Tracer Studies of Inorganic and Organic Electrophilic Fluorine Sources

by

Richard Mark Adams, B. Sc.

A Thesis
Submitted to the School of Graduate Studies
in Partial Fulfilment of the Requirements
for the Degree
Master of Science

McMaster University
July 1994
Dedicated in the memory of my grandfather, Ronald Arscott.
Master of Science (1994) McMaster University, Hamilton, Ont.
(Chemistry)

TITLE: FLUORINE-18 TRACER STUDIES OF INORGANIC AND ORGANIC ELECTROPHILIC FLUORINATING AGENTS

AUTHOR: Richard Mark Adams, B. Sc. (McMaster, University)

SUPERVISORS: Professor Gary J. Schrobilgen
Assistant Professor Raman V. Chirakal

NUMBER OF PAGES: XII, 102
ABSTRACT

Fluorine-18 labelled \( F_2 \), produced by the nuclear reaction, \( ^{18}O(p,n)^{18}\text{F} \), and recovered from an oxygen-18 gas target, has been used to elucidate the mechanism for the formation of \( \text{XeF}^+\text{AsF}_6^- \) from \( \text{Xe, F}_2, \) and \( \text{AsF}_5 \) under low temperature and dark conditions. Formation of \( \text{XeF}^+\text{AsF}_6^- \) was confirmed by Raman spectroscopy. A method was designed to allow for the dilution of the \( ^{18}\text{F} \) activity onto a pool of carrier \( ^{19}\text{F} \), such that suitable quantities of low specific activity \( ^{18}\text{F} \) could be produced for the mechanistic study of this reaction. Based on the \( ^{18}\text{F} \) distributions within the products and unreacted \( ^{18}\text{F} \) and \( \text{AsF}_5 \), it was shown that an \( \text{F}_2\text{AsF}_5 \) activated complex containing an electrophilic fluorine reacts with the weak electron donor, xenon gas, in a Lewis acid-base type reaction. The absence of random fluorine exchange within the activated complex indicated that a transient \( \text{F}^5+ \) was responsible for the enhanced oxidizing ability of the \( \text{F}_2\text{AsF}_5 \) complex, rather than the production of a formal "\( \text{F}^+\)" or \( \text{F}^- \) intermediate. Fluorine-18 investigations into the reaction of the \( \text{F}_2\text{AsF}_5 \) activated complex with other possible electron donors have shown some \( ^{18}\text{F} \) transfer with krypton gas. Attempts to establish the formation of \( \text{KrF}^+ \) using \( ^{19}\text{F} \) NMR spectroscopy have shown no evidence for the presence of the cation in the \( \text{KrF}_2/\text{AsF}_5 \) system. The systems \( \text{KrF}_2/\text{HF/SbF}_5 \) and \( \text{OF}_2/\text{F}_2/\text{AsF}_5 \) were not seen to undergo a reaction.

The results of such sensitive radiotracer experiments required a complete analysis of the composition of the target gas delivered from the \( ^{18}O(p,n)^{18}\text{F} \) oxygen gas target; the presence of reactive agents other than \( ^{18}\text{F} \) could affect the distribution of activities in reaction mixtures. Oxygen difluoride, which was suspected as a possible side product of
the double bombardment method, was identified as a constituent of the target gas by $^{19}$F NMR characterization. An analysis of the effect of the variation of irradiation parameters has concluded that the quantity of $[^{18}$F]$\text{OF}_2$ activity is independent of the production irradiation parameters and is most likely a consequence of the presence of small amounts of O$_2$ within the target during the recovery irradiation.

The application of CsSO$_4$F as an electrophilic fluorinating agent has provided preliminary evidence for the fluorination of biologically active aromatic amino acids. Cesium fluoroxysulphate was found to react with 3,4-dihydroxyphenylalanine (L-Dopa) in an CH$_3$CN solution containing BF$_3$ to produce a mixture 2-, 5-, and 6-fluoro-L-dopa. Fluorine-19 NMR spectroscopy was used to confirm the presence of the 2-, 5-, and 6-fluoro-isomers of fluorodopa in the reaction mixture.
ACKNOWLEDGEMENTS

I would like to thank first and foremost my supervisors Dr. Gary J. Schrobilgen and Dr. Raman V. Chirakal. The support and guidance which I received throughout this project was most thoughtful and was sincerely appreciated.

I would also like to thank Dr. E. S. Garnett, Director of Nuclear Medicine, McMaster University Medical Centre, for making available the cyclotron facilities. Very special thanks to Dr. J. C. P Sanders, Dr. W. J. Casteel, and J. Marc (Pookie) Whalen for their patient assistance and advice when supervisors were nowhere to be found. I would like to acknowledge Dr. Casteel for performing the Raman analysis contained in this work.

The technical assistance provided by the staff of the McMaster University NMR facility was greatly appreciated.

A sincere thanks to the rest of the lab group, Dr. H. P. Mercier, Ayaaz Pirani, Janette Pulc and Nicolas Leblond, for the good times and laughs. Best wishes to all in your future endeavours.

A heartfelt goodbye to the many other people I had the pleasure of getting to know and spending time with over my few years here, Dr. O. E. Hileman, Dr. Luc Girard, Suzie Rigby, Theresa Fauconnier, Pippa Lock, Ralph Ruffolo, John Valliant, The Ninnie and Zog, the misunderstood little kid.

I would like to acknowledge the financial support provided by the Department of Chemistry (1992-93) and the Ministry of Universities and Colleges (OGS 1993-94).
TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION .................................................. 1
  1.1. General .............................................................. 1
  1.2. Isotopes of Fluorine .............................................. 2
  1.3. Fluorine-18, Production and Recovery ......................... 4
  1.4. Application of $^{18}$F to Inorganic Chemistry .................. 5
  1.5. Purpose and Scope of this Work .................................. 10

CHAPTER 2: EXPERIMENTAL ............................................... 12
  2.1 Vacuum Techniques .................................................. 12
  2.2 Starting Materials and Gas Mixtures .............................. 13
  2.3 Instrumentation .................................................... 17
      2.3.1 Nuclear Magnetic Resonance Spectroscopy .................. 17
      2.3.2 Raman Spectroscopy .......................................... 18
      2.3.3 $^{18}$F Detection ............................................. 19
  2.4 Fluorine-18 Studies ................................................. 20
      2.4.1 $^{18}$F Target and Support System ............................ 20
      2.4.2 $^{18}$F Production and Recovery .............................. 20
      2.4.3 $^{18}$F Correction for Decay .................................. 22
  2.5 Preparation of $^{18}$F Precursors .................................. 22
      2.5.1 [18F]HF ..................................................... 22
2.5.2 Production of Very Low Specific Activity $[{^{18}F}]F_2$ .............. 23
2.5.3 Transfer and Distribution of $[{^{18}F}]F_2$ ........................... 23
2.6 Target Gas Analysis .................................................. 24
  2.6.1 Identification of OF$_2$ ........................................... 24
  2.6.2 Target Gas Analysis Experiments ............................ 25
2.7 Lewis Acid Activation of Fluorine ................................. 25
  2.7.1 $^{18}F$ Study of the F$_2$/AsF$_5$ Exchange ..................... 26
  2.7.2 $^{18}F$ Study of the Xe/F$_2$/AsF$_5$ Reaction .................. 27
  2.7.3 $^{18}F$ Study of the Kr/F$_2$/AsF$_5$ Reaction .................. 28
  2.7.4 Reaction of Kr/F$_2$/HF/SbF$_5$ ............................... 30
  2.7.5 Reaction of OF$_2$/F$_2$/AsF$_5$ ............................... 30
2.8 Electrophilic Fluorination Reactions ............................. 31
  2.8.1 Preparation of and Assay Cesium Fluorosulphate .......... 31
  2.8.2 Reactions of CsSO$_4$F with Aromatic Amino Acids .......... 32
    2.8.2.1 CsSO$_4$F with DOPA in CH$_3$CN ......................... 33
    2.8.2.2 CsSO$_4$F with L-DOPA in BF$_3$/CH$_3$CN ................ 33
    2.8.2.3 Low-temperature Fluorinations .......................... 35
  2.8.4 Separation and Identification of the 2-,5-, and 6-flouro Isomers of Fluoro-L-dopa ............................................. 36
CHAPTER 3: FLUORINE-18 GAS ANALYSIS OF THE $[^{18}\text{F}]\text{F}_2$
RECOVERED FROM AN $^{18}\text{O}_2$ GAS TARGET .......... 38

3.1 INTRODUCTION .................................................. 38
3.1.1 Single Irradiation Method ................................. 39
3.1.2 Double Irradiation Method ................................. 40
3.1.3 Prior Observation of $\text{OF}_2$, and $\text{FONO}_2$ .......... 41
3.1.4 Formation of $\text{OF}_2$ and Properties of $\text{OF}_2$ ...... 42
3.2 RESULTS AND DISCUSSION ................................. 43
3.3 CONCLUSIONS .................................................. 47

CHAPTER 4: APPLICATION OF $^{18}\text{F}$ TO THE INVESTIGATION OF THE
LEWIS ACID ACTIVATION OF $\text{F}_2$ ......................... 49

4.1 INTRODUCTION .................................................. 49
4.2 RESULTS AND DISCUSSION .................................. 53
4.2.1 Exchange in the Binary System ......................... 53
4.2.2 Evidence for the Existence of the $\text{AsF}_5/\text{F}_2$ Activated
Complex .......................................................... 55
4.3 CONCLUSIONS .................................................. 65
CHAPTER 5: ATTEMPTED PREPARATION OF HIGHER OXIDIZING
SPECIES USING THE LEWIS ACID-F₂ ACTIVATED
COMPLEX ........................................ 67

5.1 INTRODUCTION .................................................. 67
5.1.1 Oxidative Fluorinators and the Oxidizer Strength Scale .... 67
5.1.2 Mechanistic Suitability and Unknown Oxidizers ............ 69

5.2 RESULTS AND DISCUSSION .................................. 71
5.2.1 Attempted Synthesis of OF₃⁺AsF₆⁻ • • • • • • • • • • • • • • • • • • • • 71
5.2.2 Attempted Synthesis of KrF⁺ Salts of the Lewis Acids AsF₃
and SbF₃ ..................................................... 72

5.3 CONCLUSIONS .................................................. 76

CHAPTER 6: POSSIBLE USE OF CsSO₄F AS AN ¹⁸F INORGANIC
PRECURSOR FOR THE REGIOSPECIFIC
ELECTROPHILIC FLUORINATION OF AROMATIC
AMINO ACIDS .................................................... 78

6.1 INTRODUCTION .................................................. 78
6.1.1 Cesium Fluoroxysulphate and Other Electrophilic
Fluorinating Agents ............................................. 79
6.1.2 Regiospecific Nature of Cs⁺SO₄F⁻ ............................ 81
6.2 RESULTS AND DISCUSSION ........................................ 83
   6.2.1 NMR Spectroscopy of Cs⁺SO₄F⁻ .......................... 83
   6.2.2 Aqueous Decomposition Study and ¹⁸F Tracer Experiment . 84
   6.2.3 Separation and Identification of Fluorinated Products from
          Low Temperature Reactions .......................... 86
   6.2.4 ¹⁹F NMR of Fluoro-isomers of L-Dopa .................... 90
6.3 CONCLUSIONS: Application to Fluorine-18 Labelling and Future
   Work ....................................................... 90

REFERENCES ....................................................... 94

APPENDIX .......................................................... 101
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Isotopes of Fluorine</td>
<td>3</td>
</tr>
<tr>
<td>3.1</td>
<td>Target Gas Analysis Data</td>
<td>46</td>
</tr>
<tr>
<td>4.1</td>
<td>$^{18}$F-Exchange Activities for the $[^{18}$F]$\text{AsF}_2$/F$_2$ and AsF$_5$/[$^{18}$F]F$_2$ systems</td>
<td>54</td>
</tr>
<tr>
<td>4.2</td>
<td>Xe/F$_2$/AsF$_3$ $^{18}$F Exchange Experiments</td>
<td>57</td>
</tr>
<tr>
<td>4.3</td>
<td>Correlation Between Radiochemical and Gravimetric Yields of XeF$^+$/AsF$_6^-$</td>
<td>62</td>
</tr>
<tr>
<td>4.4</td>
<td>$^{18}$F Study of the Decomposition of XeF$^+$/AsF$_6^-$ to Xe$_2$F$_3$/AsF$_6^-$</td>
<td>63</td>
</tr>
<tr>
<td>5.1</td>
<td>Comparative $^{18}$F Exchange Values</td>
<td>74</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 2.1. Metal vacuum line components ........................................ 14
Figure 2.2. Stainless steel/PFA-FEP vacuum line ............................ 15
Figure 2.3. High pressure reactor for NMR sample preparation .......... 16
Figure 2.4. Target support system ............................................... 21
Figure 2.5. Apparatus configuration for $^{18}$F Lewis acid experiments .... 29
Figure 2.6. Apparatus used for the room temperature and low temperature fluorinations ......................................................... 34
Figure 3.1. $^{19}$F NMR (282.409 MHz) of OF$_2$ ..................................... 44
Figure 4.1 $^{19}$F NMR (282.409 MHz) spectra of pure F$_2$ (top) and an F$_2$/AsF$_5$ mixture ................................................................. 58
Figure 4.2 Raman spectra of XeF$^+$AsF$_6^-$ (top) and Xe$_2$F$_3^+$AsF$_6^-$ ................. 64
Figure 6.1 Fluorine-19 NMR spectrum (470.600 MHz) of Cs$^+$SO$_4$F$^-$ .......... 85
Figure 6.2. Fluorine-19 NMR spectra (470.600 MHz) of the decomposition of Cs$^+$SO$_4$F$^-$ .......................................................... 87
Figure 6.3. HPLC chromatograms .................................................... 89
Figure 6.4. Fluorine-19 NMR spectrum (282.409 MHz) of the reaction mixture from Cs$^+$SO$_4$F$^-$ plus L-dopa. ................................. 91

xii
CHAPTER 1
INTRODUCTION

1.1. General

Fluorine gas was first prepared in 1886 by Henri Moissan from the electrolysis of anhydrous hydrogen fluoride in the presence of potassium fluoride.¹ The gaseous species isolated at the anode was noted to be a new substance of remarkable reactivity.¹ The electronegativity of fluorine, 4.10,² is the highest of all the elements. Molecular fluorine is also the most strongly oxidizing element known. Compounds containing fluorine also have shown remarkably enhanced oxidizing ability; the most powerful chemical oxidizers presently known are the KrF⁺ salts³ prepared from the reaction of KrF₂ with Lewis acids.⁴–⁵

Electrophilicity describes the reactivity of a compound towards an electron rich centre. Oxidation occurs if electron density is formally removed from such a centre. An oxidative fluorination reaction occurs when an electron deficient fluorine atom(s) is transferred from one reagent to another. The oxidized centre formally receives a six-electron F⁺ atom thus increasing the formal oxidation state by two. An illustrative example is provided by the reaction between a KrF⁺ salt and BrF₅⁶

\[
\text{KrF}^+\text{AsF}_6^- + \text{BrF}_5(\text{l}) \rightarrow \text{BrF}_6^+\text{AsF}_6^- + \text{Kr}(\text{g})
\]  

(1.1)

The ability to label a reactive species such as the KrF⁺ cation with fluorine-18 would allow the course of such reactions to be traced. The relative distribution of activity in the
products would provide information concerning the reaction mechanism and the rate of the reaction.

Hypofluorites and other compounds which have fluorine bonded directly to other highly electronegative atoms also tend to be strong electrophilic fluorine sources. Inorganic and organic hypofluorites such as CsSO₄F⁶ and CF₃COOF⁷ respectively, tend to substitute fluorine onto electron-rich organic centres. The regiospecific substitution of ¹⁸F onto the aromatic ring of aromatic amino acids has already been achieved with [¹⁸F]CF₃COOF⁸. Fluorine-18 labelled fluoroxyxsulphate may be a candidate for a simpler, more efficient synthesis of ¹⁸F-labelled biologically active compounds.

1.2. Isotopes of Fluorine

Fluorine has six radioactive isotopes with half-lives greater than 1 sec, six of which are found to be radioactive.⁹ Fluorine-19 is the only naturally occurring stable isotope. The isotopes ¹⁷F and ¹⁸F have a deficit of neutrons and decay by positron emission; ²⁰F, ²¹F, ²²F and ²³F have a surfeit of neutrons and decay by negative beta emission. The nuclear properties of all the isotopes of fluorine are given in Table 1.1.

Fluorine-18 is the only radioactive isotope of fluorine with a half-life long enough (109.7 min) to be useful for most radiotracer studies. Fluorine-18 decays by emitting a 0.64 MeV positron that will annihilate an electron to produce two 0.511 MeV gamma rays in almost opposite directions. Emission of the 0.511 MeV gamma rays can be easily detected by routine nuclear detectors which makes ¹⁸F a useful isotope for the study of inorganic reaction mechanisms.
<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Decay Mode</th>
<th>Product</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{17}$F</td>
<td>$\beta^+$</td>
<td>$^{17}$O</td>
<td>64.7 sec</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>$\beta^+$</td>
<td>$^{18}$O</td>
<td>109.7 min</td>
</tr>
<tr>
<td>$^{19}$F</td>
<td>stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{20}$F</td>
<td>$\beta^-$</td>
<td>$^{20}$Ne</td>
<td>11.0 sec</td>
</tr>
<tr>
<td>$^{21}$F</td>
<td>$\beta^-$</td>
<td>$^{21}$Ne</td>
<td>4.2 sec</td>
</tr>
<tr>
<td>$^{22}$F</td>
<td>$\beta^-$</td>
<td>$^{22}$Ne</td>
<td>4.2 sec</td>
</tr>
<tr>
<td>$^{23}$F</td>
<td>$\beta^-$</td>
<td>$^{23}$Ne</td>
<td>2.2 sec</td>
</tr>
</tbody>
</table>

Table 1.1. Isotopes of Fluorine$^9$
Its applications to the field of nuclear medicine through the use of Positron Emission Tomography has allowed image reconstruction to produce \textit{in vivo} images with typical spatial resolutions of only a few millimetres.\textsuperscript{10}

1.3. Fluorine-18, Production and Recovery

The methods for the production of \(^{18}\text{F}\) can be separated into two groups, those that result in the production of \(^{18}\text{F}^-\) atoms and those which result in the production of aqueous \(^{18}\text{F}^-\) anions.

Aqueous \(^{18}\text{F}\)-fluoride production methods require the use of either a cyclotron or a nuclear reactor. The irradiation of \(^6\text{Li}_2\text{CO}_3\) with a neutron flux is used to initiate the nuclear reaction, \(^6\text{Li}(n,\alpha)^3\text{H}\), which, in turn, produces a source of tritium for the nuclear reaction \(^{16}\text{O}(t,n)^{18}\text{F}\). The \(^{18}\text{F}^-\) product, recovered by dissolving the irradiated \text{LiCO}_3 in \text{H}_2\text{O}, however, is always contaminated with the \(^3\text{H}\) radionuclide from the first nuclear reaction. An alternative method for the production of \(^{18}\text{F}\)-fluoride utilizes the \(^{18}\text{O}(p,n)^{18}\text{F}\) reaction. An \(\text{H}_2^{18}\text{O}\) target is irradiated with protons produced from either an accelerator or a cyclotron. The \(^{18}\text{F}^-\) ion can be collected \textit{in situ} on an anion exchange column.\textsuperscript{11}

Methods involving \(^{18}\text{F}\) atoms are more numerous and, to date, have found more applications. The reactions \(^{19}\text{F}(n,2n)^{18}\text{F}\) and \(^{19}\text{F}(\gamma,n)^{18}\text{F}\) have been used to label inorganic fluorides under anhydrous conditions.\textsuperscript{12} The most common method for the production of \(^{18}\text{F}^-\) atoms, however, is the \(^{20}\text{Ne}(d,\alpha)^{18}\text{F}\) reaction.\textsuperscript{13} Deuterons from either an accelerator or cyclotron are used to irradiate neon gas to produce \(^{18}\text{F}\) atoms. The activity can be recovered from the target as \([^{18}\text{F}]-\text{F}_2\), \(\text{H}^{18}\text{F}\), \(^{18}\text{F}\text{NO}\) or \(\text{Cl}^{18}\text{F}\) if the neon gas contains small
quantities of carrier F₂, H₂, NO, or Cl₂, respectively.¹⁴ Solid inorganic fluorides can be labelled with ¹⁸F by the deuteron irradiation of neon gas in a target whose walls are coated with a thin layer of the desired fluoride.

The present work is largely concerned with the production of [¹⁸F]F₂. The ¹⁸O(p,n)¹⁸F reaction is convenient for use with a proton only cyclotron. For 10 MeV protons, the thick target yield for an ¹⁸O₂ target is 150 mCi/µA.¹⁵ The thick target environment describes the target pressure required to completely absorb the proton beam. Fluorine-18 activity is recovered from the target as [¹⁸F]F₂ containing carrier ¹⁹F₂.

1.4. Application of ¹⁸F to Inorganic Chemistry

Historically, the use of fluorine-18 in the field of inorganic chemistry has been quite limited. This can be primarily attributed to the method of production which requires access to an accelerator, cyclotron, reactor, or a fast neutron source that is reasonably close to the working laboratory. Nonetheless, tracer studies with the ¹⁸F isotope have proven to be a useful technique in the early experiments of Dodgen and Libby,¹⁶ who used fluorine-18 to detect exchange between HF and F₂ at high temperatures in the gaseous states. In conjunction with room temperature ³⁸Cl tracer studies of the corresponding chlorine system, the authors were able to differentiate between the exchange mechanism occurring for F₂/HF, and those of the remaining halogens with their corresponding hydrogen halides.

Fluorine-18 has also been used to deduce structural information. One of the more notable examples is the Lewis acid-base adduct BF₃-SF₄.¹⁷ Information regarding the
structure of the adduct, which is formed from the room temperature reaction of equimolar amounts of the two gases and decomposed by the addition of tetrahydrofuran, was obtained from the relative $^{18}$F distribution in the decomposition products when only one of the initial gases had been labelled. The results gave conclusive evidence for symmetrical fluorine bridging between the boron and sulphur centres, i.e., $F_3B-\text{F-}SF_3$.

The preparation of $^{18}$F-labelled inorganic fluorides as well as other $^{18}$F radiotracer experiments carried out on inorganic systems prior to 1980 has been reviewed. More recently, $^{18}$F labelling has been used to investigate the existence of hypervalent compounds of nitrogen and chlorine.

Hypervalent compounds, defined by Shriver et al. as "those compounds in which the Lewis octet structures demand more than an octet of electrons around at least one atom" have proven to be elusive for those compounds having second row central atoms. Nitrogen pentafluoride has been suggested to form from the low temperature UV-irradiation of mixtures of NF$_3$ and F$_2$. Alternatively, NF$_5$ was suspected as an unstable intermediate in the pyrolysis of NF$_4^+$AsF$_6^-$ at 175 °C:

$$\text{NF}_4^+\text{AsF}_6^- \rightleftharpoons [\text{NF}_5] + \text{AsF}_5 \quad (1.2)$$

$$[\text{NF}_5] \rightleftharpoons \text{NF}_3 + \text{F}_2 \quad (1.3)$$

however, all attempts to isolate the species failed.

Fluorine-18 was first utilized in the study of NF$_5$, along with $^{15}$N, in isotopic exchange studies between NF$_4^+$AsF$_6^-$ and $[^{18}\text{F}]\text{AsF}_5$, $[^{18}\text{F}]\text{NF}_3$, and $[^{15}\text{N}]\text{NF}_3$. Results of
this study suggested the structure NF₄⁺F⁻ as the intermediate. The analogous NH₅ species was investigated by hydrogen-deuterium labelling, the results of which suggested the existence of a NH₅D intermediate for the reaction of the NH₄⁺O₂CCF₃ melt with LiD.²⁴ However, these results were disputed on the basis that, the H₂ to D₂ ratio within the decomposition products [85%NH₃ + 15%NH₂D] + [66%HD + 21%H₂ + 13%D₂], exceeded the theoretical ratio for a non-catalysed isotopic exchange.²⁵

In response to the observation that NF₄⁺SbF₆⁺, when treated with LiF, gave a decomposition mixture consisting of NF₃, F₂ and LiSbF₆, Olah et al.²⁴ suggested the use of an ¹⁸F-labelled fluoride ion donor to detect the nucleophilic attack of F⁻ on nitrogen. Initial theoretical calculations²⁶ indicated that all pentacoordinate nitrogen species are unstable with respect to decomposition

\[
\text{NX}_5 \longrightarrow \text{NX}_3 + X_2
\]  

(1.4)

However, more recent high-level calculations²⁷,²⁸ predict that NF₅ is stable with all calculated vibrational frequencies positive.

The reaction between NF₄⁺ and the fluoride ion donor, HF₂⁻, was studied by use of [¹⁸F]CsHF₂ and NF₄PF₆.¹⁸ The [¹⁸F]NF₄HF₂ formed at room temperature in HF solvent decomposes upon removal of the HF between 25 and 100 °C. Attack of the [¹⁸F]F⁻ on the nitrogen would result in the [¹⁸F]NF₅ intermediate. Upon decomposition, the ¹⁸F activity would be statistically scrambled between the NF₃, HF, F₂ and CsPF₆. If the [¹⁸F]F⁺ were to attack at one of the four fluorine ligands, ¹⁸F activity would never be transferred to the
NF$_3$ (equation 1.5)

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{N}^+ & \quad \text{F} - \text{H} - \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

\[
\text{F} \text{H} \text{F} \rightarrow \text{NF}_3 + [^{18}\text{F}]\text{F}_2 + [^{18}\text{F}]\text{HF} \quad (1.5)
\]

The experimental results showed essentially no $^{18}$F activity (well below the experimental error) on the NF$_3$ and thus provided unambiguous proof that NF$_5$ was not an intermediate in the reaction.

Unlike iodine, for which the complete series of halogen fluorides is known, ClF$_7$ and BrF$_7$, are the only members of the series XF, XF$_3$, XF$_5$, XF$_7$, which have not been prepared. The existence of ClF$_7$ has been studied through the reaction of ClF$_6^+$AsF$_6^-$ with $[^{18}\text{F}]\text{FNO}^{19}$

\[
\text{ClF}_6^+\text{AsF}_6^- + [^{18}\text{F}]\text{FNO} \rightarrow [^{18}\text{F}]\text{ClF}_7 + \text{NO}^+\text{AsF}_6^- \quad (a) \rightarrow \text{ClF}_5 + [^{18}\text{F}]\text{F}_2 + \text{NO}^+\text{AsF}_6^- \quad (1.6)
\]

\[
\bigg[ \begin{array}{c}
(\text{b}) \\
\end{array} \bigg] \rightarrow [^{18}\text{F}]\text{ClF}_5 + [^{18}\text{F}]\text{F}_2 + \text{NO}^+\text{AsF}_6^-
\]

The reaction pathway labelled (a) represents the attack of the fluoride ion at a fluorine ligand while pathway (b) represents attack at the Cl centre. In the absence of any extraneous exchange pathways, the existence of ClF$_7$ as an unstable intermediate would be indicated by the presence of the $[^{18}\text{F}]\text{ClF}_5$ in the products. Indeed the experimental results indicated the presence of $[^{18}\text{F}]\text{ClF}_5$; however, all other possible exchange pathways which could transfer $^{18}$F activity on to the unlabelled ClF$_5$ produced from pathway 1.6a,
had not been ruled out. Therefore, evidence for the existence of the ClF₇ species was not conclusive.

Interestingly, the simple binary exchange between [¹⁸F]NOF and ClF₅, resulted in the random distribution of ¹⁸F which required the ClF₆⁻ anion as an intermediate

\[
[¹⁸F]FNO + ClF₅ \longrightarrow [¹⁸F][NO⁺ClF₆⁻] \longrightarrow [¹⁸F]FNO + [¹⁸F]ClF₅ \quad (1.7)
\]

Experimental results showed complete random exchange of fluorines between the [¹⁸F]NOF and [¹⁸F]ClF₅. In conjunction with ¹⁹F NMR and vibrational spectroscopic studies, the existence of the ClF₆⁻ anion was conclusively proven.¹⁹

Fluorine-18 radiotracer experiments can also be used for the elucidation of inorganic reaction mechanisms. Oxygen difluoride was noted as a possible product of the reaction between fluorine and aqueous media.²⁹ The procedure of passing fluorine over ice has been found to produce mixtures of OF₂, HOF, O₂, and H₂O₂.³⁰ Fluorine-18 was used in conjunction with ¹⁸O in double labelling experiments to elucidate the stoichiometry for the reaction of HOF with F₂. The hypofluorous acid formed from the reaction of F₂ with H₂O was shown to react in a 1:1 mole ratio with gaseous non-radioactive fluorine³⁰

\[
F₂ + [¹⁸F]HOF \longrightarrow [¹⁸F]OF₂ + HF \quad (1.8)
\]

The above examples demonstrate that ¹⁸F can be used to detect unstable reaction
intermediates and determine or verify previously uncertain reaction pathways. In most cases, however, the radiotracer technique is used in conjunction with another method of analysis or detection, or previous knowledge of the chemistry involved.

1.5. Purpose and Scope of this Work

The use of fluorine-18 as a radiolabel is becoming more common as techniques such as Positron Emission Tomography (PET) demand the routine production of $^{18}$F precursors which can substitute $^{18}$F into biological molecules for in vivo studies. In addition, inorganic chemists can make use of $^{18}$F radiotracer studies to probe the mechanistic pathways of reactions involving fluorine, or seek evidence for the existence of novel fluorine-containing chemical species which may not be stable or isolable. Consequently, the performance of a $^{18}$F producing target must be continually evaluated, as the factors affecting target mixtures, compositions, and radiochemical production efficiency, must be well understood.

The $^{18}$O$_2$ gas target has the ability to produce various primary electrophilic species such as $[^{18}$F]$F_2$ and $[^{18}$F]OF$_2$. It has been the purpose of previous work, and will be an integral part of the current study, to refine the parameters that determine relative distributions of $^{18}$F-containing species produced by the $^{18}$O$_2$ target.

The Lewis acid enhanced oxidative fluorination of xenon gas by F$_2$, previously observed by Stein and Bartlett et al. has been studied by means of radiofluorine labelling, in hopes that the mechanism of fluorination could be conclusively determined. Preliminary studies, which used $[^{18}$F]AsF$_3$ as the radiolabel, indicated that a binary
interaction between AsF$_5$ and F$_2$, produced a more powerful fluorinator capable of oxidizing xenon under extremely mild conditions. The objectives of the current work are to perform more $^{18}$F-tracer experiments, this time with use of $[^{18}\text{F}]$F$_2$ as the radiolabel, to elucidate further the nature of the AsF$_5$-F$_2$ activated complex, and to investigate the relative oxidizing strength of this and other Lewis acid-F$_2$ activated complexes.

Finally, Cs$^+$SO$_4$F, which has been reported to be a useful electrophilic fluorinator of organic compounds, will be studied to determine its usefulness as a selective fluorinating agent for specific aromatic amino acids currently of interest to the field of nuclear medicine.
2.1 Vacuum Techniques

Due to the air-sensitive natures of many of the compounds used in this work, all manipulations were carried out on vacuum lines made of 316 stainless steel, nickel, PFA (perfluoroalkoxyethylene co-polymer), FEP (perfluorethylene-propylene co-polymer) and Teflon. The metal vacuum line (Figure 2.1) was constructed of 3/8-in. 316 stainless steel high pressure valves (Autoclave Engineers, 30VM6071) joined with nickel connectors. Manifold pressures were measured using an MKS (model PDR-SB) power supply in conjunction with MKS pressure transducers (0-1000 Torr ± 0.5% reading) having inert, wetted surfaces of Inconel.

A second metal vacuum line composed of integral bonnet needle valves (Whitey model 316 SS 1KS4) connected with 304 SS tubing (1/4-in. o.d) was used (Figure 2.2). This line was also equipped with a fluoroplastic submanifold to be used solely for manipulations involving anhydrous hydrogen fluoride. Valves having PFA stems and bodies (Whitey model PFA-4RPS4) were connected by thick walled FEP tubing (1/4-in. o.d x 1/8-in. i.d.). Manifold pressures in this vacuum line were measured using a Monel Bourdon gauge, 0 - 1500 Torr (Helicoid).

All FEP reaction vessels used in this work were equipped with either Kel-F needle valves or 316 SS valves (Whitey models 316SS-1KS4, 316SS-OMR2). Reaction vessels were made of 304 stainless steel and equipped also with 316 SS valves. A special high pressure reactor was constructed for the preparation of NMR samples from high pressure...
reactions. The double tube apparatus, consisted of an inner 4-mm FEP NMR tube fitted inside a medium walled PFA tube for added strength (Figure 2.3). After the pressure from the reaction was relieved, the outer tube was cut off just below the valve with a pipe cutter (care was taken not to score the inner tube). The NMR sample tube was then heat sealed under vacuum.

The fluorine-noble gas mixtures were prepared and stored in passivated 1 L nickel vessel equipped with 316 SS high pressure valves (Autoclave Engineers).

All vacuum components and reaction vessels were passivated under 1 atm. of F₂ for at least 1 hr. before use.

2.2 Starting Materials and Gas Mixtures

Fluorine gas (Air Products) was pressurized in a 75 mL stainless 304 SS Whitey cylinder equipped with a SS valve (Whitey, 316SS-1KS4) over KF that had been previously dried under vacuum at 250 °C for 12 hrs. to remove any HF. The fluorine was further purified by photolysis at -196 °C followed by fractional distillation from the photolysis vessel at -183 °C in a liquid oxygen bath to a 1 L nickel receiving vessel at -196 °C. Helium, neon, xenon, and krypton gases (Air Products) having minimum chemical purities greater than 99.995% and research grade 1% F₂ in neon (Matheson) were used without further purification. The 5% F₂ in krypton mixture was made by pressurization of a 1 L nickel vessel with purified F₂ at room temperature followed by the condensation of the appropriate amount of Kr at -196 °C. Arsenic pentafluoride was prepared from AsF₃ and F₂ as outlined by Hoffman³⁴ and then purified by passing the
Metal vacuum line components; (A) outlet to liquid nitrogen and charcoal traps followed by a two stage direct drive rotary vacuum pump (Edwards, E2M8) - hard vacuum, (B) outlet to soda lime and liquid nitrogen traps followed by a two stage direct drive rotary vacuum pump - rough vacuum, (C) dry nitrogen inlet, (D) fluorine inlet, (E) 0 - 1500 Torr Monel Bourdon gauge (F) pressure transducers 0 - 1000 Torr, (G) pressure transducer 0 - 1 Torr, (H) 3/8-in. 316 SS high pressure valve (Autoclave Engineers, 30VM6071), (I) 316 SS tee, (J) 316 SS cross, (K) 316 SS L, (L) nickel connectors
Figure 2.2. Stainless steel/PFA-FEP vacuum line:

Stainless steel manifold; (A) to PFA manifold, (B) outlet to soda lime tower, liquid nitrogen trap and charcoal trap followed by a two stage direct drive rotary vacuum pump - rough vacuum, (C) outlet to liquid nitrogen trap and charcoal trap followed by a two stage rotary vacuum pump - hard vacuum, (D) fluorine inlet, (E) nitrogen inlet, (F) 0 - 1500 Torr Monel Bourdon gauge, (G) ¼-in. 316 SS high pressure needle valve (Whitey, 316SS-1KS4), (H) 316 SS tee, (I) 316 stainless steel cross, (J) ¼ in 316 stainless steel Swagelok connectors;

Fluoroplastic manifold; (K) 0 - 30 lb/in.$^2$ gauge with Teflon pressure transmitter, (L) Teflon union connectors, (M) ¼ in. PFA needle valve (Whitey Co., PFA-4RPS4), (N) PFA tee, (O) thick wall (¼ in. o.d., 1/8-in. i.d.) FEP connector
Figure 2.3. High pressure reactor for NMR sample preparation; (A) Kel-F valve, (B) 4-mm o.d FEP NMR tube sealed at the bottom and flared at the top, (C) 3/4-in. o.d PFA tube, i.d. blown out to match NMR tube o.d., sealed at the bottom and flared at the top, (D) compression nut
gas through a loosely packed 3/8-in. o.d. FEP U-tube containing dry NaF. The purification of HF (Harshaw Chemical Co.) has been described elsewhere. Oxygen difluoride (Ozark-Mahoning) was used without further purification.

Enriched \([^{18}\text{O}]\text{O}_2\) (\(^{18}\text{O}\) isotopic purity, 95 - 98.5%) was obtained from Isotec, Ohio, USA, and from Euroiso-top, France having a chemical purity ranging from 99.5 - 99.99%. Cesium sulphate (99.999%), CH\(_3\)CN (HPLC grade), 3,4-dihydroxyphenylalanine (L-Dopa) (Aldrich) were obtained commercially and used without further purification. Antimony trifluoride was obtained commercially (Aldrich) and purified by vacuum sublimation in a glass vessel at 200 °C.

2.3 Instrumentation

2.3.1 Nuclear Magnetic Resonance Spectroscopy

Low temperature \(^{19}\text{F}\) NMR spectra were recorded at 282.409 MHz on a Bruker AC-300 spectrometer. Spectra were accumulated in 250 to 5000 scans in 18 kHz spectral widths (acquisition time 0.459 s, 2.18 Hz/point) using a pulse width of 6.0 μs. The samples were referenced with respect to external neat CFCl\(_3\).

Room temperature \(^{19}\text{F}\) NMR spectra of fluorinated aromatic amino acid samples were recorded at 470.600 MHz on a Bruker AM-500 spectrometer. Typical spectra were recorded in 500 to 5000 scans in 10 - 20 kHz spectral widths (e.g. acquisition time 0.918 s, 1.09 Hz/point).
2.3.2 Raman Spectroscopy

Raman samples were excited using the 514.5 nm line of an Ar ion laser (Spectra Physics Model 2016) and the spectra were recorded on a Jobin-Yvon Model S-3000 triple spectrograph system equipped with a 0.32-m prefilter, adjustable 25 mm entrance slit, and a 1.00 m monochromator. Holographic gratings were used for the prefilter (600 grooves mm\(^{-1}\), blazed at 500 nm) and monochromator (1800 grooves mm\(^{-1}\), blazed at 550 nm) stages. An Olympus metallurgical microscope (Model BHSM-L-2) was used for focusing the excitation laser to a 1 \(\mu\)m spot on the micro sample. The spectra were recorded with the use of a Spectraview-2D CCD detector equipped with a 25 mm chip (1152 x 298 pixels).

The Raman spectrum of XeF\(^{+}\)AsF\(_6\) was recorded in the macro chamber cooled to -70 °C in a cold nitrogen stream. The laser power was 240 mW at the sample. The premonochromater, intermediate, and monochromater slit settings were 200 \(\mu\)m, 2.7 mm, and 200 \(\mu\)m, respectively, yielding a resolution of 1 cm\(^{-1}\). A total of 15 reads each having 60 sec. integration times were summed.

The Raman spectrum of (Xe\(_2\)F\(_3\))\(^{+}\)AsF\(_6\) was recorded at room temperature on a powdered sample sealed inside a baked out Pyrex melting point capillary. The laser power at the sample was 65 mW and slit settings (\textit{vida supra}) yielded a resolution of 1 cm\(^{-1}\). A total of 15 reads each having 45 s integration times were summed.

The instrument was calibrated with the indene lines at 730.4 and 1018.3 cm\(^{-1}\) in pure indene so that the spectral line positions were accurate to ±1 cm\(^{-1}\).
2.3.3 $^{18}$F Detection

Fluorine-18 activities were measured by use of a radioisotope calibrator that had a dynamic range of 10 μCi to 2 Ci (Capintec Inc. Model CRC-12) and consisted of a 6 cm. i.d. and 25 cm. deep well surrounded by an ionization chamber filled with argon gas. The chamber walls were made of aluminum and the outside wall was shielded with 1/8-in. thick lead. The current produced in the ionization chamber, caused by the interaction of the photons with the gas molecules, was read as a digital readout. The sensitivity of the ionization chamber was determined using radioactive standards supplied by the U.S. National Bureau of Standards and/or the Laboratoire de Métrologie de la Radioactivité, France. The accuracy of the calibrator was determined with $^{57}$Co and $^{60}$Co standard sources and it is reported to be ± 2% for γ-rays with ≥ 0.1 Mev energies.

In the present work, some error in the measurement of radioactivity was observed as a result of the different geometries of the vessels used to contain or trap the sources of activity. Fluorine gas as $^{[18}$F]$F_2$ was assayed at the beginning of experiments in a 4-mm FEP reaction vessel and then separated and trapped by pumping through a copper U-trap containing soda lime. Measurement of the activity in the copper trap typically was found to be 10 - 15% higher than the initial activity measured in the FEP vessel. Also, variations in the measurement of the $^{[18}$F]$F_2$ between the condensed phase at -196 °C and the gas phase were observed in the FEP reaction vessels. This error, typically 1 - 3%, could be avoided by performing all assays involving $^{[18}$F]-F$_2$ at -196 °C.
2.4 Fluorine-18 Studies

2.4.1 $^{18}$F Target and Support System

The target was designed and constructed by CTI Cyclotron Systems, Berkeley, California and it consisted of a water-cooled nickel-200 body with a conical bore (14.9 mL). Additional details on the materials and construction of the target have been described elsewhere. The support system, including delivery systems and vacuum lines is outlined in the schematic (Figure 2.4).

2.4.2 $^{18}$F Production and Recovery

A Siemens 11 MeV proton-only cyclotron (RDS-112) and the double irradiation method were used to produce $^{18}$F$_2$ using the nuclear reaction $^{18}$O(p,n)$^{18}$F. Before the production irradiation, the target and $^{18}$O-gas manifold were evacuated. The target was then pressurized with 14 - 16 atm. of enriched $^{18}$O$_2$ and irradiated for typically 30 min. with a 30 µA proton beam. After the initial irradiation, the $^{18}$O$_2$ was retrieved into the cryo-trap consisting of a 40 mL stainless steel cylinder containing molecular sieves (Varian Vacsorb 944-0000) at -196 °C (Figure 2.4). The target was pumped again and flushed with neon to remove trace amounts of $^{18}$O$_2$. In preparation for the recovery irradiation, the target was pressurized with a carrier fluorine-noble gas mixture, having a composition and amount dependent upon the method used to recover $^{18}$F. Typically, if the $^{18}$F was to be recovered as $[^{18}$F]HF, 24 atmospheres of neon containing 30 - 70 µmoles of carrier $^{19}$F$_2$ was used to pressurize the target. If the activity were to be recovered as $[^{18}$F]-F$_2$, approximately 14 atmospheres of krypton containing 200 - 300
Figure 2.4. Target support system; (A) $^{18}$O$_2$ reservoir, (B) $^{18}$O$_2$ cryotrap, (C) bellows valves (Nupro SS 2H), (D) Nupro 5 micron filters, (E) $^{18}$O$_2$ target (Section 2.4.1 for composition and construction), (F) 0 - 1000 Torr Monel Gauge (Granville Phillips 275), (G) Ne (Air Products), (H) 1% F$_2$/Ne mixture (Matheson), (I) needle valve (Nupro SS-SS1); R83, R92, R93, R94, and R95 solenoid valves under computer control (Precision Dynamics Inc. A2011-S84)
μmoles of carrier $^{19}$F$_2$ was used. The target was irradiated for the recovery irradiation with a beam current of 15 μA for 15 min. The $^{18}$F was eluted from the target by opening the outlet valve and condensing the target gas mixture at -196 °C into the desired receiving vessel in the hot cell.

2.4.3 $^{18}$F Correction for Decay

In all of the experiments that involved $^{18}$F, the measured activities were corrected for decay back to the beginning of the experiment, $d_t = 0$. Activities were corrected for decay with use of equation (2.1).

$$.Activity^{18}F = [A_o] \left[1 - e^{\frac{-d_t}{t_{1/2}}} \right]$$

$A_o$ = initial $^{18}$F, $T$ = elapsed time after $T = 0$, $t_{1/2}$ = radioisotope half-life, 109.7 min.

2.5 Preparation of $^{18}$F Precursors

2.5.1 $[^{18}$F]HF

For the purpose of this work, the $^{18}$F activity was recovered as either $[^{18}$F]F$_2$ or $[^{18}$F]HF. Labelled $[^{18}$F]HF was prepared by condensing the Ne/$[^{18}$F]F$_2$ target mixture into a 40 mL stainless steel vessel containing H$_2$ (2.28 mmol) and anhydrous HF (1.14 mmol) at -196 °C. The mixture was allowed to react for 30 min. at room temperature and then Ne and any unreacted H$_2$ and F$_2$ were pumped off at -196 °C.
2.5.2 Production of Very Low Specific Activity $[^{18}\text{F}]\text{F}_2$

The recovery of $[^{18}\text{F}]\text{F}_2$ was also carried out by pressurizing the target for the recovery irradiation to 7 atm. with a mixture of 5% F$_2$ in krypton and then a further pressurization with pure krypton to bring the target pressure up to 14 atm. After the recovery irradiation, the target mixture was condensed into a 40 mL 304 SS Whitey cylinder containing 2000 - 3000 Torr of $^{19}\text{F}_2$ carrier at -196 °C. Before the transfer of the $[^{18}\text{F}]\text{F}_2$, the receiving vessel was warmed to 50 °C to allow complete exchange of the $^{18}\text{F}$ from the target mixture with the $^{19}\text{F}$ of the carrier pool, and consequently, provide a homogeneous $[^{18}\text{F}]\text{F}_2$ mixture. Exclusion of this step was found to result in poor transfer yields of the $^{18}\text{F}$ activity.

2.5.3 Transfer and Distribution of $[^{18}\text{F}]\text{F}_2$

After the $^{18}\text{F}/^{19}\text{F}$ exchange step, the receiving vessel that contained Kr plus $[^{18}\text{F}]\text{F}_2$ was again cooled to -196 °C. The vessel was then opened to a calibrated volume of the vacuum line producing a fluorine vapour pressure of 280 Torr. The receiving vessel was warmed slightly with a liquid oxygen bath (-183 °C) to increase the vapour pressure in the vessel and the manifold to the desired level (400-600 Torr). When the desired pressure was reached, the manifold was closed to the receiving vessel, the manifold pressure recorded, and the gas was condensed into the reaction vessel at -196 °C through a separate port. The amount of fluorine transferred was be calculated from the pressure of F$_2$ above the 280 Torr vapour pressure at -196 °C condensed from the calibrated volume. The radiochemical yield of the transfer was simply equal to the $^{18}\text{F}$ activity in the reaction vessel divided by the $^{18}\text{F}$ activity initially in the Kr/$[^{18}\text{F}]\text{F}_2$ mixture.
Since the volumes of the receiving vessel and the calibrated manifold remained constant, the radiochemical transfer could be easily quantified. The theoretical radiochemical transfer is given in equation (2.2)

\[
(1^{18}F \text{ Reaction Vessel}) = \frac{(\text{Manifold pressure} - 300 \text{ Torr})}{(\rho \text{Torr of carrier } F_2, \text{ receiving vessel})} \times (1^{18}F \text{ Receiving Vessel})
\]

(2.2)

2.6 Target Gas Analysis

2.6.1 Identification of OF\(_2\)

All NMR samples were prepared in 4-mm FEP tubes. A reference sample was made from an authentic sample of OF\(_2\) (Ozark-Mahoning). Oxygen difluoride was condensed into an FEP NMR sample tube at -196 °C until a small amount of the pale yellow liquid was visible at the bottom of the tube. Anhydrous HF was then condensed into the tube until the desired sample height of 5 cm was attained. The sample tube was then sealed under a static vacuum at -196 °C in order to prevent any loss of the OF\(_2\). The NMR spectrum of the reference sample was collected at -60 °C in order to prevent an overpressure within the FEP NMR tube due to OF\(_2\).

In order to prepare a target sample which would contain as much OF\(_2\) as possible, 15 psi of \(^{18}\text{O}_2\) was left in the target during the recovery irradiation. Also, the F\(_2\)/Ne mixture was changed from 1% F\(_2\) in Ne to 5% F\(_2\) in Ne. Prior to the recovery irradiation, the target was pressurized to 296 psi with the 5% F\(_2\) mixture. The procedure for the synthesis of \(^{18}\text{F}\)HF was carried out as usual up to and including the removal of the
unreacted F₂/H₂/Ne at -196 °C. At this point the remaining contents of the vessel were condensed into an FEP NMR tube at -196 °C. A sequence of condensing, pumping the manifold to remove any volatiles, and then condensing from the reaction vessel, was repeated several times to ensure complete transfer. Anhydrous HF was then condensed on top of the target mixture to make up the rest of the sample height. The ³⁹F spectrum was collected at room temperature in 62,565 scans. An external D₂O lock was also used.

2.6.2 Target Gas Analysis Experiments

The determination of the amount [¹⁸F]OF₂ in the target gas mixture was accomplished by the fractional separation of volatiles between -196 and -94 °C. The general synthesis of [¹⁸F]HF was used since total retention of the ¹⁸F activity is expected. In all experiments, the Ne/F₂ target mixture was condensed into a reaction vessel containing 760 Torr of carrier HF and 1000 Torr of H₂ at ambient temperatures. The reaction vessel was warmed to room temperature and allowed to exchange for 25 to 30 min. After this time, the vessel was cooled to -196 °C and pumped on in order to remove any unreacted F₂, H₂ or excess Ne. The reaction vessel was then warmed to -94 °C in a methanol slush bath. At this temperature the vapour pressures of OF₂ and HF are 760 Torr and 1 Torr, respectively, thus making it possible to separate the remaining two components of the mixture.

2.7 Lewis Acid Activation of Fluorine

The apparatus used for all Lewis acid/F₂ activation studies consisted of a target
mixture receiving vessel (40 mL 304 SS Whitey cylinder equipped with a 316 SS Whitey 
OMR2 valve), FEP reaction vessel equipped with Kel-F valve, and a copper U-trap filled 
with soda lime. The $^{18}$F receiving vessel was transferred from the hot cell (Figure 2.4) to 
the vacuum line after the target mixture had been condensed at -196 °C. A portion of the 
$[^{18}F]F_2$ was condensed into reaction vessel at -196 °C. The $[^{18}F]F_2$ was separated and 
trapped on a copper trap maintained at room temperature and filled with soda lime. The 
general apparatus configuration on the vacuum line is shown in Figure 2.5 at the end of 
this section.

2.7.1 $^{18}$F Study of the $F_2$/$AsF_5$ Exchange

Arsenic pentafluoride (1.0 mmol) was condensed into a 1/4-in. o.d thick-walled 
FEP tube (2 mL) equipped with a Kel-F valve at -196 °C. Fluorine-18, as $[^{18}F]F_2$ (0.5 
mmol) was transferred into the reaction vessel at -196 °C as previously described (Section 
2.5.3) and then assayed for the initial $^{18}$F activity. The $^{18}$F activity at the beginning of the 
experiment was 42 mCi. The reaction vessel was warmed to -70 °C in a methanol bath. 
The $F_2$ pressure within the reaction vessel, as a result of a compression factor of 18.5, 
was between 4 and 5 atm. Therefore, the use of the of the thick walled FEP tube for the 
reaction vessel in this particular experiment, and all subsequent high pressure reactions, 
was imperative in order to prevent bursting due to overpressurization. The reactants were 
allowed to exchange for 1 hr. at -70 °C before cooling to -196 °C. The $[^{18}F]F_2$ was 
separated from the $AsF_5$ and trapped by pumping through a room temperature copper 
U-trap containing soda lime. The reaction vessel was warmed briefly to -70 °C and then
the pumping process at -196 °C was repeated to ensure that all the $^{18}$F$F_2$ was removed from the AsF$_5$. The reaction vessel was assayed for the $^{18}$FAsF$_5$ and the copper trap was assayed for the $^{18}$F$F_2$ (Table 4.1)

2.7.2 $^{18}$F Study of the Xe/F$_2$/AsF$_5$ Reaction

Arsenic pentafluoride (1.4 mmol) and Xe (0.5 mmol) were condensed into a 1/4-in. o.d. thick-walled FEP reaction vessel equipped with a Kel-F valve (Figure 2.5). The $^{18}$F$F_2$ was transferred into the reaction vessel as previously described (see Section 2.5.3). Initial $^{18}$F activities in the reaction vessel ranged from 40 to 100 mCi. The combined F$_2$/Xe pressure at -70 °C was calculated to be 8.6 atm. The reaction vessel was warmed to -70 °C in a methanol bath such that the reaction could proceed in liquid AsF$_5$ under dark conditions. Exchange times for this and subsequent experiments ranged from 1 to 3 hrs. and the FEP reactors were gently agitated by a mechanical shaker throughout the reaction. Also, subsequent reactions were run with different stoichiometries and reaction pressures were maintained below 20 atm. as the Kel-F valves tended to leak across the seats above this pressure. A pale yellow precipitate, later confirmed to be XeF$^+$AsF$_6^-$ was seen to form in the AsF$_5$ solvent as early as 15 min. following initiation of the reaction under the highest pressure experiments. After exchange, the reaction vessel was cooled to -196 °C and the $^{18}$F$F_2$ was removed by pumping through a room temperature copper U-trap containing soda lime. The reaction vessel was warmed again to liquid AsF$_5$ temperatures (ca. -70 °C), cooled to -196 °C and pumped on again to remove trace amounts of $^{18}$F$F_2$. At this point the copper trap was assayed for the $^{18}$F$F_2$
as well as the reaction vessel, containing the XeF₂⁻AsF₆⁻ salt, unreacted AsF₃ and Xe. After pumping on the reaction vessel at -70 °C to remove the AsF₃, the reaction vessel was assayed again for $^{18}$F activity, which, when subtracted from the previous measurement, gave the activity for $[^{18}\text{F}]\text{AsF}_3$. The experiment was either stopped at this point and the sample studied by Raman spectroscopy to confirm the presence of the XeF₂⁺ salt, or the reaction vessel was warmed to room temperature, and pumped on to remove further AsF₅ liberated by the decomposition of the XeF₂⁺ salt. A final assay of the reaction vessel gave an activity for $[^{18}\text{F}]\text{Xe}_2\text{F}_3^+\text{AsF}_6^-$ (See Table 4.2).

2.7.3 $^{18}$F Study of the Kr/FJAsF₅ Reaction

An $^{18}$F tracer study similar to that described in the previous section was performed which substituted krypton gas for xenon. The procedure was followed exactly as in the preceding section. Exchange times ranged from 1 to 2 hrs. Initial $^{18}$F activities ranged from 30 to 40 mCi. Reaction pressures for the vessel at -70 °C ranged from 8.6 to 16 atm. In all of the experiments involving Kr, no salt was seen to form as in the Xe experiments thus the reaction vessel was normally only assayed after the removal of the $[^{18}\text{F}]\text{F}_2$ at -196 °C and for the $[^{18}\text{F}]\text{AsF}_5$ after pumping at -70 °C.

In order to give the reaction more time to proceed, non-radioactive experiments were performed which allowed the reaction to run for 24 hours or more. In all such experiments no salt precipitation was observed.
Figure 2.5. Apparatus configuration for $^{18}$F Lewis acid experiments; (A) $^{18}$F target mixture receiving vessel, (B) 1/4-in. o.d, 1/8-in. i.d. FEP reaction tube equipped with Kel-F valve, (C) copper U-trap filled with soda lime and equipped with 316 stainless steel valves (Whitey, 316SS-1KS4)
2.7.4 Reaction of Kr/F₂/HF/SbF₃

Antimony trifluoride (0.6 mmol) was transferred in the drybox to a ¼-in. FEP reaction vessel equipped with a Kel-F valve. Anhydous HF (1.2 mmol) was condensed at -196 °C onto the SbF₃. The resulting mixture was warmed to -78 °C and then pressurized with an atmosphere of fluorine. While the vessel was warmed slowly to room temperature, the mixture was agitated to facilitate the fluorination of the SbF₃. The process of replenishing the fluorine pressure at -78 °C and then warming and agitating was repeated until all of the SbF₃ had dissolved. The residual F₂ was pumped off at -196 °C. Krypton gas (0.8 mmol) was condensed into the vessel at -196 °C followed by F₂ (0.8 mmol). The reaction mixture was warmed to approximately -50 °C in a methanol bath and allowed to react in the dark. The vessel had to be maintained below the freezing point of the solution to avoid crystalline SbF₅·xHF solvate. No apparent reaction was evident over a period of 24 hrs.

2.7.5 Reaction of OF₂/F₂/AsF₅

Arsenic pentafluoride (1.8 mmol) was condensed into a ¼-in. thick-wall FEP reaction vessel at -196 °C. Oxygen difluoride (1.0 mmol) followed by F₂ (1.0 mmol) were also condensed into the vessel at -196 °C. The reaction vessel was warmed to -70 °C in a methanol bath and allowed to react in the dark under agitation. The reaction was halted after 24 hrs. when no solid was observed and no apparent change in the solution was observed.
2.8 Electrophilic Fluorination Reactions

2.8.1 Preparation of and Assay Cesium Fluoxysulphate

A total of 10 mL of a 1.986 M solution of CsSO₄ was prepared. The solution was transferred into an 1/2-in. FEP reaction vessel and cooled to -5 °C in an ice-salt mixture (Figure 2.6.). Fluorine, as 20% F₂ in N₂, was bubbled through the CsSO₄ solution over the course of 1 hr. using a 1/16-in. FEP tube. The small bore of the F₂ inlet tube and the height of CsSO₄ solution in the reaction vessel optimized the contact between the F₂ mixture and CsSO₄ solution. The quantity of 20% F₂ in N₂ mixture which passed through the CsSO₄ solution was measured in the graduated cylinder and was 1.6 L or 14.3 mmol. Fluorine was therefore the limiting reagent as 19.9 mmol of CsSO₄ was used. Previous procedures used for the synthesis CsSO₄F have called for a 2-to 3-fold excess of fluorine. However, due to the nature of the apparatus used, the efficiency of the reaction was improved; thus the reaction was halted once no further fluoroxysulphate was observed to precipitate.

Upon completion of the reaction, the reaction mixture was centrifuged at 3000 rpm for 25 min. The supernatant was decanted and the solid suspended in ice cold water and centrifuged and decanted a second time. Then the solid was dried overnight under high vacuum. The yield of CsSO₄F based on the quantity of fluorine used was 83.5%.

Fluorine-19 NMR spectroscopy was used to confirm the formation of CsSO₄F and also to look at the amount of fluorosulphate impurity. The NMR samples were prepared in CH₃CN solvent immediately before acquisition of the spectrum. The spectrum was
acquired at room temperature in 560 scans.

An NMR study of the decomposition of fluoroxysulphate to flourosulphate was performed in order to obtain an estimate for the lifetime of CsSO₄F in H₂O. A room temperature sample of CsSO₄F in H₂O was prepared immediately before acquisition of the ¹⁹F spectrum. The first spectrum was acquired for 10 min. and then halted. A second spectrum was acquired approximately 30 min. after dissolution of CsSO₄F in H₂O. The relative intensities of the SO₄F⁻ and FSO₃⁻ resonances were compared.

2.8.2 Reactions of CsSO₄F with Aromatic Amino Acids

It was initially postulated that, due to the aqueous conditions under which the synthesis of fluoroxysulphate is carried out and the possibility of dissolving compounds such as L-dopa in slightly acidic solutions, fluorinations of such compounds could be carried out by directly mixing the aqueous reaction mixture from the CsSO₄F synthesis, with a solution containing the dissolved amino acid. The procedure essentially followed the previously described synthesis of CsSO₄F with the exception that a 1% F₂ in Ne mixture was used as the fluorine source instead of a N₂/F₂ mixture. This reduced the quantity of SO₄F⁻ below the saturation level. At the same time, a solution of L-dopa was prepared in H₂O by adding a 1/2 mL of aqueous HF. The centrifuge steps were omitted from the synthesis. Approximately 1 mL of solution from the SO₄F⁻ preparation was added to the a chilled Teflon vial containing the L-dopa solution. After a period of 30 min. a 0.2 mL portion of the reaction mixture was taken, diluted to approx. 1 mL, and injected into a reverse phase Whatman ODS-2 HPLC column. The mobile phase was
4.5% tetrahydrofuran (THF) and 0.15% trifluoroacetic acid (TFA) in water. An L-dopa reference had already been run to determine its retention time.

2.8.2.1 CsSO₄F with DOPA in CH₃CN

The reaction between CsSO₄F and L-dopa was repeated in CH₃CN. Acetonitrile was added directly to the two reactants. The reaction was carried out for 30 min. at room temperature after which time the reaction mixture was divided into two 1 mL. No colour change had occurred during the reaction time. Water (1 mL) was added to the first portion, and a 0.15% TFA in H₂O solution (1 mL) was added to the second. The samples were separated using HPLC and L-dopa spikes were added to help identify the peaks due to L-dopa in the chromatogram.

2.8.2.2 CsSO₄F with L-DOPA in BF₃/CH₃CN

A 0.1 M solution of BF₃ in CH₃CN was first prepared for this reaction. A known pressure (450 Torr) of BF₃ from a 41 mL calibrated volume was condensed into a Pyrex glass flask equipped with Teflon Rotoflo valve containing 10 mL of CH₃CN. The solution was degassed by freezing the solution to -196 °C, pumping on the solid, and then thawing. This process was repeated twice. All manipulations involving the transfer of the BF₃/CH₃CN solutions were carried out under an inert atmosphere of nitrogen in a glove bag.
Figure 2.6. Apparatus used for the room temperature and low temperature fluorinations in BF$_2$/CH$_3$CN; (A) 1/2-in. o.d. FEP U-trap cooled to -196 °C in a liquid N$_2$ bath, (B) 1/4-in. o.d FEP reaction vessel equipped with PFA needle valve (Whitey, PFA-4RPS4) cooled to -44 °C in a methanol bath.
Solid fluoroxysulphate, L-dopa, and a Teflon coated magnetic stirring bar were added to a 3/8-in. FEP reaction vessel equipped with a PFA valve. The reaction vessel was then transferred to the glove bag where approximately 1 mL of the BF$_3$/CH$_3$CN solution was added. The reaction vessel was then resealed and transferred to the vacuum line. An FEP U-trap was placed between the reaction vessel and the vacuum line port. The reaction was allowed to proceed at room temperature for 30 min. while being stirred. Upon completion of the reaction, the mixture was pumped to dryness and the solvent trapped at -196 °C in the U-trap. Once the solvent had been pumped off, the product was redissolved in H$_2$O with a 1/2 mL of 1M HCl. Small portions (0.3 to 0.5 mL) of the dissolved reaction product were separated on the ODS-2 HPLC column. An L-dopa reference was run to establish its retention time.

2.8.2.3 Low-temperature Fluorinations

In order to reduce some of the more severe oxidation side reactions, observed as the rapid production of dark coloured, insoluble solids, slightly milder reaction conditions were needed such that mostly electrophilic fluorination of the aromatic amino acid would occur. Also more dilute solutions of both the amino acid and fluoroxysulphate were prepared separately and then cooled prior to mixing in order to control the rate of the reaction at the beginning by maintaining a low temperature.

Fluoroxysulphate (13.3 mg) and L-dopa (10.6 mg) were weighed and then transferred into a glove bag which was then purged with dry nitrogen for 1 hr. Approximately 0.5 mL of the BF$_3$/CH$_3$CN solution was added to the CsSO$_4$F contained
in the FEP reaction vessel and frozen in a liquid nitrogen bath. In a separate test tube, the L-dopa was dissolved in 1 mL of the BF₃/CH₃CN solution and transferred into the reaction vessel on top of the frozen SO₄F solution. The entire mixture was frozen at -196 °C. The reaction vessel was sealed under the nitrogen atmosphere and equipped with a PFA valve. The apparatus was hooked up to the vacuum line, evacuated at -196 °C, placed over a magnetic stir plate, and then warmed to -40 °C in a methanol bath. The reaction commenced as the solvent melted at about -44 °C and the stirring began. Best results were obtained when the temperature was kept as low as possible throughout the first few min. of the reaction. After 15 min, the reaction vessel was allowed to warm to room temperature. This was best accomplished by discontinuing further addition of liquid nitrogen to the methanol bath and allowing the bath to slowly warm up on its own. After 1 hr, the reaction vessel was opened to the vacuum and the solvent pumped off and trapped in the liquid nitrogen U-trap. Once the product was pumped to dryness, it was dissolved in water, containing a 1/2 mL of dilute 1.2 M HCl and then separated using HPLC.

2.8.4 Separation and Identification of the 2-, 5-, and 6-fluoro Isomers of Fluorodopa

All reaction mixtures were separated on a Whatman ODS-2 reverse phase column. This column is known to separate 6-fluoro-L-dopa from dopa. The mobile phase used with this column was 0.15% TFA, 4.5% THF in water. A 280 nm UV detector was used. Typical flow rates were 2.5 to 3.0 mL/min and absorbence co-efficients ranged from 0.08 to 0.32 L^3 mol⁻¹ cm⁻¹.
Samples collected for $^{19}$F NMR spectroscopy were first separated on the Whatman ODS-2 column. Sample peaks were collected with use of the UV chromatogram. These samples were evaporated to dryness on a rotary evaporator to remove any residual TFA and THF from the product. The samples were redissolved in approximately 1.5 mL of H$_2$O and then injected onto a Vydac column using a 0.1% acetic acid/H$_2$O mobile phase. The flow rate was set at 1.5 mL/min. This column was known$^{38}$ to separate the fluorinated products from the non-fluorinated products. The collected peaks were again evaporated to dryness to remove any remaining traces of TFA. Samples from several reactions were combined together in order to prepare a sample of sufficient concentration for $^{19}$F NMR spectroscopy. The NMR sample was prepared in D$_2$O/DCI solvent.
CHAPTER 3
FLUORINE-18 GAS ANALYSIS OF THE \([^{18}F]F_2\)
RECOVERED FROM AN \(^{18}O_2\) GAS TARGET

3.1 INTRODUCTION

The production of a target gas mixture containing \([^{18}F]F_2\), to be used as a source of electrophilic fluorine for radiopharmaceutical labelling, inherently requires a thorough knowledge of the composition and reactivity of such a mixture. Also, as \([^{18}F]F_2\) is becoming a more commonly used tool for the investigation of inorganic reaction mechanisms, the chemical purity of such gas mixtures also becomes a concern.

The methods used for the production of \([^{18}F]F_2\) are generally dependent on such factors as the nuclear reaction being employed, the method of bombardment, and the target and recovery system. The targetry developments and ability to produce \([^{18}F]F_2\) via the nuclear reaction \(^{20}\text{Ne}(d,\alpha)^{18}\text{F}\) in cyclotrons or linear accelerators with deuteron capabilities is well established.\(^{14,39,40}\) The production of \([^{18}F]F_2\) in the current work utilizes the nuclear reaction \(^{18}\text{O}(p,n)^{18}\text{F}\) carried out in an 11 MeV proton-only cyclotron. The techniques available to users of this system for the reliable production and quantitative recovery of high purity \([^{18}F]F_2\) are still limited.\(^{41}\)

The determination of the thick target saturation yield for \(^{18}\text{F}\) at 10 MeV (protons and deuterons) by Ruth \textit{et al.}\(^{42}\) in 1979 showed that the \(^{18}\text{O}(p,n)^{18}\text{F}\) reaction was three times more efficient than the \(^{20}\text{Ne}(d,\alpha)^{18}\text{F}\) reaction. As a result of this clear advantage, two methods, a single (1S) and double step (2S) synthesis, were developed for the
production of $^{18}\text{F}]\text{F}_2$ from $^{18}\text{O}_2$. With the exception of a few variations on these original procedures to examine different target environments, surprisingly little work has been done on the improvement of these methods, and development of further techniques for the production of $^{18}\text{F}]\text{F}_2$ from $^{18}\text{O}_2$.

3.1.1 Single Irradiation Method

The development of techniques for the production of $^{18}\text{F}]\text{F}_2$ was initiated by Nickles et al. in 1984. The single irradiation procedure (1S), though simpler than the double irradiation (2S) method, did not prove to be as efficient and contained drawbacks which would make it impractical for the routine production of $^{18}\text{F}]\text{F}_2$. The 1S method involved the direct irradiation of an $^{18}\text{O}_2$ / carrier $^{19}\text{F}_2$ mixture. The 1S method accomplished the conversion of $^{18}\text{O}$ to $^{18}\text{F}$ simultaneously with the mixing of the $^{18/19}\text{F}$ and the target gas recovered from this method contained large quantities of the unreacted $^{18}\text{O}_2$. In addition, the dissociation of molecular $\text{O}_2$ and $\text{F}_2$ to atomic species during the irradiation process, resulted in the formation of $\text{OF}_2$. The characterization of the $\text{OF}_2$, and the analysis of relative amounts of $^{18}\text{F}]\text{OF}_2$ and $^{18}\text{F}]\text{F}_2$ found for a 1S target gas, have recently been studied. In addition to the low chemical purity and low radiochemical yield of the $^{18}\text{F}]\text{F}_2$ recovered through this process, the consumption of $^{18}\text{O}_2$ presented a significant financial barrier ($500.00$/litre at STP in 1993) for the routine use of this method.
3.1.2 Double Irradiation Method

The double irradiation method (2S), designed primarily for use with passivated nickel targets, was successful in eliminating many of the problems associated with the single irradiation method. During the first bombardment, the $^{18}\text{F}$ activity produced from the irradiation of pure $^{18}\text{O}_2$ was assumed to adhere to the passivated walls of the target through the exchange labelling equation (3.1)

$$^{18}\text{F}^{-} + \text{NiF}_2 \rightleftharpoons \text{F}^{-} + [^{18}\text{F}]\text{NiF}_2$$  (3.1)

The composition of the walls was found to be a non-homogeneous mixture of Ni, NiO, NiF$_2$, and some nickel hydroxides.$^{45}$ However, for the purpose of understanding the fluorine exchange processes, the passivated walls are best thought of as a uniform NiF$_2$ surface. At the end of the first bombardment, the charge of $^{18}\text{O}_2$ is recovered from the target by cryogenic trapping. The target is then charged with fluorine in a noble gas mixture which is then irradiated with the ionizing beam producing atomic fluorine. The carrier atomic fluorine picks up the $^{18}\text{F}$ activity through the reverse of equation (3.1). Recombination of the atoms at the end of bombardment yields a uniform mixture of $^{18}\text{F}$-$^{19}\text{F}$ and $^{19}\text{F}_2$ (denoted as [${^{18}\text{F}}$]F$_2$). Variations in [${^{18}\text{F}}$]F$_2$ yield with the kind of noble gas used and/or relative composition has been previously investigated.$^{15,41}$ High radiochemical yields were also found to be dependent on the rigorous exclusion of contaminants such as CO$_2$ and N$_2$ as these have been found to be precursors for the formation of unreactive [${^{18}\text{F}}$]CF$_4$ and [${^{18}\text{F}}$]NF$_3$ in the target environment.$^{39}$
The use of the double irradiation method, or the "classic" 2S method, eliminates the wasteful use of the isotopically pure $^{18}$O$_2$ as only a very small amount of the gas is actually consumed during each production sequence. Recovery of the $^{18}$O$_2$ charge prior to the recovery irradiation of the carrier fluorine mixture also serves to minimize the production of significant amounts of $[^{18}\text{F}]\text{OF}_2$.

3.1.3 Prior Observation of OF$_2$, and FONO$_2$

The first spectroscopic evidence for the presence of OF$_2$ in a target mixture was provided by Bida et al. using $^{19}$F NMR spectroscopy. They utilized the single irradiation method and a modified double irradiation method which left the charge of $^{18}$O$_2$ in the target for the second irradiation. In addition to the OF$_2$ resonance at 250 ppm (relative to CFCl$_3$), a resonance for fluorine nitrate, FONO$_2$, was observed at 220 ppm for a sample of a target gas mixture obtained from the classic 2S method. The formation of FONO$_2$, originally synthesized by Cady et al., was suggested to be a result of contamination of the target with N$_2$ and O$_2$, ultimately leading to the formation NO$_2$. The formation of FONO$_2$ under these conditions follows the equations,

\begin{align}
\cdot\text{NO}_2 + F_2\text{O} & \rightleftharpoons F\text{NO}_2 + \cdot\text{OF} \\
\cdot\text{OF} + \cdot\text{NO}_2 & \rightarrow \text{FONO}_2
\end{align}

leading to the overall equation,
These equations indicate that, if fluorine nitrate was formed in an environment containing OF$_2$, then nitryl fluoride, FNO$_2$, should also have been present. A careful literature search did not reveal a value for the $^{19}$F chemical shift of FNO$_2$, though an early $^{19}$F NMR experiment had reported the $^1J(^{19}$F - $^{14}$N) coupling. The results presented in the previous work$^{43}$ did not report that any attempt had been made to observe the $^{19}$F resonance of FNO$_2$ in the fluorine on nitrogen(V) region of the $^{19}$F NMR spectrum.

3.1.4 Formation of OF$_2$ and Properties of OF$_2$

Much attention has already been paid to the properties and reactivity of the oxygen fluorides.$^{52,53,54}$ Also, since this work is concerned primarily with the specific environment of a cyclotron target, an in depth discussion of the formation of OF$_2$ and higher oxygen fluorides has been omitted.

The elevated temperatures and pressures up to 40 atm present within the thick target environment during the cyclotron irradiation can supply sufficient energy to atomize molecular fluorine and initiate reaction pathways leading to unstable oxygen fluoride species. Common sources of energy used for the preparation of oxygen fluorides are heat, ultra-violet radiation and electrical discharges. Radical species such as OF· and O$_2$F·, whose properties and structures have been well characterized,$^{55,56}$ react with atomic fluorine to produce the compounds O$_2$F$_2$ and OF$_2$. The O$_2$F$_2$ molecule is unstable above -160 °C and decomposing back to O$_2$F·, and ultimately to O$_2$ + F· so that the formation
of OF₂ can be represented by the following reaction pathways

\[
\text{Initiation} \quad \text{O}_2\text{(stable)} \rightleftharpoons 2\text{O}^- \quad \text{and} \quad \text{F}_2\text{(stable)} \rightleftharpoons 2\text{F}^- \quad (3.5)
\]

\[
\text{O}^- + \text{F}^- \rightarrow \text{OF}^- \quad \text{O}_2 \quad \text{F}^- \rightarrow \text{OF}_2\text{(stable)} \quad \text{O}_2\text{F}^- + \text{F}^- \rightarrow \text{O}_2\text{F}_2
\]

Higher oxygen fluorides, such as O₃F₂, are normally synthesized in a low temperature (-196 °C) electrical discharge and rapidly decompose to O₂ and F₂ at temperatures above -160 °C, and therefore are not encountered in the present work. From the above pathways, the only products expected to be observed, once the target environment has been returned to ambient conditions, are O₂, F₂ and OF₂. Reaction of the oxygen fluorides with nitrogen oxides, discussed earlier (Section 3.1.3), are secondary to the above reactions and would only affect the final ratio of stable products, not the pathways leading to their formation.

3.2 RESULTS AND DISCUSSION

During the production shoot, the only two chemical species present in the target are oxygen and fluorine. Considering the high temperatures and pressures within the target during irradiation, the formation of oxygen fluorides would be expected. Oxygen difluoride is the only stable oxygen fluoride under ambient conditions. During the synthesis of [¹⁸F]HF, total retention of the activity is expected at -94 °C. However, approximately 4% of the activity was lost when pumping between -196 and -94 °C (vapour pressures of OF₂ are 1 Torr and 23.3 atm. at -196 and -94 °C, respectively).
Figure 3.1. $^{19}$F NMR (282.409 MHz) of OF$_2$ recorded at -72 °C in HF solvent

(a) target gas, 62,565 scans and, (b) an authentic OF$_2$ sample, 250 scans;

$\delta = 250.9$ ppm, recorded at -72 °C in HF solvent
These observations are consistent with the vapour pressures for OF$_2$ at these temperatures. Consequently, $^{19}$F NMR was used to identify OF$_2$ as a substituent of the target mixture.

An authentic sample of OF$_2$, used as a reference, showed a single peak at $\delta(^{19}\text{F}) = 250.9$ ppm. The target sample, which was acquired overnight, clearly shows the same singlet at 250.9 ppm (Figure 3.1). Also, fluorine nitrate, which could be a possible impurity in the target mixture in the event that either $^{18}$O$_2$ gas or the F$_2$/Ne mixture were to contain nitrogen contaminants, was not observed.

Since OF$_2$ appeared to be the only other significant $^{18}$F-containing species in the target mixture, it was of interest to investigate the parameters that might determine the relative amounts of $[^{18}\text{F}]$OF$_2$ formed during the cyclotron irradiation process. The relative amount of $[^{18}\text{F}]$F$_2$ could be considered equivalent to the amount of $[^{18}\text{F}]$HF as the reaction of $[^{18}\text{F}]$F$_2$ with H$_2$ should be quantitative. In some cases, however, not all of the $[^{18}\text{F}]$F$_2$ was converted to $[^{18}\text{F}]$HF; the reasons for incomplete conversion remain unclear. Nonetheless, the determination of $[^{18}\text{F}]$OF$_2$ was not affected. The length of the production irradiation, the carrier fluorine target pressure for the recovery irradiation, and the relative amounts of $^{18}$O$_2$ present during the recovery irradiation, have all been independently varied, (Table 3.1).

The quantity of $[^{18}\text{F}]$OF$_2$ produced by the classic 2S method remained at approximately 4% ± 1% despite variation of the production irradiation time from 20 to 60 min. No significant trend was observed above the experimental error associated with separation of OF$_2$ and assaying of the $[^{18}\text{F}]$OF$_2$. The composition of the recovery irradiation target gas mixture was changed, first by increasing the amount of carrier
Table 3.1. Target Gas Analysis Data

EOB1, Irradiation Time Variation

<table>
<thead>
<tr>
<th>Expt</th>
<th>Production Irr.</th>
<th>Recovery Irr.</th>
<th>%^{19}F\text{OF}\text{2}</th>
<th>%^{18}F\text{HF}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min.</td>
<td>Amount 1%Fz, psi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>117</td>
<td>3.6</td>
<td>87.3</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>102</td>
<td>3.5</td>
<td>85.9</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>96</td>
<td>4.9</td>
<td>55.1</td>
</tr>
</tbody>
</table>

1\%Fz, EOBz, Target Mixture Variation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>%^{19}F\text{OF}\text{2}</th>
<th>%^{18}F\text{HF}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>30</td>
<td>170</td>
<td>4.0</td>
<td>58.3</td>
</tr>
<tr>
<td>5c</td>
<td>30</td>
<td>212</td>
<td>2.8</td>
<td>95.5</td>
</tr>
<tr>
<td>6c</td>
<td>30</td>
<td>170</td>
<td>7.0</td>
<td>59.5</td>
</tr>
</tbody>
</table>

Single Irradiation

7. 30 min.; 50 psi 5\%Fz in Kr plus 150 psi \text{^{18}O}_z

(a) Production irradiation beam currents were all 30 \mu A.

(b) Recovery irradiations were all 15\mu A for 15 min.

(c) Modified 2S method; 30 psi \text{^{18}O}_z was left in the target prior to the recovery irradiation.
fluorine (Table 3.1, experiment 4), and then by leaving a small charge of $^{18}$O$_2$ in the target during the recovery irradiation (a modified double irradiation). Finally, a classic 1S irradiation was performed.

It should also be noted that, because of limitations in the pumping system used to evacuate the target between the production and recovery bombardments, a small amount of $^{18}$O$_2$ was always present during the recovery irradiation.

Variation of the production irradiation parameters (strength of the beam current excluded) did not appear to have an effect on the relative amount of $[^{18}$F]OF$_2$ produced with this method. It was also apparent that the relative amount of $[^{18}$F]OF$_2$ produced was dependent upon the amounts of $^{18}$O$_2$ and carrier fluorine present during irradiation. Significantly more $[^{18}$F]OF$_2$ was produced relative to $[^{18}$F]F$_2$ for the 1S method demonstrated by the results in Table 3.1 (53.2% $[^{18}$F]OF$_2$).

### 3.3 CONCLUSIONS

The presence of $[^{18}$F]OF$_2$ in the target mixtures that resulted from classic double irradiation methods used to produce high specific activity $[^{18}$F]F$_2$ was most likely caused by trace amounts of $^{18}$O$_2$ that remained in the target during the recovery irradiations. Minimization of the amount of $[^{18}$F]OF$_2$ in target mixtures could be accomplished by the more efficient evacuation of the target before the recovery irradiation. Unfortunately, the pumping system was an integral part of the target support system and was not easily changed.

Conversely, OF$_2$ has been shown to be an alternative electrophilic fluorinating
agent. The results of this study demonstrate that the target mixture can comprise more than $[^{18}\text{F}]\text{OF}_2$. This compares with 10 - 20% reported for single and modified double irradiation procedures previously reported. The $[^{18}\text{F}]\text{OF}_2$ which could be separated from the $[^{18}\text{F}]\text{F}_2$ by removal of fluorine at -196 °C could be obtained in reasonable quantities. This, in turn, provides another $^{18}\text{F}$-labelled inorganic molecule available for radiochemical labelling.
CHAPTER 4
APPLICATION OF ¹⁸F TO THE INVESTIGATION OF THE
LEWIS ACID ACTIVATION OF F₂

4.1 INTRODUCTION

It is well known that some sort of activation of molecular fluorine is required before it is capable of oxidizing noble gases. Xenon gas can be oxidized to XeF₂ by simple exposure of Xe/F₂ mixtures to solar ultraviolet or thermal radiation;⁵⁸ the resulting fluoride is stable at room temperature as a crystalline solid. The analogous oxidation of krypton to KrF₂, which uses activation sources such as electrical discharge⁵⁹ or UV photolysis,⁶⁰ requires that the evolved fluoride be stabilized on a low temperature surface within the reactor. The formation of these noble-gas fluorides by the methods cited above involve the production and activation of fluorine atoms. Fluorine gas which can be thermally or photolytically dissociated, has a \( \Delta H_{\text{dissoc}} \) equal to 37.72 kcal mol⁻¹.⁶¹

The synthetic route to compounds such as XeF⁺AsF₆⁻, has traditionally begun with the preparation of the XeF₂, followed by reaction with a Lewis acid, such as AsF₅.⁶² The fluoride ion acceptor abilities of the Lewis acids BF₃, AsF₅, SbF₅, described by Bartlett and Robinson,⁶³ were demonstrated by the removal of a fluoride ion from IF₇ to produce the IF₆⁺ cation.⁶⁴ The fluoride ion acceptor abilities of the Lewis acids have been utilized to prepare many noble gas cations.⁶⁵ The first NF₄⁺ salts were prepared by reaction of mixtures of NF₃, F₂ and a Lewis acid, MF₅⁺ (M = B, As, an Sb).
Tolberg et al.\textsuperscript{66} prepared NF\textsubscript{4}\textsuperscript{+}SbF\textsubscript{6} at HF at 200 °C with a total pressure of 150 atm. At the same time, Christe et al.\textsuperscript{67} were able to prepare NF\textsubscript{4}\textsuperscript{+}AsF\textsubscript{6} in a glow discharge tube at -78 °C and a total pressure of 80 Torr. The corresponding boron salt was also prepared; however, independent workers noted that difficulty in synthesizing NF\textsubscript{4}\textsuperscript{+} salts increased with decreasing Lewis acidity.\textsuperscript{68,69} This suggested that the Lewis acid might have been responsible for the enhanced oxidizing ability of the fluorine.\textsuperscript{66} Original papers by Christe,\textsuperscript{70} however, postulated that the generation of either NF\textsubscript{3}\textsuperscript{+} or F\textsuperscript{+} radical cations, and subsequent reaction with F\textsubscript{2} or NF\textsubscript{3}, respectively, were responsible for the formation of NF\textsubscript{4}\textsuperscript{+} salts. These contradicting arguments provided no clear understanding as to what role the Lewis acids actually played in the synthesis of NF\textsubscript{4}\textsuperscript{+} salts.

Later,\textsuperscript{71} through kinetic studies of the decomposition of the salts NF\textsubscript{4}\textsuperscript{+}AsF\textsubscript{6} and NF\textsubscript{4}\textsuperscript{+}BF\textsubscript{4}, the following reversible reaction mechanism was elucidated

\begin{equation}
NF_3 + F_2 + MF_n \rightarrow NF_4^+[MF_{n+1}] \tag{4.1}
\end{equation}

\begin{align}
F_2 & \rightleftharpoons 2F^- \tag{4.2} \\
F^- + NF_3 & \rightleftharpoons \cdot NF_4 \tag{4.3} \\
\cdot NF_4 + AsF_5 & \rightleftharpoons \cdot NF_3^+AsF_6^- \tag{4.4} \\
\cdot NF_3^+AsF_6^- + F^- & \rightleftharpoons NF_4^+AsF_6^- \tag{4.5}
\end{align}

In equation (4.4), the Lewis acid, AsF\textsubscript{5}, can be seen to act merely as a fluoride ion acceptor, stabilizing the \cdot NF\textsubscript{3}\textsuperscript{+} radical cation. Recombination of \cdot NF\textsubscript{3}\textsuperscript{+} with the fluorine
atoms, produced by thermal or UV-irradiation in equation (4.2), results in the formation of the NF$_4^+$ cation. The Lewis acid cannot truly be described as an activator in this reaction as neither the oxidation state nor the oxidizing power of the nitrogen species are increased as a result of interaction with the Lewis acid (equation (4.4)). Formal oxidation of the nitrogen by atomic fluorine occurs in steps (4.3) and (4.5), neither of which involves any interaction with molecular AsF$_5$. Consequently, dissociation of F$_2$ alone, by thermal or UV-irradiation, is the activation step for the reaction pathway.

The first authentic demonstration of Lewis acid enhancement of the oxidizing power of fluorine was by the spontaneous reactions of xenon, fluorine and antimony pentafluoride.$^{32}$ Equimolar mixtures of the Xe and F$_2$ were found to react spontaneously in the presence of liquid SbF$_5$ at room temperature, without the use of UV-radiation to give pale yellow solutions characteristic of the XeF$_2^+$ cation (equation 4.6)

\[
\text{Xe} + \text{F}_2 + 2\text{Sb}_2\text{F}_{11}^- \rightarrow \text{XeF}_2^+\text{Sb}_2\text{F}_{11}^-. \tag{4.6}
\]

The labile intermediate emerald green Xe$_2^+$ cation was formed from the reaction between the XeF$_2^+$ cation and elemental xenon according to equation (4.7)

\[
3\text{Xe} + 3\text{XeF}_2^+\text{Sb}_2\text{F}_{11}^- + 2\text{SbF}_5 \leftrightarrow 2\text{Xe}_2\text{Sb}_2\text{F}_{11}^-\cdot\text{XeF}_2^+\text{Sb}_2\text{F}_{11}^- \tag{4.7}
\]

Depletion of the Xe followed by further oxidation of Xe$_2^+$ by excess F$_2$ and SbF$_5$ resulted in complete oxidation to Xe(II) to form the XeF$_2^+$ cation.
The Xe$^+_2$ cation was identified by its stretching band at 123 cm$^{-1}$ in the Raman spectrum.$^{72}$ Stein was the first to propose a binary interaction between the molecular fluorine and the Lewis acid.$^{32}$

$$\text{SbF}_5 + F_2 \rightarrow F_5\text{SbF}^5\cdot\cdot\cdot\text{F}^8$$  \hspace{1cm} (4.8)

Enhanced oxidizing abilities of Lewis acid-elemental fluorine combinations, had also been observed in the synthesis of O$_2^+$AsF$_6^-$ from O$_2$, F$_2$, and AsF$_5$, but only through photochemical$^{73}$ or thermal$^{74}$ activation of the mixture. Stein$^{32}$ also attempted to synthesize the dioxygenyl salt from O$_2$ and the F$_2$/SbF$_5$ combination but no reaction was observed.

Recently, Bartlett et al.$^{33}$ observed that xenon gas was oxidized to the XeF$^+$ and Xe$^+_2$F$_3$ salts by F$_2$ in the presence of liquid AsF$_5$, and to XeF$_2$ by F$_2$ in the presence of the weak Lewis acid, anhydrous HF. Attempted oxidation of O$_2$ by F$_2$/AsF$_5$ mixtures failed as it did in the work by Stein.$^{32}$

The electron affinities for the general reaction

$$e + \frac{1}{2}F_{2(g)} + A_{(g)} \rightarrow AF^-_{(g)}$$  \hspace{1cm} (4.9)

were determined for A = BF$_3$, GeF$_4$, AsF$_5$, to be 152, 161, and $> 171$ kcal mol$^{-1}$, respectively.$^{75}$ The electron affinity of PtF$_6$ (184 kcal mol$^{-1}$), which forms the dioxygenyl salt, O$_2^+$PtF$_6^-$, in its reaction with molecular O$_2$, is only marginally higher than that of AsF$_5$. It may therefore be inferred that the electron affinity of the F$_2$/SbF$_5$ complex must
be comparable to that of PtF$_6$. Therefore, based solely on the electron affinity values, F$_2$/A combinations for the stronger Lewis acids would be expected to be as capable of oxidizing oxygen to O$_2^+$, as PtF$_6$. The thermodynamics for the O$_2$ and noble gas systems have been considered$^{33}$ and the results suggest the Lewis acid/F$_2$ oxidation pathway is only suitable for "F" acceptors such as the noble gases, and not for single electron donors such as O$_2$.$^{76}$ In the latter case, oxidation occurs as a result of electron transfer, driven by the electron affinity of an oxidizing species, e.g. PtF$_6$.

4.2 RESULTS AND DISCUSSION

4.2.1 Exchange in the Binary System

The binary AsF$_5$/F$_2$ system has been studied with use of either $[^{18}\text{F}]$AsF$_5$ or $[^{18}\text{F}]$F$_2$ as the radiofluorine label. The theoretical distribution for a rapid random exchange of the fluorines between the two species would lead to a relative $^{18}\text{F}$ distribution of 71.4% on AsF$_5$ and 28.6% on F$_2$. This assumes, however, that the exchange is fast and fluorine is completely scrambled within the time constraints of the experiment, which is, in turn, determined by the 109.7 min. half-life of the $^{18}\text{F}$ isotope.

The experimental results (Table 4.1) demonstrate that the binary AsF$_5$/F$_2$ system does not undergo fluorine exchange at liquid AsF$_5$ temperatures, in the dark, and for F$_2$ pressures up to 4.5 atm over a period of up to 2 hrs. For the exchange reactions starting with $[^{18}\text{F}]$F$_2$, up to 1% of the initial activity is found to remain on the walls of the FEP reaction vessels. This phenomenon is most likely due to further passivation of the walls.
Table 4.1. $^{18}$F-Exchange Activities for the $[^{18}$F$]_{\text{AsF}_5}/\text{F}_2$ and $\text{AsF}_5/[^{18}$F$]\text{F}_2$ systems

<table>
<thead>
<tr>
<th>$^{18}$F Source</th>
<th>Conditions,°C.</th>
<th>Initial $^{18}$F, mCi</th>
<th>%$^{18}$F on AsF$_5^b$</th>
<th>%$^{18}$F on F$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. $[^{18}$F$]_{\text{AsF}_5}$</td>
<td>-60, dark</td>
<td>37.9</td>
<td>$\approx$100</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(71.4)</td>
<td>(28.6)</td>
</tr>
<tr>
<td>2. $[^{18}$F$]_{\text{F}_2}$</td>
<td>-70, dark</td>
<td>66.4</td>
<td>0.6</td>
<td>98.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(67.6)</td>
<td>(32.4)</td>
</tr>
<tr>
<td>3. $[^{18}$F$]_{\text{F}_2}$</td>
<td>-70, dark</td>
<td>41.8</td>
<td>0.4</td>
<td>$\approx$100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(83.3)</td>
<td>(16.7)</td>
</tr>
</tbody>
</table>

(a) All exchange experiments were performed in liquid AsF$_5$

(b) Percentages in parentheses are the absolute distributions for complete exchange calculated from the theoretical relative distribution and the mole ratio (1:1 in the experiments above).
of the vessel by fluorine. Therefore, the $^{18}\text{F}$ activity seen on AsF$_5$ (experiments 2 and 3, Table 4.1) can be attributed to wall passivation and is within the experimental error. Transfer of small amounts of $^{18}\text{F}$ activity onto the fluorine in the experiment employing $[^{18}\text{F}]\text{AsF}_5$ tracer may be due to trace impurities, such as HF, in the starting materials.

Absence of fluorine exchange in the binary system indicates, that any exchange of $^{18}\text{F}$ in the ternary systems must result from a chemical reaction or exchange between the products formed and the starting materials.

4.2.2 Evidence for the Existence of the AsF$_3$/F$_2$ Activated Complex

The existence of the AsF$_3$/F$_2$ activated complex, along with the suspected mechanism of the oxidation of xenon gas in the presence of molecular fluorine and liquid AsF$_5$, have been established.$^{31}$ Starting with $[^{18}\text{F}]\text{AsF}_5$, a significant fraction of the $^{18}\text{F}$ was transferred onto the relatively insoluble salt, XeF$^+$AsF$_6^-$, formed in the solution.

$$[^{18}\text{F}]\text{AsF}_5 + \text{F}_2 + \text{Xe} \rightarrow \text{F}_3\text{AsF}^+\text{XeF}^+ + \text{F}_2 + \text{AsF}_5 \quad (4.10)$$

Actual $^{18}\text{F}$ activity

|       | $1.9\% \pm 0.2\%$ | $0.0^a$ | $98\%^b$ |

(a) below measurable limits, (b) calculated by difference from $[^{18}\text{F}]\text{XeF}^+\text{AsF}_6^-$

Observation of the pale yellow salt (in the absence of HF) is in agreement with the results reported by Bartlett et al.$^{33}$ The absence of $[^{18}\text{F}]\text{F}_2$ in the separated products (equation 4.10) eliminated the possibility of a radical based mechanism being responsible for the
oxidation of xenon gas. Based on the $^{18}$F radiotracer results (Table 4.2), it was concluded that molecular fluorine was heterolytically cleaved as follows:

$$\text{Xe} + \text{F}_2 + \text{AsF}_5 \rightarrow \text{Xe} \cdots \underset{\delta^+}{\text{F}} \cdots \underset{\delta^-}{\text{F}} \cdots \text{AsF}_5 \rightarrow \text{XeF}^+\text{AsF}_6^- \quad (4.11)$$

The formation of the three bodied intermediate may in fact be preceded by the equilibrium,

$$\text{F}_2 + \text{AsF}_5 \rightleftharpoons \delta^+\text{F} \cdots \delta^-\text{F} \cdots \text{AsF}_5 \quad (4.12)$$

which produces the weakly bound, transient $\text{F}_2 \cdots \text{AsF}_5$ activated complex. A $^{19}$F NMR study of mixtures of gaseous $\text{F}_2$ and liquid $\text{AsF}_5$ at -78 °C did not reveal any significant change in the $\text{F}_2$ chemical shift relative to pure $\text{F}_2$. Interestingly, the rather broad linewidth of gaseous $\text{F}_2$ (approx. 10 ppm at half height) narrows dramatically when dissolved in $\text{AsF}_5$ (Figure 4.1). A small population of $\text{F}^-$ radicals, which are present in the gas phase, would be responsible for the line broadening. Once dissolved in the $\text{AsF}_5$, the $\text{F}^-$ radicals may then be sequestered by the solvent as $\text{AsF}_6^-$ radicals, ultimately narrowing the $\text{F}_2$ resonance. Nonetheless, the $\text{F}_2\cdots\text{AsF}_5$ complex could not be detected as changes in the $\text{F}_2$ chemical shift.

In comparison to the $\text{NF}_4^+$ formation mechanism, interaction of the Lewis acid in this case, results in the formation of a more oxidizing species, specifically, the $\text{F}^{8+}$. 
Table 4.2. Xe/F₂/AsF₅ ¹⁸F Exchange Experiments

<table>
<thead>
<tr>
<th>Expt.</th>
<th>¹⁸F Source</th>
<th>Initial ¹⁸F Activity, mCi</th>
<th>%¹⁸F exchanged</th>
<th>Conditions T, °C</th>
<th>P, atm</th>
<th>Rxn. time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[¹⁸F]-AsF₅</td>
<td>32.4</td>
<td>1.9 ± 0.2</td>
<td>-60</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>[¹⁸F]-F₂</td>
<td>41.9</td>
<td>6 ± 1</td>
<td>-70</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>[¹⁸F]-F₂</td>
<td>86.0</td>
<td>24 ± 1</td>
<td>-70</td>
<td>9</td>
<td>165</td>
</tr>
</tbody>
</table>

(a) All reactions were carried out in liquid AsF₅ in the dark with mechanical agitation.
Figure 4.1 $^{19}$F NMR (282.409 MHz) spectra of pure F$_2$ (top) and an F$_2$/AsF$_5$ mixture (bottom) recorded at -78 °C; $\delta = 424.6$ ppm, both spectra acquired in ca. 1000 scans.
The purpose of the present work is to investigate the same reactions beginning with radiolabelled $[^{18}\text{F}]\text{F}_2$. In this case, the AsF$_5$ was expected to act as both a source of unlabelled reactant for the activated complex and as a solvent for the oxidation reaction. In the absence of any extraneous exchange reactions, and assuming the reaction were to go to completion within the constraints of the isotopic half-life, the idealized $^{18}\text{F}$ distribution would be

$$
\begin{array}{c|c|c|c}
\text{Xe} & [^{18}\text{F}]\text{F}_2 & \text{AsF}_5\text{(excess)} & \rightarrow [^{18}\text{F}]\text{XeF}^+\text{AsF}_6^- + \text{AsF}_5 \\
100\% & 0\% & 100\% & 0\%
\end{array}
$$

However, it has been shown that reaction times on the order of days are required to achieve significant yields. Also, $^{19}\text{F}$ NMR studies have shown that exchange occurs between the AsF$_5$ solvent and AsF$_6^-$ anions. In excess AsF$_5$ solvent, the $^{18}\text{F}$ activity could be rapidly exchanged off the anion and on to the solvent according to equilibrium (4.14)

$$
[^{18}\text{F}]\text{AsF}_6^- + \text{AsF}_5\text{(excess)} \rightleftharpoons [^{18}\text{F}]\text{As}_2\text{F}_{11}^- \rightleftharpoons \text{AsF}_6^- + [^{18}\text{F}]\text{AsF}_5\text{(excess)}
$$

An additional exchange pathway is likely operative whereby the $^{18}\text{F}$ activity is transferred from the cation to the anion

$$
\text{AsF}_5 + [^{18}\text{F}-\text{Xe}^+]-\text{F-AsF}_5 \rightleftharpoons \text{AsF}_5--^{18}\text{F}-\text{Xe--F--AsF}_5 \rightleftharpoons [^{18}\text{F}]\text{AsF}_6^---\text{Xe-F} + \text{AsF}_5
$$
Owing to the small relative number of cation fluorines (1/7 of the total for XeF⁺AsF₆⁻) compared to the large excess of solvent fluorines, most of the ¹⁸F activity incorporated into the XeF⁺ cation by equation (4.13) is expected to be rapidly exchanged off the cation, ultimately finding its way to the solvent.

The experimental results in Table 4.2 are consistent with the activated-complex mechanism when the above exchange pathways are considered. In experiment #1, which used [¹⁸F]AsF₅ as the ¹⁸F source, no ¹⁸F was expected to be transferred to the fluorine if a free radical mechanism were operative.

\[
[¹⁸F]AsF₅ + F₂ + Xe \rightarrow [¹⁸F]F₂As⁻\overset{δ⁻}{\overset{δ⁺}{-}}F⁻\overset{δ⁺}{-}F⁻Xe \\
\text{F₂AsFXeF} + F₂ + AsF₅
\]  

(4.16)

Actual ¹⁸F activity  
1.9% ± 0.2% 0.0a 98%b

(a) below measurable limits, (b) calculated by difference from [¹⁸F]XeF⁺AsF₆⁻

The radiochemical yield was calculated as the amount of ¹⁸F activity transferred from the initial ¹⁸F source. For experiments which used [¹⁸F]F₂ and unlabelled AsF₅ solvent, the radiochemical yield was calculated as the amount of activity remaining in the reaction vessel after the [¹⁸F]F₂ was removed. For experiments in which [¹⁸F]AsF₅ is the initial radiofluorine labelled substance, the radiochemical yield was calculated as the amount of ¹⁸F activity remaining on the salt after both F₂ and AsF₅ had been removed.

The radiochemical yield can be correlated with the gravimetric yield based on the
activated-complex mechanism. If $F_2$ is the limiting reagent, the gravimetric yield can be calculated from the number of moles of $F_2$ initially present and the number of moles $Xe_2F_3^+AsF_6^-$ recovered after pumping the reaction vessel at room temperature. The salt, $XeF^+AsF_6^-$, is known to lose half a mole of $AsF_5$ when pumped under vacuum at ambient temperatures.\(^77\)

$$2XeF^+AsF_6^- \xrightarrow{\text{vac}} Xe_2F_3^+AsF_6^- + AsF_5\uparrow$$ \hspace{1cm} (4.17)

The experimental results are summarized in Table 4.3 and show that, based on the activated complex mechanism, the $^{18}F$ activity transferred can account for the mass of $Xe_2F_3^+AsF_6^-$ recovered at the end of the experiment. Furthermore, if the activated-complex mechanism is correct and rapid exchange occurs with the solvent, all $F$ sites in $XeF^+AsF_6^-$ should be equally populated by $^{18}F$.

When the reaction is carried out in a minimum of $AsF_5$ solvent (expt. 2; Table 3.2), the available fluorine sites on the solvent were reduced. Therefore, after removal of the $AsF_5$ solvent at $-78^\circ C$, a reasonable amount of the $^{18}F$ activity could be maintained on the $XeF^+AsF_6^-$ salt. Consequently, the removal of a mole of $AsF_5$ from 2 moles of $XeF^+AsF_6^-$ at room temperature should leave behind only 9/14 of the $^{18}F$ activity on the $Xe_2F_3^+AsF_6^-$ salt. The $^{18}F$ results for one such experiment are given in Table 4.4.

The composition of the salt after removal of the $AsF_5$ at $-78^\circ C$ was shown to be $XeF^+AsF_6^-$ by low-temperature Raman spectroscopy (Figure 4.1). The salt, $XeF^+AsF_6^-$,
Table 4.3. Correlation Between Radiochemical and Gravimetric Yields of XeF₄AsF₆

<table>
<thead>
<tr>
<th>Expt.</th>
<th>% Radiochemical Yieldᵃ</th>
<th>% Gravimetric Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>24 ± 1</td>
<td>21 ± 2</td>
</tr>
</tbody>
</table>

(a) Radiochemical yields are based on ¹⁸F activity transferred and are artificially high as they include small amounts of ¹⁸F activity adhering to the vessel walls.
Table 4.4. $^{18}$F Study of the Decomposition of XeF$^+$AsF$_6^-$ to Xe$_2$F$_3^+$AsF$_6^-$ Under Dynamic Vacuum

<table>
<thead>
<tr>
<th></th>
<th>% $^{18}$F remaining on the Xe$_2$F$_3^+$AsF$_6^-$ salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual*</td>
<td>Theoretical</td>
</tr>
<tr>
<td>After 1st pumping cycle</td>
<td>70</td>
</tr>
<tr>
<td>After 2nd pumping cycle</td>
<td>67</td>
</tr>
</tbody>
</table>

(a) The actual $^{18}$F activity is expected to be artificially high due to F$_2$ up take by the walls of the vessel.
Figure 4.2  Raman spectra of XeF$^+$AsF$_6^-$ (top) and Xe$_2$F$_3^+$AsF$_6^-$ (bottom)
was identified by the $\nu[\text{Xe-F}]$ stretching band at 607 cm$^{-1}$ and the $\nu[\text{Xe-\cdot-F}]$ bridging fluorine stretch at 345 cm$^{-1}$.

The salt, $\text{Xe}_2\text{F}_3^+\text{AsF}_6^-$, recovered after $\text{XeF}^+\text{AsF}_6^-$ was pumped on under high vacuum at room temperature, was identified by its three $\nu[\text{Xe}_2\text{F}_3^+]$ characteristic stretching bands at 586, 598, and 606 cm$^{-1}$ (Figure 4.2).

4.3 CONCLUSIONS

The $^{18}\text{F}$ studies of the Lewis acid enhanced oxidative fluorination of xenon have been studied by using $[^{18}\text{F}]\text{AsF}_5$ and $[^{18}\text{F}]\text{F}_2$ as radiotracer. The results are complicated by the exchange reactions that are found to occur between a newly formed $[^{18}\text{F}]\text{AsF}_6^-$ anion and an unlabelled $\text{AsF}_5$ solvent. When the $^{18}\text{F}$ source is $[^{18}\text{F}]\text{AsF}_5$ these exchange reactions are "invisible" since the activity is transferred from the solvent to the salt directly through the reaction

$$
\text{Xe} + \text{F}_2 + [^{18}\text{F}]\text{AsF}_5 \rightarrow \text{XeF}^+[^{18}\text{F}]\text{AsF}_6^-
$$

(4.18)

In this case, the amount of salt formed is small relative to the amount of the solvent, therefore, statistics do not favour exchange of $^{18}\text{F}$ activity off of the solvent. Of primary importance, was the absence of $[^{18}\text{F}]\text{F}_2$ which precludes the possibility of a radical mechanism.

Moreover, experiments that used $[^{18}\text{F}]\text{F}_2$ as an $^{18}\text{F}$ source provided direct observation of the fast exchange reactions that have been observed between the insoluble $\text{XeF}^+\text{AsF}_6^-$ salt and $\text{AsF}_5$ solvent.
The results observed in all of the above experiments are consistent with the Lewis acid enhanced oxidation of the noble-gas, xenon, which must proceed through a three-bodied intermediate (equation 4.11). Whether all three reactants, Xe, F₂ and AsF₅, combine in a concerted interaction, or are preceeded by the formation of a binary species, as of yet, cannot be differentiated. Nonetheless, the co-existence of molecular fluorine with a strong fluoride ion acceptor, such as AsF₅, results in a more strongly oxidizing environment towards weak electron donors such as noble-gases.
CHAPTER 5
ATTEMPTED PREPARATION OF HIGHER OXIDIZING SPECIES USING
THE LEWIS ACID-F\textsubscript{2} ACTIVATED COMPLEX

5.1 INTRODUCTION

5.1.1 Oxidative Fluorinators and the Oxidizer Strength Scale

The activated complex, F\textsubscript{5}As--F-F, is an oxidative fluorinator as it has been shown that a formal "F\textsuperscript{*}" is transferred from the activated complex to the xenon atom. Consequently, it should be possible to determine the relative oxidizing strength of the activated complex experimentally. A major difference between F\textsubscript{5}As--F-F and other oxidative fluorinators, is that it is a transient binary species involving two reactant molecules, and consequently, must have a very large equilibrium dissociation constant. In comparison, the reaction between a 2 : 1 mole ratio of ClF and AsF\textsubscript{5}, results in the formation of Cl\textsubscript{2}F\textsuperscript{*}AsF\textsubscript{6},\textsuperscript{71} a stable oxidative fluorinating salt capable of oxidizing xenon gas to Xe\textsubscript{2}F\textsubscript{3}\textsuperscript{+}.\textsuperscript{70}

Recently, Christe, \textit{et al.}\textsuperscript{3} developed a quantitative scale relating oxidizing strengths of oxidative fluorinators. The strength of an oxidative fluorinator can be discussed in terms of the F\textsuperscript{*} detachment energy (FPD). The FPD is expressed relative to that of the hypothetical free F\textsuperscript{*} cation, which is assigned a value of 0 kcal mol\textsuperscript{-1}, and represents the amount of energy required for the reaction step

\[
\text{XF}^{\text{+}}_{\text{oxid}} \rightarrow \text{X}_{\text{prod}} + \text{F}^{\text{+}} \quad \text{(for X = Kr, FPD = 115.9 kcal mol}^{-1}) \quad \text{(5.1)}
\]
For any oxidative fluorinator, there is a conjugate, non-oxidized form \( X_{\text{prod}} \), eq. (5.1) analogous to the conjugate acid/base pairs in the Brønsted description of protonic acids and bases. The above equation represents a reductive half reaction and therefore the FPD value is positive. If the half reaction were to occur in the reverse direction, i.e., the oxidation of a substrate by "F⁺" attachment, then the FPD value would be negative.

The first step in the oxidative fluorination of xenon gas by KrF⁺ is well established and serves as a good example of an oxidative fluorination reaction.

\[
\text{KrF}^+ + \text{Xe} \rightarrow \text{XeF}^+ + \text{Kr}
\]

(5.2)

With excess KrF⁺, the reaction can proceed all the way to Xe(VI), namely the XeF₅⁺ cation, which has an FPD of 158.9 kcal mol⁻¹, just above XeF⁺ on the oxidizer strength scale. The \( \Delta H^\circ_{\text{reaction}} \) for equation (4.2) can be calculated from the FPD values for KrF⁺ and XeF⁺ listed in the oxidizer scale.

\[
\Delta H^\circ = \text{FPD}^{\text{(oxid)}} - \text{FPD}^{\text{(prod)}}
\]

(5.3)

The FPD of XeF⁺ is negative with respect to xenon since the half reaction involves formal "F⁺" attachment or an oxidation reaction. The FPD values for KrF⁺ and XeF⁺ taken from the oxidizer strength scale are 115.9 and 164.8 kcal mol⁻¹, respectively. Therefore, the calculated enthalpy of reaction, \( \Delta H^\circ = -48.9 \text{ kcal mol}^{-1} \), predicts an exothermic reaction.

The FPD values for unknown species, such as ArF⁺, have been calculated by using
the local density functional method. The oxidizer strength scale reproduced from ref. (7) is given in Appendix 1.

Experimentally, the strength an oxidizer can be compared with that of a second oxidizer by reacting the conjugate pairs (as in equation (5.2)). Obviously, reaction (5.2) would not proceed in the reverse direction as XeF is not a strong enough oxidizer to oxidize krypton. Nonetheless, the experiment could be attempted from either side of the reaction and still provide the same answer. For an oxidizer of unknown strength, such as the Lewis acid/F \textsubscript{2} activated complexes, a series of experiments of the general form

\[ \text{A--F-F } + \text{D } \rightarrow \text{AFDF}^+ \]  

where, A--F-F, represents the activated complex and D represents the reduced form of any oxidative fluorinator, can be performed to determine the oxidizing strength of the activated complex relative to other known oxidative fluorinators.

### 5.1.2 Mechanistic Suitability and Unknown Oxidizers

The Lewis acid/F \textsubscript{2} activated complex will function as an oxidizer only in the presence of a suitable substrate. Unlike other oxidative fluorinators which can be prepared and isolated as stable salts, the activated complex must be thought of as a transient species of enhanced oxidizing ability. The results from Chapter 4 have demonstrated that the oxidation of xenon by the activated complex does not proceed via a radical mechanism; consequently, the reaction proceeds without activation from external energy...
sources or radical initiation and propagation. As a result of these observations, the role of the substrate as a facilitator of the reaction must be considered. Specifically, attention must be paid to the suitability of a substrate to form a three bodied intermediate with the activated complex.

Whether or not an intimate, albeit short-lived, interaction occurs between a Lewis acid and fluorine in the absence of a donor substrate,

$$\text{MF}_{n-1} + \text{F}-\text{F} \rightleftharpoons [\text{MF}_{n-1}^{\text{a}}\text{F}^{\text{a}}\text{F}^{\text{a}}]$$  \hspace{1cm} (5.5)

the reactive site of the transition state consists of a three bodied interaction involving the activated complex and a donor species, $[\text{MF}_{n-1}^{\text{a}}\text{F}^{\text{a}}\text{F}^{\text{a}}\text{D}]$.

Oxidative fluorinators that have yet to be isolated as stable salts are dispersed throughout the oxidizer scale. Many of these species have FPD energies much greater (weaker oxidative fluorinator) than KrF$^+$. The inability to prepare such species may therefore be a result of kinetic rather than thermodynamic barriers. The oxidation of xenon by the Lewis acid-F$_2$ activated complex provides the most direct method to the preparation of XeF$^+$; the traditional method involves the formation of the neutral difluoride followed by fluoride ion abstraction using a strong fluoro acid such as AsF$_5$.$^4$ If the only method for the synthesis of more powerful oxidative fluorinators, such as ArF$^+$ and OF$_3^+$, is

$$\text{DF}_m + \text{MF}_{n-1} \rightarrow \text{DF}_{m-1}^+\text{MF}_n^-$$  \hspace{1cm} (5.6)
where $MF_{n-1}$ is a fluoro-acid, $DF_m$ is a neutral fluoride

then the nonexistence of the neutral fluoride might prevent the preparation of the potentially stable salt. In the case of the argon system where the $ArF_2$ molecule is predicted to be unbound,\textsuperscript{78} the salts, $ArF^+SbF_6^-$ and $ArF^+AuF_6^-$, are predicted to be stable.\textsuperscript{79} A synthetic route which does not require a stable neutral fluoride, such as $ArF_2$, may provide an alternative for the synthesis of stable salts of powerful oxidative fluorinators.

5.2 RESULTS AND DISCUSSION

5.2.1 Attempted Synthesis of OF$_3^+$AsF$_6^-$

If a synthetic route analogous to that used for the formation of $KrF^+$\textsuperscript{4} were to be applied to the preparation of $OF_3^+$, the neutral molecule $OF_4$ would first have to be synthesized. Electrical discharge and UV-irradiation experiments which were successful in the preparation of higher oxygen fluorides, have not shown any evidence for the existence of $OF_4$.\textsuperscript{52} Alternatively, the oxidizer scale predicts that the reaction between $KrF^+$ and $OF_2$ should produce $OF_3^+$.

$$KrF^+ + OF_2 \rightarrow OF_3^+ + Kr \quad (\Delta H^o = - 6.3 \text{ kcal mol}^{-1})$$ (5.7)

However, previous attempts at this reaction have not shown any evidence for the
formation of $\text{OF}_3^+$.

The following reaction was attempted at -70 °C in the dark:

$$\text{AsF}_5 + F_2 + \text{OF}_2 \rightarrow \text{OF}_3^+\text{AsF}_6^- \quad (5.8)$$

However, there was no visual evidence for the reaction which might have been indicated by the precipitation of a stable salt in the AsF$_5$ solvent.

5.2.2 Attempted Synthesis of KrF$^+$ Salts of the Lewis Acids AsF$_5$ and SbF$_5$

Krypton gas was substituted for Xe to determine if the Lewis acid-F$_2$ activated complex was strong enough to oxidize krypton gas to KrF$^+$.

$$\text{Kr} + F_2 + \text{AsF}_5 \rightarrow \text{KrF}^+\text{AsF}_6^- \quad (5.9)$$

The reaction was first performed with unlabelled F$_2$ to determine whether the stable salt could be prepared in macroscopic amounts. A small amount of residue was obtained at -70 °C in the liquid AsF$_5$, however, it was not thermally stable when pumped on at room temperature. The residue was tested for the presence of a strong oxidizer by dissolving the solid in BrF$_5$ and then warming. If KrF$^+$ were present, the following reaction should have occurred$^5$

$$\text{KrF}^+\text{AsF}_6^- + \text{BrF}_5 \rightarrow \text{BrF}_6^+\text{AsF}_6^- + \text{Kr} \quad (5.10)$$
Evidence for the above reaction, and consequently the oxidation of krypton to Kr(II) by the activated complex, would have been indicated by the evolution of krypton gas from the solution, or by the observation of the $^{19}\text{F}$ NMR spectrum of BrF$_6^+$ at approximately 340 ppm relative to CFCl$_3$. The $^{19}\text{F}$ resonance of BrF$_6^+$ would be split into four lines by spin-spin coupling of to each of the spin 3/2 nuclei of bromine, $^{79}\text{Br}$ and $^{81}\text{Br}$ (50.69% and 49.31% natural abundances, respectively), for a total of eight lines. Consequently, if the yield of KrF$^+$ (produced by equation (5.9)) were very low, the corresponding yield of BrF$_6^+$, observed as an 8-line multiplet, might be imperceptible. No multiplet was observed in the $^{19}\text{F}$ region around 340 ppm after 11,500 scans, however, whether this was due to an extremely low yield or complete absence of BrF$_6^+$, could not be determined. Consequently, no clear evidence was available for reaction (5.9).

Nonetheless, because of the presence of the unknown residue, the Kr/F$_2$/AsF$_5$ reaction was studied with [18F]-F$_2$. The results of two experiments with krypton plus two background experiments are given in Table 5.1. An unknown solid was later observed in solutions containing only AsF$_5$ and F$_2$ after several minutes of exposure and therefore was presumed to be inert fluorinated plastic that had sloughed from the walls of the reaction vessel.

The $^{18}\text{F}$ activity transferred from the [18F]-F$_2$ to the AsF$_5$ solvent in the binary system was less than the background error associated with the [18F]-F$_2$ passivation of the reaction vessel. In the krypton system, however, a small percentage of the $^{18}\text{F}$ activity
Table 5.1. Comparative $^{18}\text{F}$ Exchange Values for the Kr/$[^{18}\text{F}]\text{F}_2$/AsF$_5$, AsF$_5$/[$^{18}\text{F}$]F$_2$, and Xe/$[^{18}\text{F}]\text{F}_2$/BF$_3$ Systems

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Initial $^{18}\text{F}$, mCi</th>
<th>$%^{18}\text{F}$ transferred</th>
<th>Reaction Time, hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AsF$_5$/F$_2$</td>
<td>41.8</td>
<td>0.4 ± 0.4</td>
<td>1</td>
</tr>
<tr>
<td>AsF$_5$/F$_2$</td>
<td>66.4</td>
<td>0.6 ± 0.6</td>
<td>$\frac{1}{2}$</td>
</tr>
<tr>
<td>Kr/F$_2$/AsF$_5$</td>
<td>30.3</td>
<td>4.6 ± 1.9</td>
<td>1</td>
</tr>
<tr>
<td>Kr/F$_2$/AsF$_5$</td>
<td>24.9</td>
<td>2.4 ± 2.0</td>
<td>2</td>
</tr>
<tr>
<td>Xe/F$_2$/BF$_3$</td>
<td>42.3</td>
<td>0.8 ± 0.8</td>
<td>1</td>
</tr>
</tbody>
</table>
appeared to have been transferred off the $[^{18}\text{F}]\text{F}_2$. The percentage of activity transferred was, at best, only twice the magnitude of the background error margins. In addition, there was a paradoxical relationship between $^{18}\text{F}$ activity transferred and exchange time. Nonetheless, the presence of krypton gas with the AsF$_5$/F$_2$ system seemed to influence the extent to which the $^{18}\text{F}$ activity was exchanged.

In the absence of any chemical or physical evidence for the formation KrF$^+$AsF$_6^-$ salt, and, if the $^{18}\text{F}$ results are considered to be significant, an alternative explanation for the $^{18}\text{F}$ activity transfer must be sought. Possibly, a weak three bodied intermediate of the form Kr--$^5\text{F}$-F--AsF$_5$, which unlike the xenon system, does not result in the heterolytic cleavage of the molecular fluorine bond, is capable of lowering the activation barrier for fluorine exchange in the AsF$_5$-F$_2$ system.

Whether or not the $^{18}\text{F}$ results were real or an artifact of the $[^{18}\text{F}]\text{F}_2$ passivation of the apparatus, could not conclusively be determined. Interestingly, the system Xe/F$_2$/BF$_3$, which was reported by Bartlett et al. not to form the salt XeF$^+$BF$_4^-$, did not display any significant transfer of $^{18}\text{F}$ activity off of the $[^{18}\text{F}]$-F$_2$ (Table 5.1). The expected correlation between Lewis acidity and the oxidizing strength of the Lewis acid-F$_2$ complex, supported the results. It appeared that the $^{18}\text{F}$ tracer being used was sensitive enough to distinguish between the different systems. However, Bartlett also reported that attempts to prepare KrF$^+$ salts at low temperatures, using the conditions analogous to those used for the oxidative fluorination of Xe, had failed. Nonetheless, the $^{18}\text{F}$ experiments in this work could not rule out any interaction within the system.

An attempt was made to prepare KrF$^+$SbF$_6^-$ from Kr, F$_2$, and an HF/SbF$_5$ slurry
but failed to produce the salt. It was anticipated that the stronger fluoride ion acceptor would produce a more polarized \( \delta^+F \) capable of oxidizing Kr. Unfortunately, since the KrF\(^+\) salts are less stable than the corresponding XeF\(^+\) salts, lower temperatures would be preferred for the formation of the KrF\(^+\) salts. An \(^{18}\text{F}\) experiment involving pure liquid SbF\(_5\) (free of HF), which is quite viscous even at room temperature, was not attempted. Also, it would have been difficult to separate the salt from the SbF\(_5\) solvent once the reaction was completed.

5.3 CONCLUSIONS

Attempts to prepare stronger oxidative fluorinators than XeF\(^+\) salts with use of a Lewis acid/F\(_2\) activated complex failed. Fluorine-18 tracer studies of the Kr/F\(_2\)/AsF\(_5\) system failed to provide conclusive evidence concerning the nature of the interaction within the system. From the small, though significant amount of \(^{18}\text{F}\) transfer between the \([^{18}\text{F}]\text{F}_2\) and the AsF\(_5\) solvent when krypton was present, it is suggested that there is an association between Kr and the AsF\(_5\)-F\(_2\) activated complex.

Lewis acidity has been shown to affect the strength of the corresponding activated complex with F\(_2\). Consequently, the stronger F\(^-\) acceptor, SbF\(_5\), was used as a superacid solution with HF, F\(_2\) and Kr, but, no evidence for reaction was obtained. Whether or not the activated complex could still form with the H\(^+\)SbF\(_6\)- superacid remains unclear.

The apparent inability of the AsF\(_5\)-F\(_2\) activated complex to oxidize krypton to Kr(II) and OF\(_2\) to OF\(_3\)^+ places the activated complex between XeF\(^+\) and OF\(_3\)^+ on the oxidizer strength scale. The oxidative fluorinator N\(_2\)F\(^+\) has an FPD energy of
139.3 kcal mol\(^{-1}\), approximately halfway between XeF\(^+\) and KrF\(^+\).

\[ \text{N}_2 + \text{F}_2 + \text{AsF}_5 \rightarrow \text{N}_2\text{F}^+\text{AsF}_6 \]  \hspace{1cm} (5.11)

The above reaction could proceed via a reaction that is similar to the mechanism followed by the noble-gas system. Determining the spontaneity of this reaction would narrow the range in which the AsF\(_5\)-F\(_2\) activated complex would fit on the oxidizer strength scale.
CHAPTER 6
POSSIBLE USE OF CsSO₄F AS AN ¹⁸F INORGANIC PRECURSOR FOR THE
REGIOSPECIFIC ELECTROPHILIC FLUORINATION OF
AROMATIC AMINO ACIDS

6.1 INTRODUCTION

Incorporation of fluorine into organic compounds has important chemical and
pharmaceutical implications; however, the problem differs considerably from those
concerning other halogen atoms.⁸¹ Fluorine is highly reactive and therefore difficult to
control, consequently, alternative methods of incorporating fluorine into organic
compounds must be made available. The number of possible reagents capable of this task
is limited and even fewer are suitable for mild reaction conditions at room temperature.
A recent review lists all the nucleophilic and electrophilic sources of fluorine available
for the selective formation of C-F bonds.⁸²

Substitution of fluorine into organic molecules often produces derivatives with
similar and even enhanced biological activity.¹⁰,⁸³ Fluorine has a very small steric size,
and exhibits high carbon-fluorine bond energies, consequently, it is an ideal substitute for
hydrogen in organic systems.

There is considerable interest in the ability to substitute ¹⁸F onto biologically active
aromatic amino acids. For example, 3,4-dihydroxyphenylalanine (L-dopa) is metabolized
in the brain to dopamine, a neurotransmitter, by the enzyme aromatic acid decarboxylase
(AADC). The inactivity of AADC and subsequent deficiency of dopamine in the brain, leads to Parkinson's disease. It has been shown that monofluorinated derivatives (specifically $[^{18}F]6$-fluorodopa) retain much of the biological activity of the parent molecule, consequently, much effort has gone into the preparation of $^{18}F$ labelled biological tracers of this type.

6.1.1 Cesium Fluoroxy sulphate and Other Electrophilic Fluorinating Agents

Fluoroxy sulphate was first noted by Fichter as a "vergängliches Oxidationsmittel" in 1926, but was not successfully purified and characterized in the form of a stable salt until 1979 when Appleman et al. prepared and characterized $M^+SO_4F^- (M = Rb, Cs)$. The $SO_4F^-$ ion was the first example of an ionic hypofluorite, and since, has attracted considerable attention concerning its properties and reactivity. The cesium and rubidium salts of $SO_4F^-$ were found to be stable when stored at temperatures less than 0 °C and only decomposed slowly at room temperature according to the equation

\[
MSO_4F^- \rightarrow MSO_3F^- + \frac{1}{2}O_2
\]  

(6.1)

Investigations into the decomposition and reactivity of $SO_4F^-$ in aqueous media determined that it decomposed to form $O_2$, $H_2O_2$, $FSO_3^-$ and $HSO_3^-$ at room temperature. Later, it was determined that $SO_4F^-$ was stable in CH$_3$CN for a period of hours, and consequently, this solvent provided a suitable media for the first reactions between $SO_4F^-$ and aromatic compounds. Other electrophilic fluorinating agents, including molecular
fluorine itself, will substitute fluorine for hydrogen on aromatic compounds under controlled reaction conditions.\textsuperscript{89} The reactivity and selectivity of \( \text{F}_2 \) towards aromatic amino acids such as tyrosine, \( m \)-tyrosine and 3,4-dihydroxyphenylalanine have been studied using low specific activity \([^{18}\text{F}]\text{F}_2\).\textsuperscript{90} Successful \(^{18}\text{F}\) substitution of fluorine onto the aromatic ring has been obtained by low temperature fluorinations with dilute fluorine (1\% \( \text{F}_2 \) in Ne) in various acid media\textsuperscript{90} (equation 6.2, fluorination of L-dopa in HF/BF\(_3\), \( R = \text{OH} \))

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOH} \\
\text{R} & \quad \text{OH} \\
\text{F}_2 & \quad \rightarrow \\
\text{NH}_2 & \quad \text{COOH} \\
\text{R} & \quad \text{OH}
\end{align*}
\]

Regiospecific selectivity of the fluorine substitution was found to be controlled by the acidity of the solvent used.

Trifluoromethyl hypofluorite, CF\(_3\)OF, has been shown to fluorinate activated aromatic systems\textsuperscript{91} but the high toxicity and extreme reactivity of the reagent gas demand stringent safety precautions to be part of any experimental procedures involving CF\(_3\)OF.

The electrophilic fluorination chemistry of acetyl hypofluorite, CH\(_3\)COOF, has
been well developed.\(^{82}\) Also, its application to the field of nuclear medicine has been demonstrated by the successful preparation of \([^{18}\text{F}]-\text{CH}_3\text{COOF}\) from \([^{18}\text{F}]-\text{F}_2\) and acetate salts,\(^{92,93}\) and the subsequent production of \(^{18}\text{F}\)-labelled aromatic amino acids.\(^8\) Regiospecific production of \([^{18}\text{F}]-6\)-fluorodopa was achieved from an aryl mercury derivative of L-dopa functionalized at the 6-position and \([^{18}\text{F}]-\text{CH}_3\text{COOF}\).\(^{94}\)

The reaction chemistry of \(\text{XeF}_2\) with organic compounds has been reviewed.\(^{95}\) Xenon difluoride has been labelled with \(^{18}\text{F}\) and used for the selective fluorination of aromatic amino acids,\(^{96,97}\) however, due to poor radiochemical yields and the high costs of the starting materials, \(\text{XeF}_2\) has not been considered a viable electrophilic fluorinator for radiotracer work.

**6.1.2 Regiospecific Nature of \(\text{Cs}^+\text{SO}_4\text{F}^-\)**

The first reports that \(\text{Cs}^+\text{SO}_4\text{F}^-\) is a good candidate for the electrophilic fluorination of aromatic compounds were based on the results from \(\text{BF}_3\) catalyzed reactions of \(\text{SO}_4\text{F}^-\) in \(\text{CH}_3\text{CN}\) with benzene, toluene, biphenyl and naphthalene.\(^6,98\) All of the reactions gave monofluorinated compounds as the major product. Selective fluorination was observed for several compounds,\(^98\) the simplest example of which was the preferential production of 1-fluoronaphthalene over 2-fluoronaphthalene in a 5:1 ratio. Typical reaction times were 4-5 hours.

Progress has also been made towards the regioselective introduction of fluorine into aromatic molecules using \(\text{SO}_4\text{F}^-\) via fluoro-destannylation of aryl\(^{99}\) and heteroaryl
Fluoro-substituted indoles were prepared by fluorination of trimethylstannyl indole derivatives with solutions of CsSO₄F in methanol.

The most recent method for the selective fluorination of aromatics with CsSO₄F has demonstrated that SO₄F⁻ in CH₃CN will displace hydroxyalkyl substituents on aromatic rings.

For the reaction of CsSO₄F with 4-methoxybenzyl alcohol, a 70 % yield of the
monofluorinated product was recovered after one hour. It was noted that the yields for these type of reactions improved with the increasing electron donating ability of the R group attached para to the hydroxalkyl leaving group. This was an excellent indication that the SO$_4$F$^-$ ion had an increased reactivity towards electron rich or activated carbon centres.

The purpose of the current work was to obtain some preliminary results concerning the reactivity of fluoroxysulphate towards aromatic amino acids such as L-dopa, the compatibility and optimization of reaction conditions and solvents, and the regiospecific nature of the reagent towards substrates of this type.

6.2 RESULTS AND DISCUSSION

6.2.1 NMR Spectroscopy of Cs$^+$SO$_4$F$^-$

Fluorine-19 NMR spectroscopy was used to identify Cs$^+$SO$_4$F$^-$ as the major product in the reaction. The ratio of the peaks arising from SO$_4$F$^-$ and FSO$_3^-$ resonances gave a crude estimate of the purity of the product. Since fluorosulphate is not expected
to have any effect on the fluorination reactions to be studied, rigorous purification of the product was not deemed necessary.

In CH₃CN, the chemical shifts (Figure 6.1) of Cs⁺SO₄F⁻ and Cs⁺FSO₃⁻ were found to be 131.9 and 37.7 ppm, respectively (132.3 and 37.5, Appelman et al.). Both of these signals appeared as singlets as a result of the unique fluorine environments. The chemical shifts in H₂O were 153.5 ppm for SO₄F⁻ and 37.3 ppm for FSO₃⁻.

The ratio of the peak intensities for SO₄F⁻ to FSO₃⁻ for the NMR sample of the product was 15.7 to 1.5. This corresponds to 92.3% fluoroxysulphate. Since the decomposition of fluoroxysulphate follows the equation,

\[
\text{SO}_4\text{F}^- \rightarrow \text{FSO}_3^- + \frac{1}{2} \text{O}_2
\]

fluorosulphate is expected to be the only fluorine containing solid contaminant in a dried product. No other fluorine containing species were seen in the ¹⁹F NMR spectrum. It was therefore concluded that the value obtained from the relative integrated peak intensities was a reasonable estimate for the purity of the product.

6.2.2 Aqueous Decomposition Study and ¹⁸F Tracer Experiment

A ¹⁹F NMR investigation into the decomposition of SO₄F⁻ in H₂O shed further light on the difficulty of obtaining a truly pure fluoroxysulphate sample considering that each step of the synthesis, including the purification step, was carried out under aqueous
Figure 6.1  Fluorine-19 NMR spectrum (470.600 MHz) of Cs\(^+\)SO\(_4\)F\(^-\)
recorded at 30 °C in CH\(_3\)CN; (a) SO\(_4\)F\(^-\) and (b) FSO\(_3\)\(^-\).
conditions. After ten minutes in water, the ratio of the peak intensities is 8.03 : 2.14 for SO$_4$F$^-$ to FSO$_3^-$ (Figure 6.2). The spectrum collected at 30 minutes showed a ratio of 1.49 : 12.46, indicating almost all of the fluoroxysulphate was converted to fluorosulphate (Figure 6.2).

The results of these room temperature spectra emphasize the importance of consistently maintaining low temperatures throughout each step of the synthesis. In addition, the purification step, which attempts to remove the water soluble fluorosulphate from the fluoroxysulphate, will inherently induce slow decomposition of the desired product.

Production of [$^{18}$F]Cs$^+SO_4$F$^-$ from the reaction of [$^{18}$F]F$_2$ with CsSO$_4$(aq), followed directly by fluorination of the organic substrate with aqueous SO$_4$F$^-$ may have been viable if the SO$_4$F$^-$ ion was sufficiently stable in water. However, at room temperature, the decomposition of SO$_4$F$^-$ appears to be too rapid to allow a fluorination reaction to compete with the decomposition. An $^{18}$F tracer experiment revealed no fluorinated products (Section 2.8.3.) thus confirming the hypothesis.

6.2.3 Separation and Identification of Fluorinated Products from Low Temperature Reactions

The desired product of the reaction between L-dopa and SO$_4$F would be 6-fluoro-L-dopa as it is this isomer that retains the most biological activity in the brain. The presence of this isomer in the reaction mixture was demonstrated by comparison of a normal HPLC plot with one from a reaction mixture spiked with an authentic 6-fluoro-L-
Figure 6.2. Fluorine-19 NMR spectra (470.600 MHz) of the decomposition of CsSO₄F recorded at 25 °C in H₂O solvent. The top spectrum was recorded 10 min. after dissolution of CsSO₄F in H₂O. The bottom spectrum was recorded 30 min. after dissolution of CsSO₄F in H₂O; (a) SO₄F⁻ and (b) FSO₃⁻.
dopa sample. Two samples containing equal amounts of the reaction mixture were prepared, one of which was spiked with a few drops of an authentic 6-fluoro-L-dopa sample obtained from a reaction using molecular fluorine as the fluorinating agent. The peak that came at approximately 17 min. 15 sec. showed an increase in peak height relative to all other peaks (Figure 6.3). The peak which eluted at approximately 13 min. 45 sec. was assigned as unreacted L-dopa by comparison to an authentic L-dopa trace.

Chromatograms of the separated reaction mixture resulting from the fluorinations employing \( \text{SO}_2\text{F} \) in \( \text{CH}_3\text{CN/BF}_3 \) were compared to those obtained from a fluorination reaction employing molecular fluorine. The similarity of the traces provided encouraging evidence that the desired fluorinated products had been prepared. The largest quantities of the 6-fluoro-isomer were obtained from reactions carried out at -40 °C in 0.1 M BF\(_3\) in \( \text{CH}_3\text{CN} \) solutions (see procedure outlined in Section 2.8.3.3)

Not only was it of interest to add a new reagent to the currently limited number of viable fluorinating agents for these types of molecules, but, the possibility of finding a regiospecific reagent that could produce high percentages of the desired 6-fluoro-isomer is likewise of considerable importance. However, it was first of interest to obtain proof that 6-fluoro-L-dopa was in fact the compound being produced. Therefore only the peak suspected to be the 6-fluoro isomer was collected for \(^{19}\text{F} \) spectroscopy so that clean spectra could be recorded.
Figure 6.3. HPLC chromatograms (Whatman ODS-2 Partisil 10, 0.15% TFA, 4.5% THF, water) showing the reaction mixture of CsFSO$_4$ and L-dopa in BF$_3$/CH$_3$CN solvent.

Chromatogram A - reaction mixture (0.2 ml)

Chromatogram B - reaction mixture plus 6-fluoro-L-dopa spike.
6.2.4 $^{19}$F NMR of Fluoro-isomers of L-Dopa

The $^{19}$F NMR spectrum showed three resonances in the fluorinated aromatic region (Figure 6.4). Also a sharp singlet, a result of residual CF$_3$COOH, was seen at ($\delta(^{19}F) = -75$ ppm). The doublet of doublets at -126.1 ppm was assigned to 6-fluoro-L-dopa [$^3J(^{19}F-{^1}H) = 10.4$ Hz and $^4J(^{19}F-{^1}H) = 7.7$ Hz]. The doublet at -135.3 has a 11.0 Hz coupling corresponding to $^3J(^{19}F-{^1}H)$ and was therefore assigned to 5-fluoro-L-dopa. A doublet at -139.4 exhibited a 7.5 Hz coupling corresponding to $^4J(^{19}F-{^1}H)$ and was thus assigned to 2-fluoro-L-dopa. The chemical shifts reported here for the 6-, 5-, and 2-fluoro isomers of dopa reported here compare well with those cited in the literature (-126.4, -135.6, -139.7 ppm for 6-, 5-, 2-fluorodopa, respectively). Therefore, these results have shown that the desired fluorinated product could be produced and separated from the product mixture of Cs$^+$SO$_4$F + L-dopa.

Integration over each of the three resonances in this spectrum indicated that the sample contained over 80% of the desired isomer; however, a reasonable percentage of the 2-fluoro isomer would have been removed in the first HPLC. The 2-fluoro isomer, which has a retention time similar to that of unreacted L-dopa, would need to be collected along with the 6-fluoro isomer to give a reliable answer to the regiospecific nature of the reagent.

6.3 CONCLUSIONS: Application to Fluorine-18 Labelling and Future Work

Although the isolation and characterization of 6-fluoro-L-dopa synthesized from the reaction of L-dopa and Cs$^+$SO$_4$F has been successful, the quantities of the product
Figure 6.4. Fluorine-19 NMR spectrum (282.409 MHz) of the peak eluting at 17 min. 15 sec. (Figure 6.3) in the reaction mixture from Cs⁺SO₄F⁻ plus L-dopa. Recorded at 25 °C in D₂O solvent; (a) 6-fluoro-L-dopa, (b) 5-fluoro-L-dopa and (c) 2-fluoro-L-dopa.
obtained have remained quite low. Nonetheless, fluorination of the aromatic ring has been obtained without the use of initial functionalization with a metal leaving group.

Though work could continue on the optimization of reaction conditions and parameters for the fluorination of L-dopa, it would also be of interest to look at reactions with some of the other aromatic amino acids such as tyrosine and meta-tyrosine. Results from the molecular fluorine reactions indicate that these reactions may in fact proceed to give cleaner reaction mixtures with fewer oxidation products.\(^{90}\)

Future experiments could also focus more closely on finding a pathway to \(^{18}\)F labelled \(\text{SO}_4\text{F}^-\). The synthesis of \([^{18}\text{F}]\text{Cs}^+\text{SO}_4\text{F}^-\) with use of a stream of diluted \([^{18}\text{F}]\text{F}_2\) directly from the cyclotron has already been attempted. Though it was assumed the \(\text{SO}_4\text{F}^-\) ion was formed, subsequent reaction with an organic substrate did not result in \(^{18}\text{F}-\)fluoro products.

The second possibility involves fluorine exchange reactions between an easily produced \(^{18}\text{F}\) containing species and a lab bench source of high quality fluoroxysulphate. So far \([^{18}\text{F}]\text{F}^-\) appears to be the best candidate. Fluoroxysulphate is a hypofluorite and thus contains a \(\delta^+\) oxygen which may be suspectable to fluoride ion attack. This would seem to suggest that displacement of \(^{19}\text{F}\) by \([^{18}\text{F}]\text{F}^-\) may be plausible. Also, the possibility of inducing decomposition of the \(\text{SO}_4\text{F}^-\) to produce the more stable \(\text{OF}_2\) species, must also be considered.

\[
\text{SO}_4\text{F}^- + \text{F}^- \rightarrow \text{OF}_2 + \text{SO}_3^{2-} \quad (6.7)
\]
Oxygen difluoride has already been identified as a viable alternative electrophilic fluorinating agent.\textsuperscript{103} If indeed, a reaction were to occur between CsSO\textsubscript{4}F and F, to produce OF\textsubscript{2}, then there is the possibility of producing $^{18}\text{F} \text{OF}_2$ from $^{18}\text{F}$ in CH\textsubscript{3}CN with an CH\textsubscript{3}CN solution saturated with CsSO\textsubscript{4}F.

\[
\text{Cs}^+\text{SO}_4\text{F} + \text{K}^+\text{[^{18}F]F} \xrightarrow{\text{CH}_3\text{CN}} \text{[^{18}F]OF}_2 + (\text{Cs}^+)(\text{K}^+)\text{SO}_4^{2-} \quad (6.8)
\]

The reactivity and selectivity of OF\textsubscript{2} towards aromatic amino acids should also be considered.
REFERENCES


38. R. V. Chirakal, unpublished results.


80. G. J. Schrobilgen, personal communication.


93. C. Y. Shiue, P. A. Salvadori, A. P. Wolf, J. S. Fowler, R. R. MacGregor, 
96. R. V. Chirakal, G. Firnau, G. J. Schrobilgen, J. M. McKay, E. S. Garnett, 
   1991, **32**, 1010.
APPENDIX 1 Absolute Oxidizer Strength Scale and Formation Enthalpies for Oxidative Fluorinators

<table>
<thead>
<tr>
<th>oxidative fluoroniator&lt;sup&gt;a&lt;/sup&gt;</th>
<th>F&lt;sup&gt;+&lt;/sup&gt; detachment energy (kcal mol&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>formation enthalpy (kcal mol&lt;sup&gt;-1&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XF&lt;sup&gt;+&lt;/sup&gt;</td>
<td>FPD (XF&lt;sub&gt;g&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>ΔH&lt;sub&gt;f&lt;/sub&gt;&lt;sup&gt;o&lt;/sup&gt; (XF&lt;sub&gt;g&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>(HeF&lt;sup&gt;+&lt;/sup&gt;) (³π)</td>
<td>-1.6</td>
<td>423.6</td>
</tr>
<tr>
<td>(HeF&lt;sup&gt;+&lt;/sup&gt;) (¹Σ⁺)</td>
<td>(-16.2)</td>
<td>(438.2)</td>
</tr>
<tr>
<td>(F&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>0</td>
<td>422.0</td>
</tr>
<tr>
<td>(NeF&lt;sup&gt;+&lt;/sup&gt;) (³π)</td>
<td>0.6</td>
<td>421.4</td>
</tr>
<tr>
<td>(NeF&lt;sup&gt;+&lt;/sup&gt;) (¹Σ⁺)</td>
<td>(-19.6)</td>
<td>(441.6)</td>
</tr>
<tr>
<td>(F&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>60.0</td>
<td>362.0</td>
</tr>
<tr>
<td>(ArF&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>84.3</td>
<td>337.7</td>
</tr>
<tr>
<td>KrF&lt;sup&gt;+&lt;/sup&gt;</td>
<td>115.9</td>
<td>306.1</td>
</tr>
<tr>
<td>(XeF&lt;sub&gt;7&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>116.7</td>
<td>222.2</td>
</tr>
<tr>
<td>(OF&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>122.2</td>
<td>305.7</td>
</tr>
<tr>
<td>(BrF&lt;sub&gt;4&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>131.1</td>
<td></td>
</tr>
<tr>
<td>(O&lt;sub&gt;2&lt;/sub&gt;F&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>133.8</td>
<td>288.2</td>
</tr>
<tr>
<td>(ClF&lt;sub&gt;4&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>135.6</td>
<td>251.0</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;F&lt;sup&gt;+&lt;/sup&gt;</td>
<td>139.3</td>
<td>283.7</td>
</tr>
<tr>
<td>(XeF&lt;sub&gt;5&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>139.8</td>
<td>276.2</td>
</tr>
<tr>
<td>BrF&lt;sub&gt;6&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>140.8</td>
<td>178.7</td>
</tr>
<tr>
<td>(XeF&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>141.7</td>
<td>336.3</td>
</tr>
<tr>
<td>ClF&lt;sub&gt;6&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>147.3</td>
<td>215.5</td>
</tr>
<tr>
<td>XeF&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>152.4</td>
<td>243.7</td>
</tr>
<tr>
<td>ClF&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>158.7</td>
<td>224.3</td>
</tr>
<tr>
<td>XeF&lt;sub&gt;5&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>158.9</td>
<td>200.6</td>
</tr>
<tr>
<td>ClF&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;+&lt;/sup&gt;</td>
<td>161.0</td>
<td>228.4</td>
</tr>
<tr>
<td>(IF&lt;sub&gt;4&lt;/sub&gt;O&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>164.0</td>
<td></td>
</tr>
<tr>
<td>Cation</td>
<td>Mass 1</td>
<td>Mass 2</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>XeF⁺</td>
<td>164.8</td>
<td>257.2</td>
</tr>
<tr>
<td>ClF₂⁺</td>
<td>167.1</td>
<td>241.9</td>
</tr>
<tr>
<td>XeF₃O⁺</td>
<td>173.1</td>
<td></td>
</tr>
<tr>
<td>BrF₄⁺</td>
<td>174.0</td>
<td>187.0</td>
</tr>
<tr>
<td>IF₅⁺</td>
<td>175.0</td>
<td>40.4</td>
</tr>
<tr>
<td>NF₂O⁺</td>
<td>175.3</td>
<td>230.8</td>
</tr>
<tr>
<td>Cl₂F⁺</td>
<td>179.1</td>
<td>242.9</td>
</tr>
<tr>
<td>NF₄⁺</td>
<td>180.1</td>
<td>210.5</td>
</tr>
<tr>
<td>(XeFO⁺)</td>
<td>182.4</td>
<td>290.1</td>
</tr>
<tr>
<td>BrF₂⁺</td>
<td>182.4</td>
<td>217.2</td>
</tr>
<tr>
<td>ClF₃O⁺</td>
<td>193.0</td>
<td></td>
</tr>
<tr>
<td>XeFO₂⁺</td>
<td>195.3</td>
<td></td>
</tr>
<tr>
<td>BrF₂O⁺</td>
<td>200.5</td>
<td></td>
</tr>
<tr>
<td>IF₃⁺</td>
<td>212.1</td>
<td>93.9</td>
</tr>
<tr>
<td>IF₂⁺</td>
<td>213.5</td>
<td>185.7</td>
</tr>
<tr>
<td>(IF₂O⁺)</td>
<td>230.0</td>
<td></td>
</tr>
</tbody>
</table>

*The cations listed in parenthesis have so far not been isolated in the form of stable salts. All FPD values were computed for XF⁺ and X being singlet ground states and F⁺ being a triplet ground state, except for HeF⁺ and NeF⁺, which have triplet ground states. Reproduced from reference 3.