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,
(Chemistry) Hamilton, Ont.

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, $^{18}O(p,n)^{18}F$, and recovered from an oxygen-18 gas target, has been used to elucidate the mechanism for the formation of $XeF^+AsF_6^-$ from Xe, F_2, and AsF_5 under low temperature and dark conditions. Formation of $XeF^+AsF_6^-$ was confirmed by Raman spectroscopy. A method was designed to allow for the dilution of the ^{18}F activity onto a pool of carrier $^{19}F_2$ such that suitable quantities of low specific activity $[^{18}F]F_2$ could be produced for the mechanistic study of this reaction. Based on the ^{18}F distributions within the products and unreacted $[^{18}F]F_2$ and AsF_5, it was shown that an F_2-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 $F^{\delta+}$ was responsible for the enhanced oxidizing ability of the F_2-AsF_5 complex, rather than the production of a formal "F^+" or F· intermediate. Fluorine-18 investigations into the reaction of the F_2-AsF_5 activated complex with other possible electron donors have shown some ^{18}F transfer with krypton gas. Attempts to establish the formation of KrF^+ using ^{19}F NMR spectroscopy have shown no evidence for the presence of the cation in the $Kr/F_2/AsF_5$ system. The systems $Kr/F_2/HF/SbF_5$ and $OF_2/F_2/AsF_5$ 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 $^{18}O(p,n)^{18}F$ oxygen gas target; the presence of reactive agents other than $[^{18}F]F_2$ 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 $[^{18}F]OF_2$ 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 $CsSO_4F$ as an electrophilic fluorinating agent has provided preliminary evidence for the flourination of biologically active aromatic amino acids. Cesium fluoroxysulphate was found to react with 3,4-dihydroxyphenylalanine (L-Dopa) in an CH_3CN 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

LIST OF TABLES

LIST OF FIGURES

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^+ salts[3] prepared from the reaction of KrF_2 with Lewis acids.[3,4]

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 BrF_5[5]

$$KrF^+AsF_6^- + BrF_{5(l)} \longrightarrow BrF_6^+AsF_6^- + Kr_{(g)} \qquad (1.1)$$

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 $CsSO_4F$[6] and CF_3COOF,[7] respectively, tend to substitute fluorine onto electron-rich organic centres. The regiospecific substitution of ^{18}F onto the aromatic ring of aromatic amino acids has already been achieved with $[^{18}F]CF_3COOF$.[8] Fluorine-18 labelled fluoroxysulphate may be a candidate for a simpler, more efficient synthesis of ^{18}F-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 ^{17}F and ^{18}F have a deficit of neutrons and decay by positron emission; ^{20}F, ^{21}F, ^{22}F and ^{23}F 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 ^{18}F a useful isotope for the study of inorganic reaction mechanisms.

Table 1.1. Isotopes of Fluorine[9]

Nuclide	Decay Mode	Product	Half-Life
^{17}F	β^+	^{17}O	64.7 sec
^{18}F	β^+	^{18}O	109.7 min
^{19}F	stable		
^{20}F	β^-	^{20}Ne	11.0 sec
^{21}F	β^-	^{21}Ne	4.2 sec
^{22}F	β^-	^{22}Ne	4.2 sec
^{23}F	β^-	^{23}Ne	2.2 sec

Its applications to the field of nuclear medicine through the use of Positron Emission Tomography has allowed image reconstruction to produce *in vivo* images with typical spatial resolutions of only a few millimetres.[10]

1.3. Fluorine-18, Production and Recovery

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

Aqueous ^{18}F-fluoride production methods require the use of either a cyclotron or a nuclear reactor. The irradiation of $^6Li_2CO_3$ with a neutron flux is used to initiate the nuclear reaction, $^6Li(n,\alpha)^3H$, which, in turn, produces a source of tritium for the nuclear reaction $^{16}O(t,n)^{18}F$. The $^{18}F^-$ product, recovered by dissolving the irradiated $LiCO_3$ in H_2O, however, is always contaminated with the ^3H radionuclide from the first nuclear reaction. An alternative method for the production of ^{18}F-fluoride utilizes the $^{18}O(p,n)^{18}F$ reaction. An $H_2{}^{18}O$ target is irradiated with protons produced from either an accelerator or a cyclotron. The $^{18}F^-$ ion can be collected *in situ* on an anion exchange column.[11]

Methods involving ^{18}F atoms are more numerous and, to date, have found more applications. The reactions $^{19}F(n,2n)^{18}F$ and $^{19}F(\gamma,n)^{18}F$ have been used to label inorganic fluorides under anhydrous conditions.[12] The most common method for the production of ^{18}F atoms, however, is the $^{20}Ne(d,\alpha)^{18}F$ reaction.[13] Deuterons from either an accelerator or cyclotron are used to irradiate neon gas to produce ^{18}F atoms. The activity can be recovered from the target as $[^{18}F]\text{-}F_2$, $H^{18}F$, ^{18}FNO or $Cl^{18}F$ if the neon gas contains small

quantities of carrier F_2, H_2, NO, or Cl_2, respectively.[14] Solid inorganic fluorides can be labelled with ^{18}F 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 $[^{18}F]F_2$. The $^{18}O(p,n)^{18}F$ reaction is convenient for use with a proton only cyclotron. For 10 MeV protons, the thick target yield for an $^{18}O_2$ 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 $[^{18}F]F_2$ containing carrier $^{19}F_2$.

1.4. Application of ^{18}F 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 ^{18}F 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 F_2 at high temperatures in the gaseous states. In conjunction with room temperature ^{38}Cl tracer studies of the corresponding chlorine system, the authors were able to differentiate between the exchange mechanism occurring for F_2/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 BF_3-SF_4.[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., $F_3B{\cdot\cdot}F{\cdot\cdot}SF_3$.

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.[13] More recently, ^{18}F labelling has been used to investigate the existence of hypervalent compounds of nitrogen and chlorine.[18,19]

Hypervalent compounds, defined by Shriver *et al.*[20] 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.[21] Alternatively, NF_5 was suspected as an unstable intermediate in the pyrolysis of $NF_4^+AsF_6^-$ at 175 °C;[22]

$$NF_4^+AsF_6^- \rightleftharpoons [NF_5] + AsF_5 \qquad (1.2)$$

$$[NF_5] \rightleftharpoons NF_3 + F_2 \qquad (1.3)$$

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 $[^{18}F]AsF_5$, $[^{18}F]NF_3$, and $[^{15}N]NF_3$.[23] Results of

this study suggested the structure $NF_4^+F^-$ as the intermediate. The analogous NH_5 species was investigated by hydrogen-deuterium labelling, the results of which suggested the existence of a NH_4D intermediate for the reaction of the $NH_4^+O_2CCF_3$ melt with LiD.[24] However, these results were disputed on the basis that, the H_2 to D_2 ratio within the decomposition products [85%NH_3 + 15%NH_2D] + [66%HD + 21%H_2 + 13%D_2], exceeded the theoretical ratio for a non-catalysed isotopic exchange.[25]

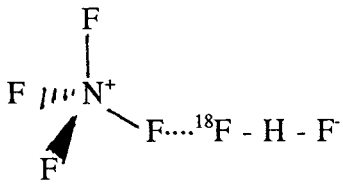
In response to the observation that $NF_4^+SbF_6^-$, when treated with LiF, gave a decomposition mixture consisting of NF_3, F_2 and $LiSbF_6$, Olah *et al.*[24] suggested the use of an ^{18}F-labelled fluoride ion donor to detect the nucleophilic attack of F^- on nitrogen. Initial theoretical calculations[26] indicated that all pentacoordinate nitrogen species are unstable with respect to decomposition

$$NX_5 \longrightarrow NX_3 + X_2 \qquad (1.4)$$

However, more recent high-level calculations[27,28] predict that NF_5 is stable with all calculated vibrational frequencies positive.

The reaction between NF_4^+ and the fluoride ion donor, HF_2^-, was studied by use of $[^{18}F]CsHF_2$ and NF_4PF_6.[18] The $[^{18}F]NF_4HF_2$ formed at room temperature in HF solvent decomposes upon removal of the HF between 25 and 100 °C. Attack of the $[^{18}F]F^-$ on the nitrogen would result in the $[^{18}F]NF_5$ intermediate. Upon decomposition, the ^{18}F activity would be statistically scrambled between the NF_3, HF, F_2 and $CsPF_6$. If the $[^{18}F]F^-$ were to attack at one of the four fluorine ligands, ^{18}F activity would never be transferred to the

NF_3 (equation 1.5)



$$\longrightarrow \quad NF_3 + [^{18}F]F_2 + [^{18}F]HF \qquad (1.5)$$

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 $[^{18}F]FNO$[19]

$$ClF_6^+AsF_6^- + [^{18}F]FNO \longrightarrow [^{18}F]ClF_7 + NO^+AsF_6^- \xrightarrow[(a)]{} ClF_5 + [^{18}F]F_2 + NO^+AsF_6^-$$

$$\Big|\!\xrightarrow[(b)]{} [^{18}F]ClF_5 + [^{18}F]F_2 + NO^+AsF_6^- \qquad (1.6)$$

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 $[^{18}F]ClF_5$ in the products. Indeed the experimental results indicated the presence of $[^{18}F]ClF_5$; 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 ClF_7 species was not conclusive.

Interestingly, the simple binary exchange between [^{18}F]NOF and ClF_5, resulted in the random distribution of ^{18}F which required the ClF_6^- anion as an intermediate

$$[^{18}F]FNO + ClF_5 \longrightarrow [^{18}F][NO^+ClF_6^-] \longrightarrow [^{18}F]FNO + [^{18}F]ClF_5 \quad (1.7)$$

Experimental results showed complete random exchange of fluorines between the [^{18}F]NOF and [^{18}F]ClF_5. In conjunction with ^{19}F NMR and vibrational spectroscopic studies, the existence of the ClF_6^- 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 OF_2, HOF, O_2, and H_2O_2.[30] Fluorine-18 was used in conjunction with ^{18}O in double labelling experiments to elucidate the stoichiometry for the reaction of HOF with F_2. The hypofluorous acid formed from the reaction of F_2 with H_2O was shown to react in a 1:1 mole ratio with gaseous non-radioactive fluorine[30]

$$F_2 + [^{18}F]HOF \longrightarrow [^{18}F]OF_2 + HF \quad (1.8)$$

The above examples demonstrate that ^{18}F 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,[31] 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[32] and Bartlett *et al.*[33] has been studied by means of radiofluorine labelling, in hopes that the mechanism of fluorination could be conclusively determined.[31] Preliminary studies, which used $[^{18}F]AsF_5$ 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 $[^{18}F]F_2$ 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, $Cs^+SO_4F^-$, 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.

CHAPTER 2

EXPERIMENTAL

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 (perfluorethylenepropylene 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 $\pm$ 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 F_2 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% F_2 in neon (Matheson) were used without further purification. The 5% F_2 in krypton mixture was made by pressurization of a 1 L nickel vessel with purified F_2 at room temperature followed by the condensation of the appropriate amount of Kr at -196 °C. Arsenic pentafluoride was prepared from AsF_3 and F_2 as outlined by Hoffman[34] and then purified by passing the

Figure 2.1. 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

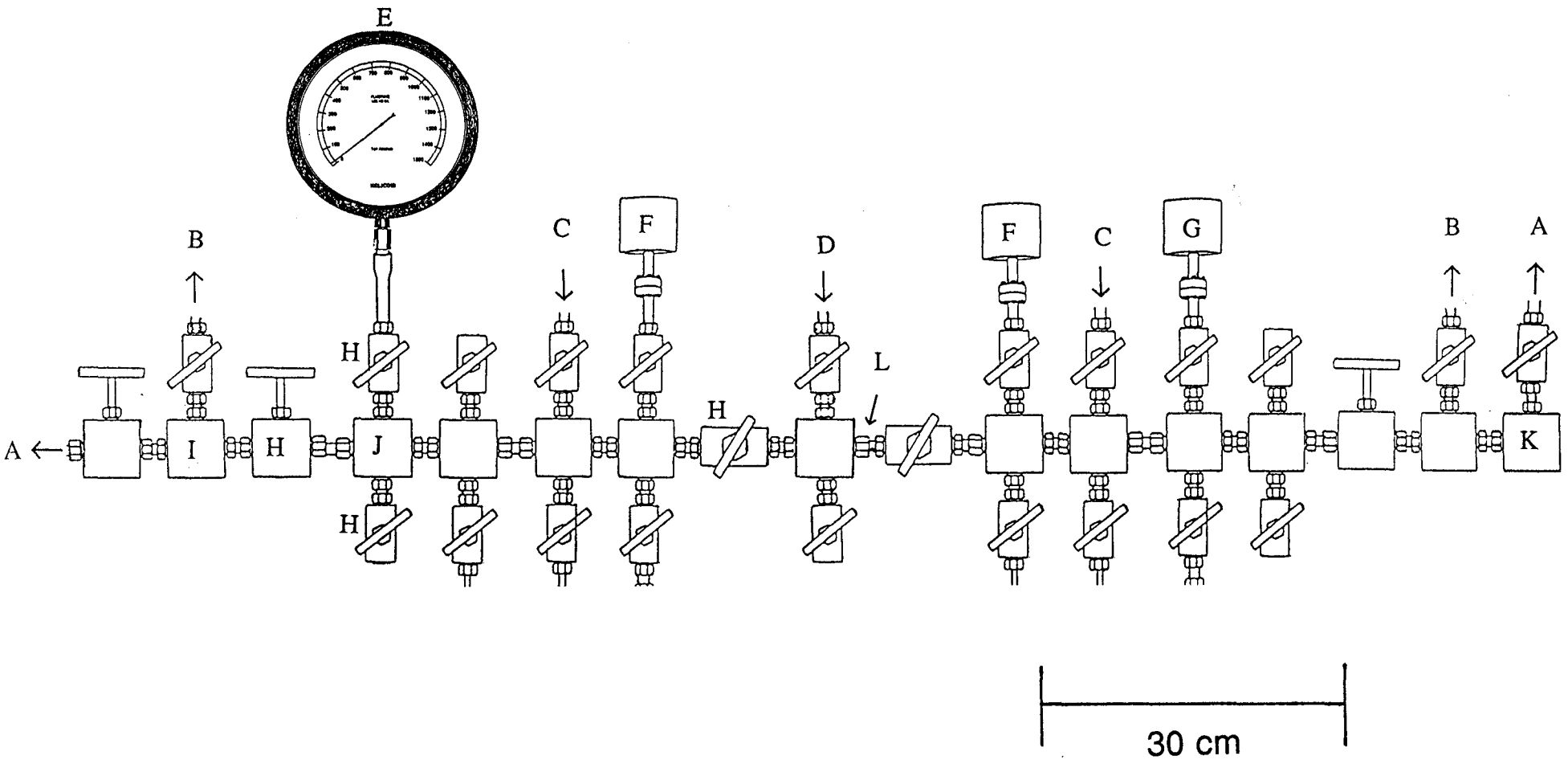

E
B
C
F
D
F
C
G
B
A
H
H
H
L
A
I
H
J
K
30 cm

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

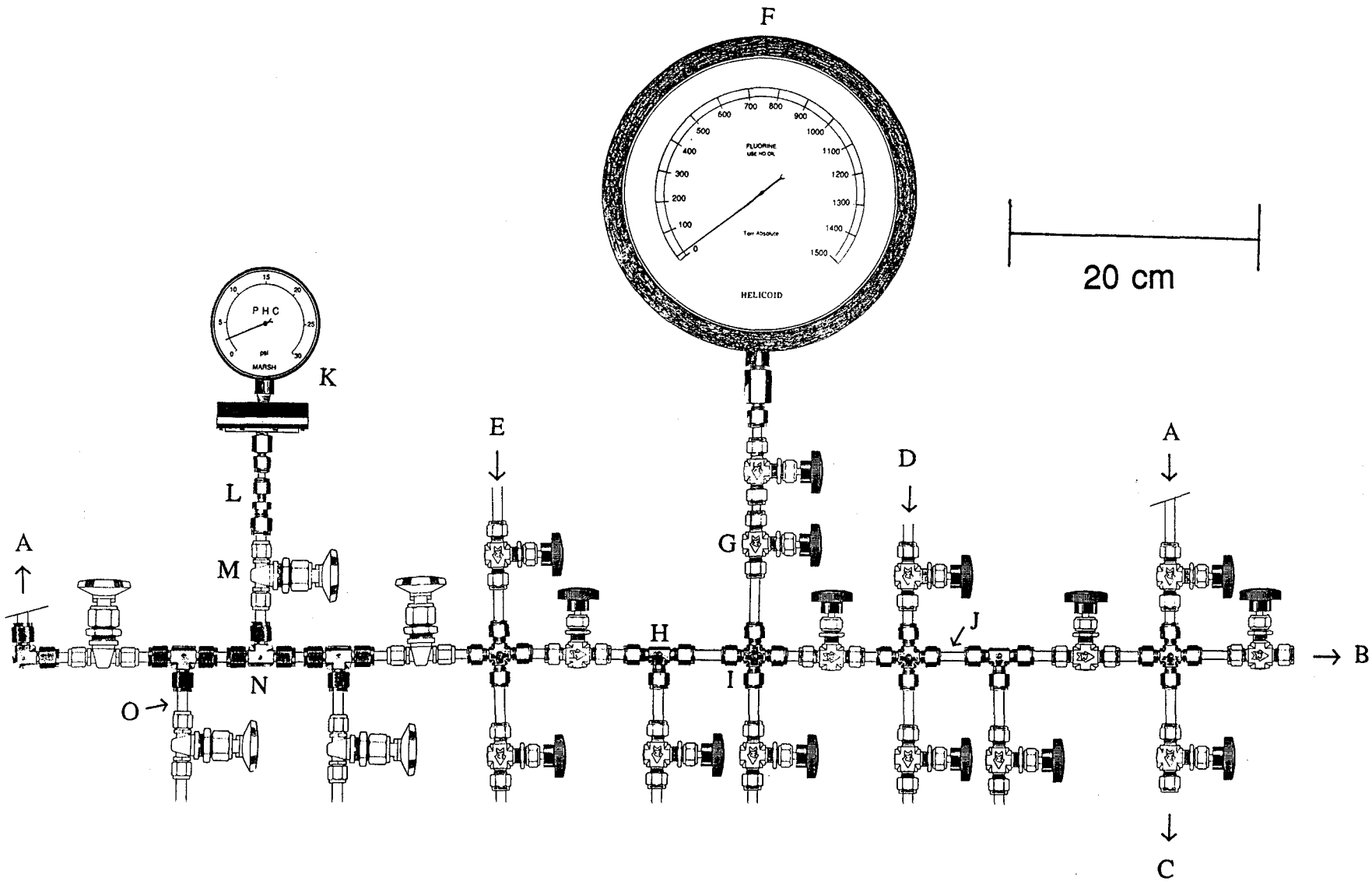
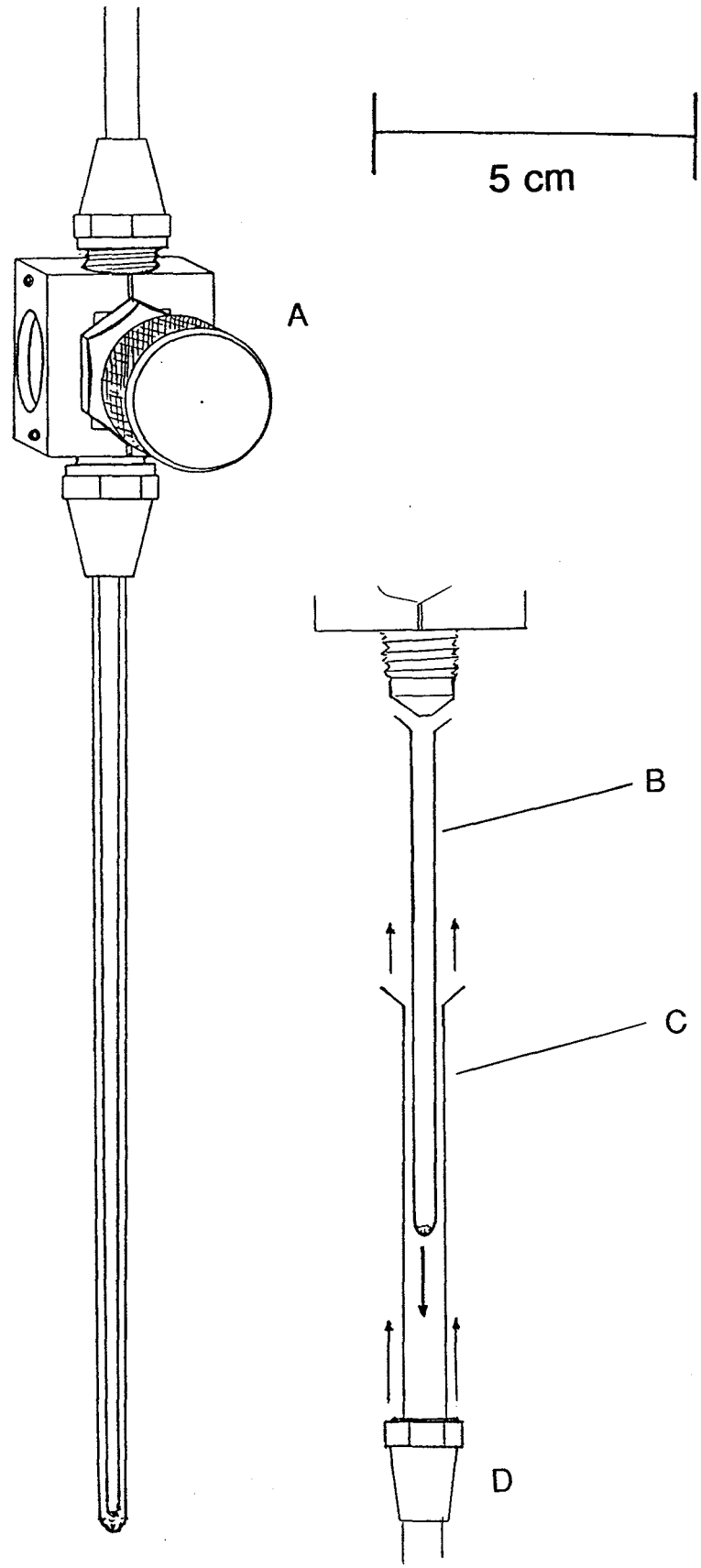

F
FLUORINE
HELICOID
Torr Absolute
20 cm
PHC
psi
MARSH
K
L
M
N
O
A
E
G
H
I
D
J
A
C
B

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) ¼-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


5 cm
A
B
C
D

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.[35] Oxygen difluoride (Ozark-Mahoning) was used without further purification.

Enriched $[^{18}O]O_2$ (^{18}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_3CN (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}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}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. acquistion 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 μm 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 premonochrometer, intermediate, and monochrometer slit settings were 200 μm, 2.7 mm, and 200 μm, 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 ($Xe_2F_3^+AsF_6^-$) 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 (*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

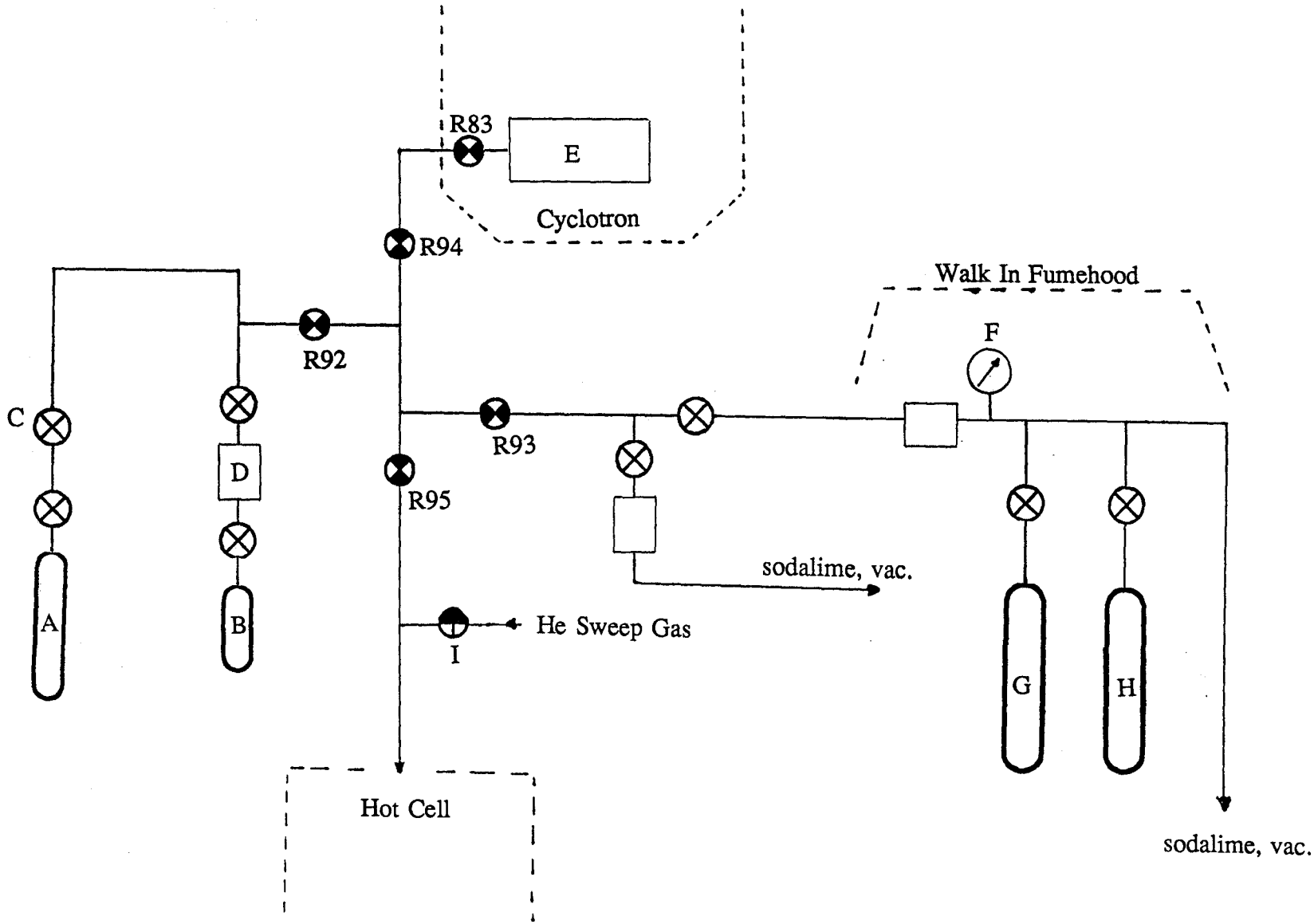
2.4.1 ^{18}F Target and Support System

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.[36] 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 computor control (Precision Dynamics Inc. A2011-S84)


R83
E
Cyclotron
R94
Walk In Fumehood
R92
F
C
D
R93
R95
sodalime, vac.
A
B
He Sweep Gas
I
G
H
Hot Cell
sodalime, vac.

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, dt = 0. Activities were corrected for decay with use of equation (2.1).

$$Activity^{18}F = [A_o]\ [1 - e^{\frac{-(\ln 2)T}{t_{1/2}}}] \qquad (2.1)$$

A_o = initial ^{18}F, T = elapsed time after T = 0 , $t_{½}$ = 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 $[^{18}F]F_2$

The recovery of $[^{18}F]F_2$ 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 $^{19}F_2$ carrier at -196 °C. Before the transfer of the $[^{18}F]F_2$, the receiving vessel was warmed to 50 °C to allow complete exchange of the ^{18}F from the target mixture with the ^{19}F of the carrier pool, and consequently, provide a homogeneous $[^{18}F]F_2$ mixture. Exclusion of this step was found to result in poor transfer yields of the ^{18}F activity.

2.5.3 Transfer and Distribution of $[^{18}F]F_2$

After the $^{18}F/^{19}F$ exchange step, the receiving vessel that contained Kr plus $[^{18}F]F_2$ 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.[37] 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[37] at -196 °C condensed from the calibrated volume. The radiochemical yield of the transfer was simply equal to the ^{18}F activity in the reaction vessel divided by the ^{18}F activity initially in the $Kr/[^{18}F]F_2$ 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)

$$(^{18}F\ Reaction\ Vessel) = \frac{(Manifold\ pressure\ -\ 300\ Torr)}{(pTorr\ of\ carrier\ F_2,\ receiving\ vessel)}\ x\ (^{18}F\ Receiving\ Vessel) \qquad (2.2)$$

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 $^{18}O_2$ 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}F]HF was carried out as usual up to and including the removal of the

unreacted $F_2/H_2/Ne$ 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 ^{19}F spectrum was collected at room temperature in 62,565 scans. An external D_2O lock was also used.

2.6.2 Target Gas Analysis Experiments

The determination of the amount $[^{18}F]OF_2$ in the target gas mixture was accomplished by the fractional separation of volatiles between -196 and -94 °C. The general synthesis of $[^{18}F]HF$ was used since total retention of the ^{18}F activity is expected. In all experiments, the Ne/F_2 target mixture was condensed into a reaction vessel containing 760 Torr of carrier HF and 1000 Torr of H_2 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 F_2, H_2 or excess Ne. The reaction vessel was then warmed to -94 °C in a methanol slush bath. At this temperature the vapour pressures of OF_2 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/F_2 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 $[^{18}F]AsF_5$ 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,[33] 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 $[^{18}F]F_2$

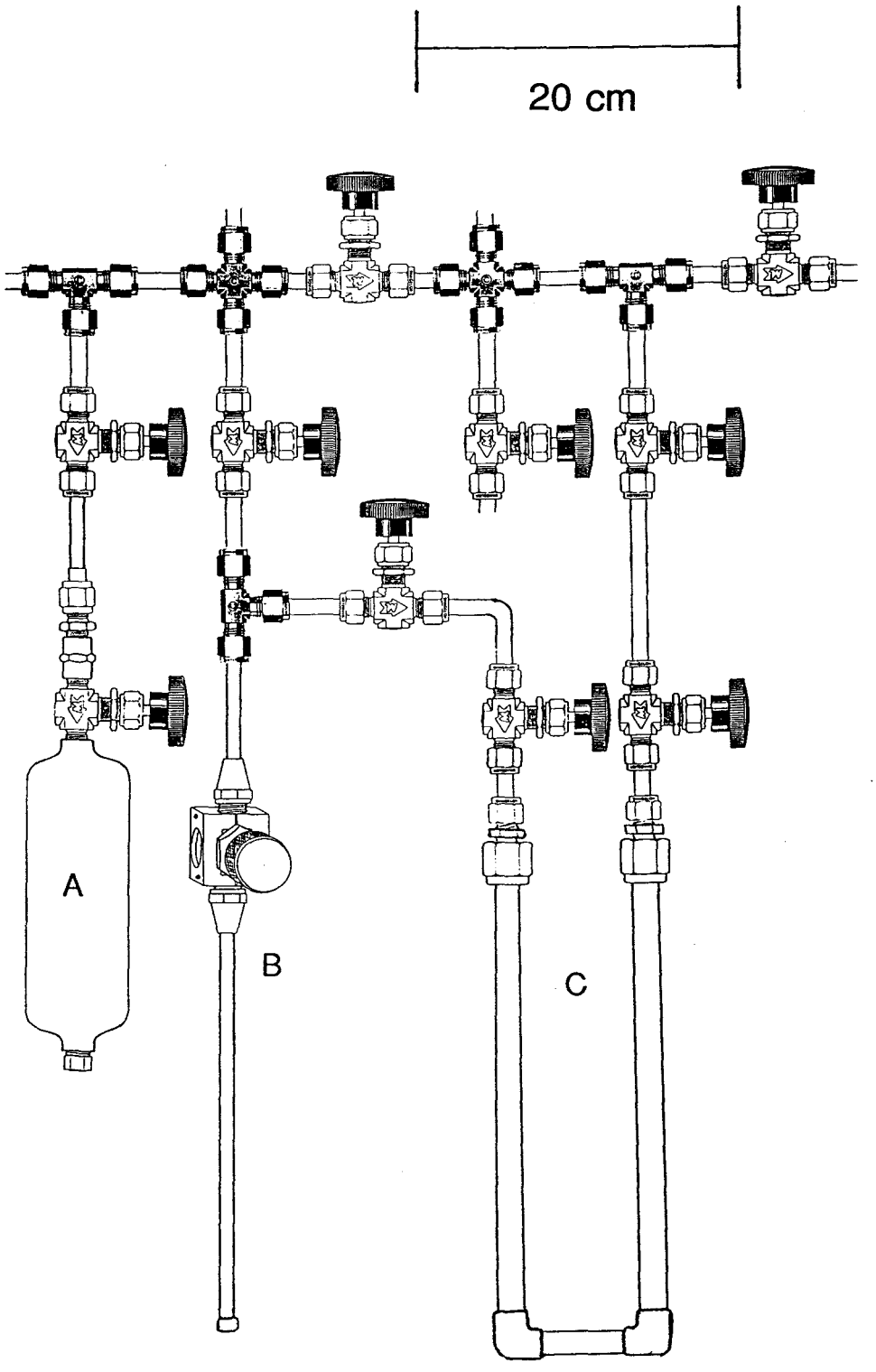
as well as the reaction vessel, containing the $XeF^+AsF_6^-$ salt, unreacted AsF_5 and Xe. After pumping on the reaction vessel at -70 °C to remove the AsF_5, the reaction vessel was assayed again for ^{18}F activity, which, when subtracted from the previous measurement, gave the activity for $[^{18}F]AsF_5$. The experiment was either stopped at this point and the sample studied by Raman spectroscopy to confirm the presence of the XeF^+ salt, or the reaction vessel was warmed to room temperature, and pumped on to remove further AsF_5 liberated by the decomposition of the XeF^+ salt. A final assay of the reaction vessel gave an activity for $[^{18}F]Xe_2F_3^+AsF_6^-$ (See Table 4.2).

2.7.3 ^{18}F Study of the $Kr/F_2/AsF_5$ 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 $[^{18}F]F_2$ at -196 °C and for the $[^{18}F]AsF_5$ 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)


20 cm
A
B
C

2.7.4 Reaction of $Kr/F_2/HF/SbF_5$

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 SbF_3. 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 SbF_3. The process of replenishing the fluorine pressure at -78 °C and then warming and agitating was repeated until all of the SbF_3 had dissolved. The residual F_2 was pumped off at -196 °C. Krypton gas (0.8 mmol) was condensed into the vessel at -196 °C followed by F_2 (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 $SbF_5 \cdot xHF$ solvate. No apparent reaction was evident over a period of 24 hrs.

2.7.5 Reaction of $OF_2/F_2/ AsF_5$

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 F_2 (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 $CsSO_4$ 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% F_2 in N_2, was bubbled through the $CsSO_4$ solution over the course of 1 hr. using a 1/16-in. FEP tube. The small bore of the F_2 inlet tube and the height of $CsSO_4$ solution in the reaction vessel optimized the contact between the F_2 mixture and $CsSO_4$ solution. The quantity of 20% F_2 in N_2 mixture which passed through the $CsSO_4$ 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 $CsSO_4$ was used. Previous procedures used for the synthesis $CsSO_4F$ 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 $CsSO_4F$ based on the quantity of fluorine used was 83.5%.

Fluorine-19 NMR spectroscopy was used to confirm the formation of $CsSO_4F$ and also to look at the amount of fluorosulphate impurity. The NMR samples were prepared in CH_3CN 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 $CsSO_4F$ in H_2O. A room temperature sample of $CsSO_4F$ in H_2O was prepared immediately before acquisition of the ^{19}F spectrum. The first spectrum was acquired for 10 min. and then halted. A second spectrum was acquired approximately 30 min. after dissolution of $CsSO_4F$ in H_2O. The relative intensities of the SO_4F^- and FSO_3^- resonances were compared.

2.8.2 Reactions of $CsSO_4F$ 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 $CsSO_4F$ synthesis, with a solution containing the dissolved amino acid. The procedure essentially followed the previously described synthesis of $CsSO_4F$ with the exception that a 1% F_2 in Ne mixture was used as the fluorine source instead of a N_2/F_2 mixture. This reduced the quantity of SO_4F^- below the saturation level. At the same time, a solution of L-dopa was prepared in H_2O by adding a 1/2 mL of aqueous HF. The centrifuge steps were omitted from the synthesis. Approximately 1 mL of solution from the SO_4F^- 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.

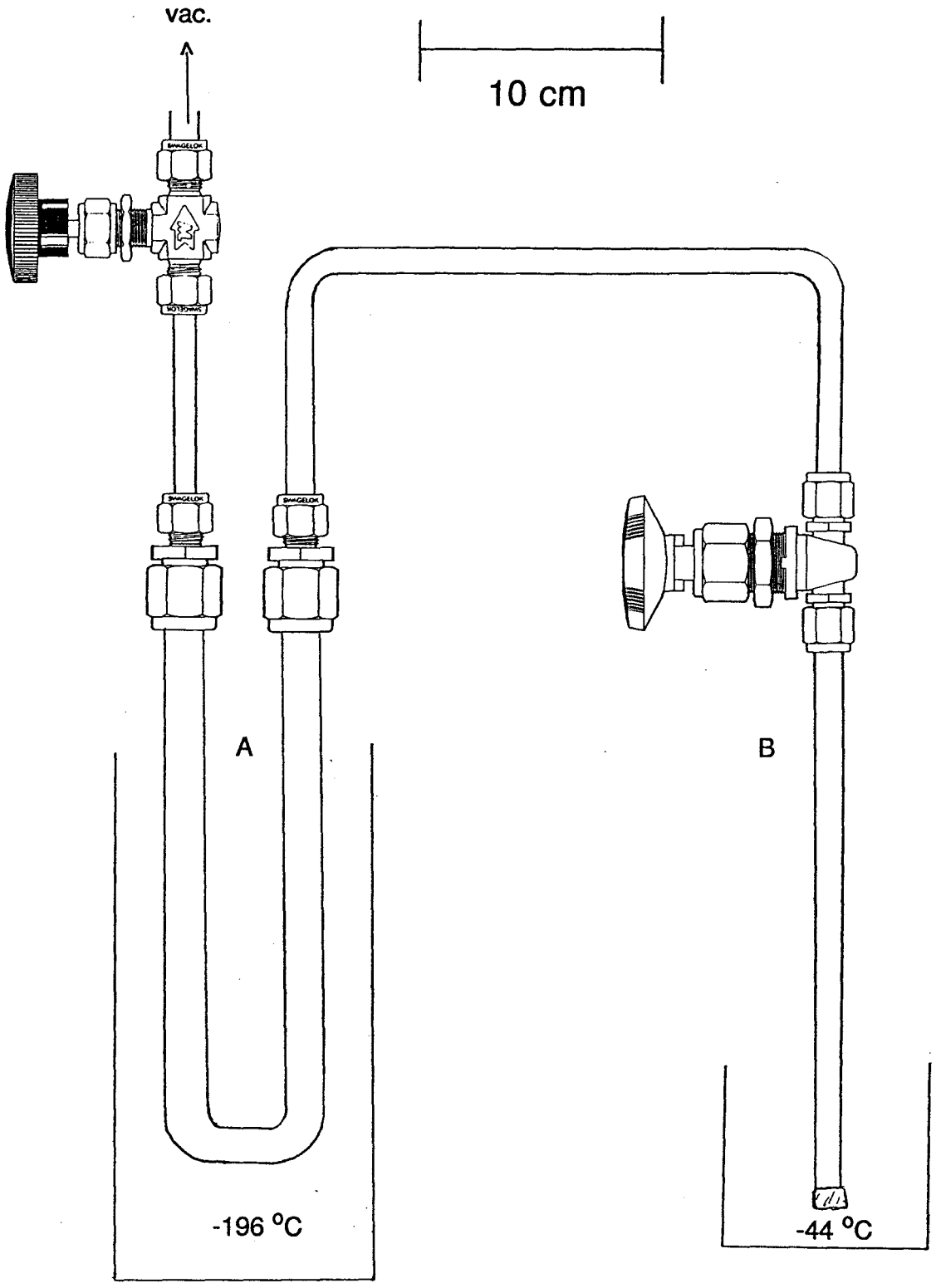
2.8.2.1 $CsSO_4F$ with DOPA in CH_3CN

The reaction between $CsSO_4F$ and L-dopa was repeated in CH_3CN. 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 H_2O 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 $CsSO_4F$ with L-DOPA in BF_3/CH_3CN

A 0.1 M solution of BF_3 in CH_3CN was first prepared for this reaction. A known pressure (450 Torr) of BF_3 from a 41 mL calibrated volume was condensed into a Pyrex glass flask equipped with Teflon Rotoflo valve containing 10 mL of CH_3CN. 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 BF_3/CH_3CN 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_3/CH_3CN; (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


vac.
10 cm
A
B
-196 °C
-44 °C

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_3CN 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_2O 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_3CN solution was added to the $CsSO_4F$ 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 BF_3/CH_3CN solution and transferred into the reaction vessel on top of the frozen SO_4F^- 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-flouro Isomers of Fluorodopa

All reaction mixtures were separated on a Whatman ODS-2 reverse phase column. This column is known[38] 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_2O and then injected onto a Vydac column using a 0.1% acetic acid/H_2O 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_2O/DCl 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 radiopharmeceutical 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 $^{20}Ne(d,\alpha)^{18}F$ 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 $^{18}O(p,n)^{18}F$ 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}F at 10 MeV (protons and deuterons) by Ruth *et al.*[42] in 1979 showed that the $^{18}O(p,n)^{18}F$ reaction was three times more efficient than the $^{20}Ne(d,\alpha)^{18}F$ reaction. As a result of this clear advantage, two methods, a single (1S) and double step (2S) synthesis, were developed for the

production of $[^{18}F]F_2$ from $^{18}O_2$.[15] With the exception of a few variations on these original procedures to examine different target environments,[41,43] surprisingly little work has been done on the improvement of these methods, and development of further techniques for the production of $[^{18}F]F_2$ from $^{18}O_2$.[44]

3.1.1 Single Irradiation Method

The development of techniques for the production of$[^{18}F]F_2$ was initiated by Nickles *et al.* in 1984.[15] 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 $[^{18}F]F_2$. The 1S method involved the direct irradiation of an $^{18}O_2$ / carrier $^{19}F_2$ mixture. The 1S method accomplished the conversion of ^{18}O to ^{18}F simultaneously with the mixing of the $^{18/19}F$ and the target gas recovered from this method contained large quantities of the unreacted $^{18}O_2$. In addition, the dissociation of molecular O_2 and F_2 to atomic species during the irradiation process, resulted in the formation of OF_2. The characterization of the OF_2, and the analysis of relative amounts of $[^{18}F]OF_2$ and $[^{18}F]F_2$ found for a 1S target gas, have recently been studied.[43] In addition to the low chemical purity and low radiochemical yield of the $[^{18}F]F_2$ recovered through this process, the consumption of $^{18}O_2$ 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}F activity produced from the irradiation of pure $^{18}O_2$ was assumed to adhere to the passivated walls of the target through the exchange labelling equation (3.1)

$$^{18}F\cdot + NiF_2 \rightleftharpoons F\cdot + [^{18}F]NiF_2 \qquad (3.1)$$

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 $^{18}O_2$ 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}F activity through the reverse of equation (3.1). Recombination of the atoms at the end of bombardment yields a uniform mixture of ^{18}F-^{19}F and $^{19}F_2$ (denoted as $[^{18}F]F_2$). Variations in $[^{18}F]F_2$ 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 $[^{18}F]CF_4$ and $[^{18}F]NF_3$ 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 $[^{18}F]OF_2$.

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.[43] 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[46] 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*,[47,48] 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,[49,50]

$$\cdot NO_2 + F_2O \rightleftharpoons FNO_2 + \cdot OF \qquad (3.2)$$

$$\cdot OF + \cdot NO_2 \longrightarrow FONO_2 \qquad (3.3)$$

leading to the overall equation,

$$2{\cdot}NO_2 + OF_2 \longrightarrow FNO_2 + FONO_2 \qquad (3.4)$$

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.[51] 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 $OF{\cdot}$ and $O_2F{\cdot}$, whose properties and structures have been well characterized,[55,56] react with atomic fluorine to produce the compounds O_2F_2 and OF_2. The O_2F_2 molecule is unstable above -160 °C and decomposing back to $O_2F{\cdot}$, and ultimately to $O_2 + F{\cdot}$ so that the formation

of OF_2 can be represented by the following reaction pathways

Initiation $O_2(\text{stable}) \rightleftharpoons 2O\cdot$ and $F_2(\text{stable}) \rightleftharpoons 2F\cdot$

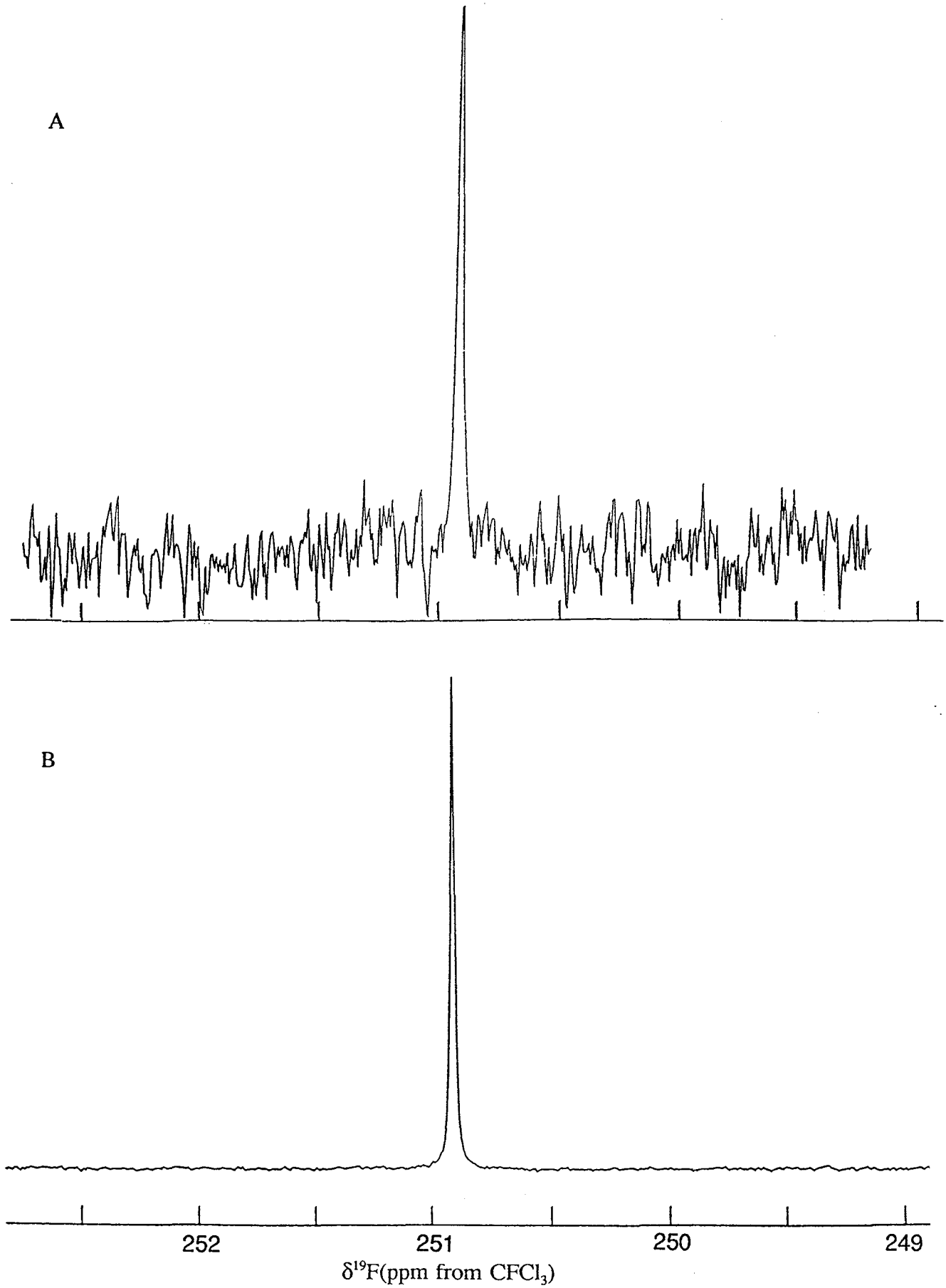
$$\begin{array}{lll} O\cdot + F\cdot \longrightarrow OF\cdot & O_2 + F\cdot \rightleftharpoons O_2F\cdot & (3.5) \\ \Downarrow & \Downarrow & \\ OF\cdot + F\cdot \longrightarrow OF_2\ (\text{stable}) & O_2F\cdot + F\cdot \rightleftharpoons O_2F_2 & \end{array}$$

Higher oxygen fluorides, such as O_3F_2, are normally synthesized in a low temperature (-196 °C) electrical discharge[52] and rapidly decompose to O_2 and F_2 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 O_2, F_2 and OF_2. 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 [^{18}F]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 OF_2 are 1 Torr and 23.3 atm. at -196 and -94 °C, respectively)[37].

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; δ = 250.9 ppm, recorded at -72 °C in HF solvent


A
B
252
251
250
249
δ19F(ppm from CFCl3)

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 $\delta(^{19}F)$ = 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 $[^{18}F]OF_2$ formed during the cyclotron irradiation process. The relative amount of $[^{18}F]F_2$ could be considered equivalent to the amount of $[^{18}F]HF$ as the reaction of $[^{18}F]F_2$ with H_2 should be quantitative. In some cases, however, not all of the $[^{18}F]F_2$ was converted to $[^{18}F]HF$; the reasons for incomplete conversion remain unclear. Nonetheless, the determination of $[^{18}F]OF_2$ 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 $[^{18}F]OF_2$ 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 $[^{18}F]OF_2$. 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

Expt.	Production Irr.[a]	Recovery Irr.[b]	%[^{18}F]OF_2	%[^{18}F]HF
	min.	Amount 1%F_2, psi		
EOB_1 Irradiation Time Variation				
1	20	117	3.6	87.3
2	40	102	3.5	85.9
3	60	96	4.9	55.1
1%F_2, EOB_2 Target Mixture Variation				
4	30	170	4.0	58.3
5[c]	30	212	2.8	95.5
6[c]	30	170	7.0	59.5
Single Irradiation				
7.	30 min.; 50 psi 5%F_2 in Kr plus 150 psi $^{18}O_2$		53.2	32.3

(a) Production irradiation beam currents were all 30 μA.

(b) Recovery irradiations were all 15μA for 15 min.

(c) Modified 2S method; 30 psi $^{18}O_2$ 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.[57] The results of this study demonstrate that the target mixture can comprise more than $[^{18}F]OF_2$. This compares with 10 - 20% reported for single and modified double irradiation procedures previously reported.[43] The $[^{18}F]OF_2$ which could be separated from the $[^{18}F]F_2$ by removal of fluorine at -196 °C could be obtained in reasonable quantities. This, in turn, provides another ^{18}F-labelled inorganic molecule available for radiochemical labelling.

CHAPTER 4

APPLICATION OF ^{18}F TO THE INVESTIGATION OF THE LEWIS ACID ACTIVATION OF F_2

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 XeF_2 by simple exposure of Xe/F_2 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 KrF_2, which uses activation sources such as electrical discharge[59] 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 $\Delta H_{(dissoc)}$ equal to 37.72 kcal mol^{-1}.[61]

The synthetic route to compounds such as $XeF^+AsF_6^-$, has traditionally begun with the preparation of the XeF_2, followed by reaction with a Lewis acid, such as AsF_5.[62] The fluoride ion acceptor abilities of the Lewis acids BF_3, AsF_5, SbF_5, described by Bartlett and Robinson,[63] were demonstrated by the removal of a fluoride ion from IF_7 to produce the IF_6^+ cation.[64] The fluoride ion acceptor abilities of the Lewis acids have been utilized to prepare many noble gas cations.[65] The first NF_4^+ salts were prepared by reaction of mixtures of NF_3, F_2 and a Lewis acid, MF_n, (M = B, As, an Sb).

$$NF_3 + F_2 + MF_n \longrightarrow NF_4^+[MF_{n+1}] \qquad (4.1)$$

Tolberg *et al.*[66] prepared $NF_4^+SbF_6^-$ in HF at 200 °C with a total pressure of 150 atm. At the same time, Christe *et al.*[67] were able to prepare $NF_4^+AsF_6^-$ 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_4^+ salts increased with decreasing Lewis acidity.[67,68,69] This suggested that the Lewis acid might have been responsible for the enhanced oxidizing ability of the fluorine.[66] Original papers by Christe,[70] however, postulated that the generation of either NF_3^+ or F^+ radical cations, and subsequent reaction with F_2 or NF_3, respectively, were responsible for the formation of NF_4^+ salts. These contradicting arguments provided no clear understanding as to what role the Lewis acids actually played in the synthesis of NF_4^+ salts.

Later,[71] through kinetic studies of the decomposition of the salts $NF_4^+AsF_6^-$ and $NF_4^+BF_4^-$, the following reversible reaction mechanism was elucidated

$$F_2 \rightleftharpoons 2F\cdot \qquad (4.2)$$

$$F\cdot + NF_3 \rightleftharpoons \cdot NF_4 \qquad (4.3)$$

$$\cdot NF_4 + AsF_5 \rightleftharpoons \cdot NF_3^+AsF_6^- \qquad (4.4)$$

$$\cdot NF_3^+AsF_6 + F\cdot \rightleftharpoons NF_4^+AsF_6^- \qquad (4.5)$$

In equation (4.4), the Lewis acid, AsF_5, can be seen to act merely as a fluoride ion acceptor, stabilizing the $\cdot NF_3^+$ radical cation. Recombination of $\cdot NF_3^+$ 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^+ cation (equation 4.6)

$$Xe + F_2 + 2Sb_2F_{11}^- \longrightarrow XeF^+Sb_2F_{11}^- \qquad (4.6)$$

The labile intermediate emerald green Xe_2^+ cation was formed from the reaction between the XeF^+ cation and elemental xenon according to equation (4.7)

$$3Xe + 3XeF^+Sb_2F_{11}^- + 2SbF_5 \rightleftharpoons 2Xe_2Sb_2F_{11}^-\cdot XeF^+Sb_2F_{11}^- \qquad (4.7)$$

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^+ 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]

$$SbF_5 + F_2 \longrightarrow F_5SbF^{\delta-}\cdots F^{\delta+} \qquad (4.8)$$

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 $Xe_2F_3^+$ 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

$$e + \tfrac{1}{2}F_{2(g)} + A_{(g)} \longrightarrow AF^-_{(g)} \qquad (4.9)$$

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 $[^{18}F]AsF_5$ or $[^{18}F]F_2$ 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}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}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 $[^{18}F]F_2$, 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 $[^{18}F]AsF_5/F_2$ and $AsF_5/[^{18}F]F_2$ systems

	^{18}F Source	Conditions,°C [a]	Initial ^{18}F,mCi	% ^{18}F on AsF_5 [b]	% ^{18}F on F_2
1.	$[^{18}F]$-AsF_5	-60 , dark	37.9	≈100	0.016
				(71.4)	(28.6)
2.	$[^{18}F]$-F_2	-70 , dark	66.4	0.6	98.8%
				(67.6)	(32.4)
3.	$[^{18}F]$-F_2	-70 , dark	41.8	0.4	≈100
				(83.3)	(16.7)

(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}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}F activity onto the fluorine in the experiment employing $[^{18}F]AsF_5$ 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}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_5/F_2 Activated Complex

The existence of the AsF_5/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 $[^{18}F]AsF_5$, a significant fraction of the ^{18}F was transferred onto the relatively insoluble salt, $XeF^+AsF_6^-$, formed in the solution.

$$[^{18}F]AsF_5 + F_2 + Xe \longrightarrow F_5AsF\text{-}XeF^+ + F_2 + AsF_5 \qquad (4.10)$$

Actual ^{18}F activity		1.9% ± 0.2%	0.0[a]	98%[b]

(a) below measurable limits, (b) calculated by difference from $[^{18}F]XeF^+AsF_6^-$

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 $[^{18}F]F_2$ 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:

$$Xe + F_2 + AsF_5 \longrightarrow Xe\text{---}^{\delta+}F\text{---}^{\delta-}F\text{---}AsF_5 \longrightarrow XeF^+AsF_6^- \quad (4.11)$$

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

$$F_2 + AsF_5 \rightleftharpoons {}^{\delta+}F\text{--}^{\delta-}F\text{--}AsF_5 \quad (4.12)$$

which produces the weakly bound, transient F_2---AsF_5 activated complex. A ^{19}F NMR study of mixtures of gaseous F_2 and liquid AsF_5 at -78 °C did not reveal any significant change in the F_2 chemical shift relative to pure F_2. Interestingly, the rather broad linewidth of gaseous F_2 (approx. 10 ppm at half height) narrows dramatically when dissolved in AsF_5 (Figure 4.1). A small population of F· radicals, which are present in the gas phase, would be responsible for the line broadening. Once dissolved in the AsF_5, the F· radicals may then be sequestered by the solvent as AsF_6· radicals, ultimately narrowing the F_2 resonance. Nonetheless, the F_2-AsF_5 complex could not be detected as changes in the F_2 chemical shift.

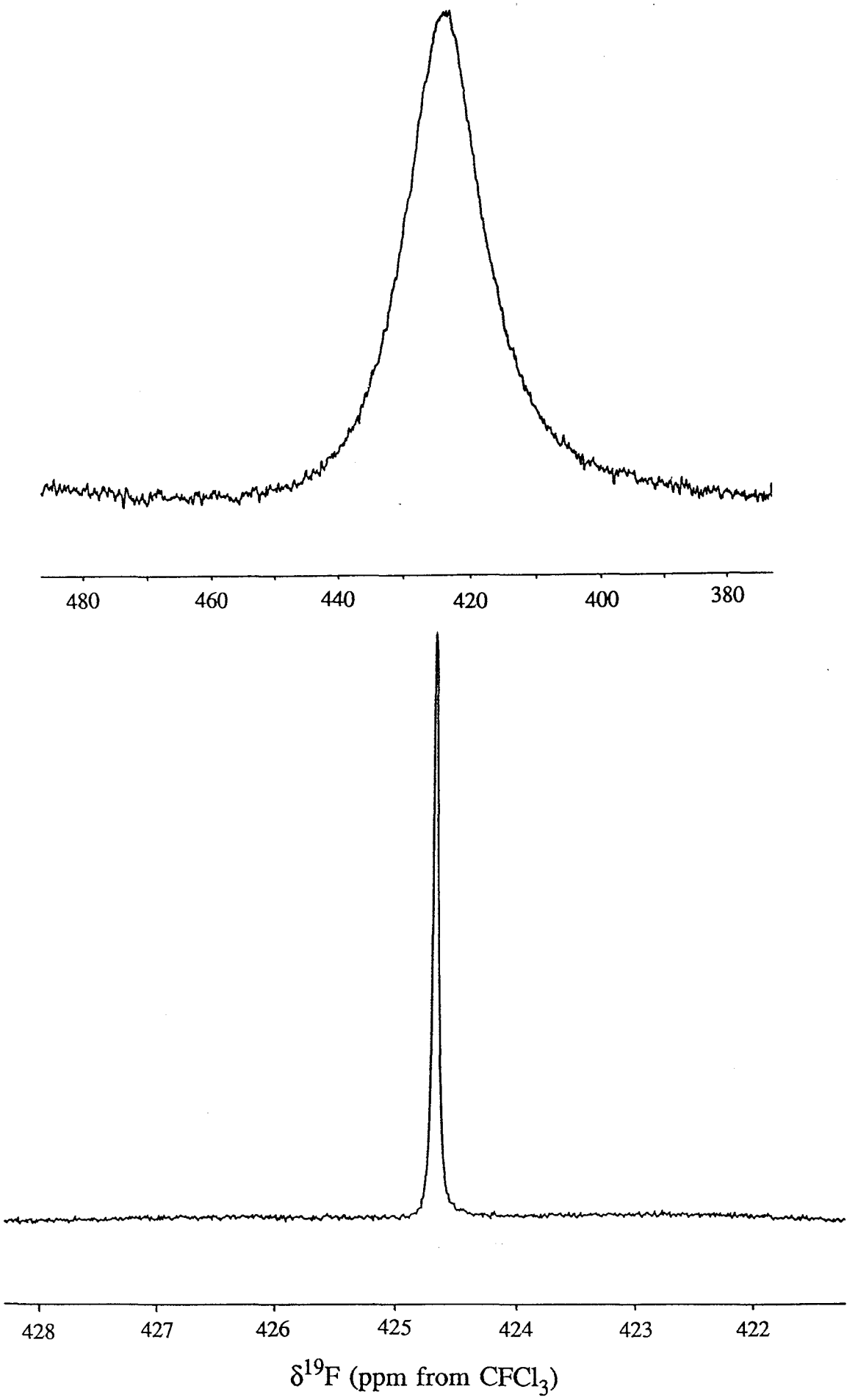
In comparison to the NF_4^+ formation mechanism, interaction of the Lewis acid in this case, results in the formation of a more oxidizing species, specifically, the $F^{\delta+}$.

Table 4.2. $Xe/F_2/AsF_5$ ^{18}F Exchange Experiments

Expt.	^{18}F Source	Initial ^{18}F Activity, mCi	$\%^{18}F$ exchanged	Conditions T, °C	Conditions P, atm	Rxn. time, min
1	$[^{18}F]$-AsF_5	32.4	1.9 ± 0.2	-60	1	30
2	$[^{18}F]$-F_2	41.9	6 ± 1	-70	9	60
3	$[^{18}F]$-F_2	86.0	24 ± 1	-70	9	165

(a) All reactions were carried out in liquid AsF_5 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; δ = 424.6 ppm, both spectra aquired in ca. 1000 scans.


480
460
440
420
400
380
428
427
426
425
424
423
422
δ19F (ppm from CFCl3)

The purpose of the present work is to investigate the same reactions beginning with radiolabelled $[^{18}F]F_2$. 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}F distribution would be

$$\underset{}{Xe} + \underset{100\%}{[^{18}F]F_2} + \underset{0\%}{AsF_{5(excess)}} \longrightarrow \underset{100\%}{[^{18}F]XeF^+AsF_6^-} + \underset{0\%}{AsF_5} \qquad (4.13)$$

However, it has been shown that reaction times on the order of days are required to achieve significant yields. Also, ^{19}F NMR studies have shown that exchange occurs between the AsF_5 solvent and AsF_6^- anions. In excess AsF_5 solvent, the ^{18}F activity could be rapidly exchanged off the anion and on to the solvent according to equilibrium (4.14)

$$[^{18}F]AsF_6^- + AsF_{5(excess)} \rightleftharpoons [^{18}F]As_2F_{11}^- \rightleftharpoons AsF_6^- + [^{18}F]AsF_{5(excess)} \qquad (4.14)$$

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

$$AsF_5 + [^{18}F\text{-}Xe^+]\text{--}F\text{-}AsF_5 \rightleftharpoons AsF_5\text{--}^{18}F\text{--}Xe\text{--}F\text{--}AsF_5 \rightleftharpoons [^{18}F]AsF_6^-\text{--}Xe\text{-}F + AsF_5 \qquad (4.15)$$

Owing to the small relative number of cation fluorines (1/7 of the total for $XeF^+AsF_6^-$) compared to the large excess of solvent fluorines, most of the ^{18}F 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 $[^{18}F]AsF_5$ as the ^{18}F source, no ^{18}F was expected to be transferred to the fluorine if a free radical mechanism were operative.

$$[^{18}F]AsF_5 + F_2 + Xe \longrightarrow [^{18}F]F_5As\text{--}^{\delta-}F\text{--}^{\delta+}F\text{--}Xe \longrightarrow F_5AsF^-XeF^+ + F_2 + AsF_5 \qquad (4.16)$$

Actual ^{18}F activity	$1.9\% \pm 0.2\%$	0.0^a	$98\%^b$

(a) below measurable limits, (b) calculated by difference from $[^{18}F]XeF^+AsF_6^-$

The radiochemical yield was calculated as the amount of ^{18}F activity transferred from the initial ^{18}F source. For experiments which used $[^{18}F]F_2$ and unlabelled AsF_5 solvent, the radiochemical yield was calculated as the amount of activity remaining in the reaction vessel after the $[^{18}F]F_2$ was removed. For experiments in which $[^{18}F]AsF_5$ is the initial radiofluorine labelled substance, the radiochemical yield was calculated as the amount of ^{18}F activity remaining on the salt after both F_2 and AsF_5 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]

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

total # F positions	14	9	5

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 °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 °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 $XeF^+AsF_6^-$

Expt.	% Radiochemical Yield[a]	% Gravimetric Yield
2	6 ± 1	5 ± 1
3	24 ± 1	21 ± 2

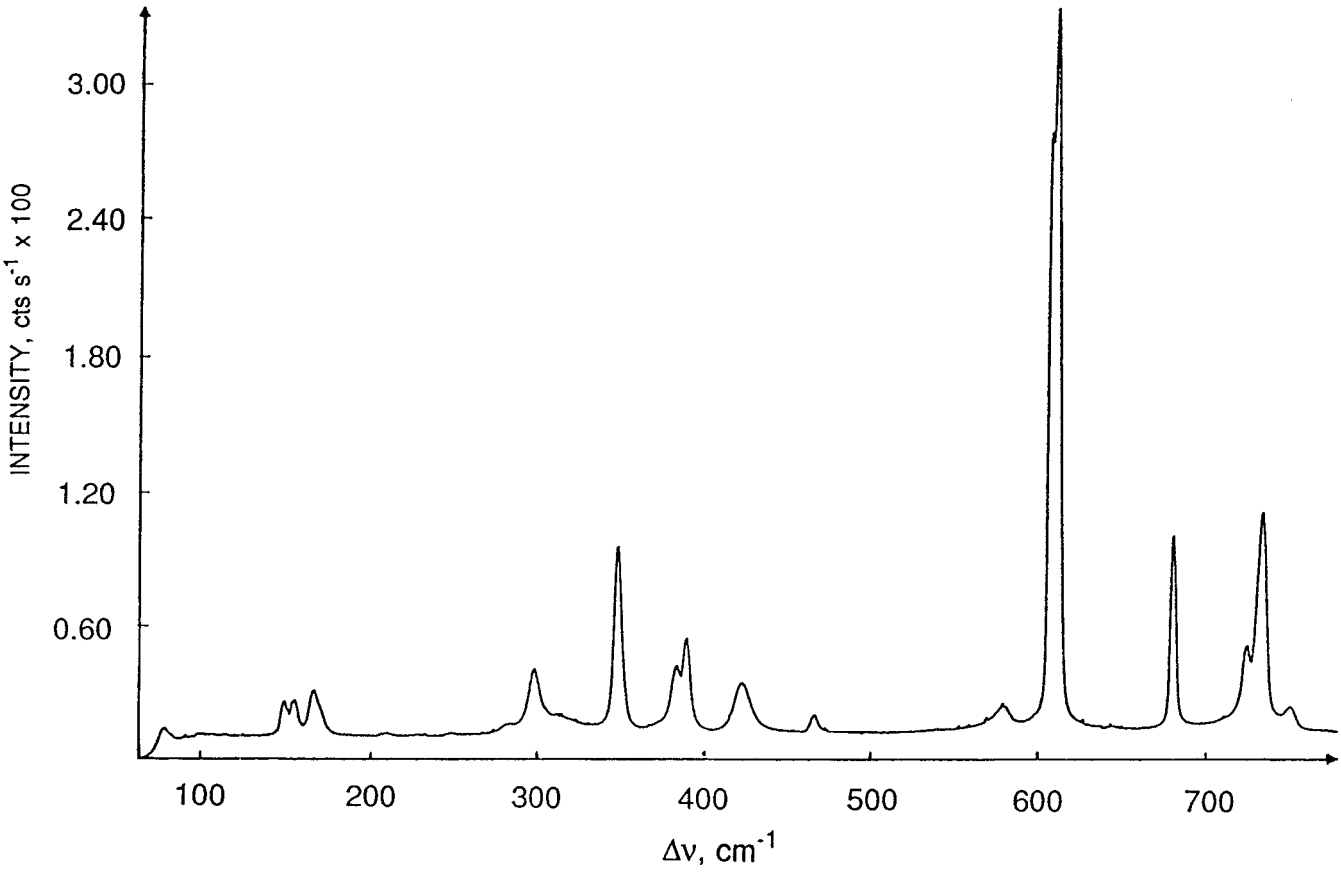
(a) Radiochemical yields are based on ^{18}F activity transferred and are artificially high as they include small amounts of ^{18}F activity adhering to the vessel walls.

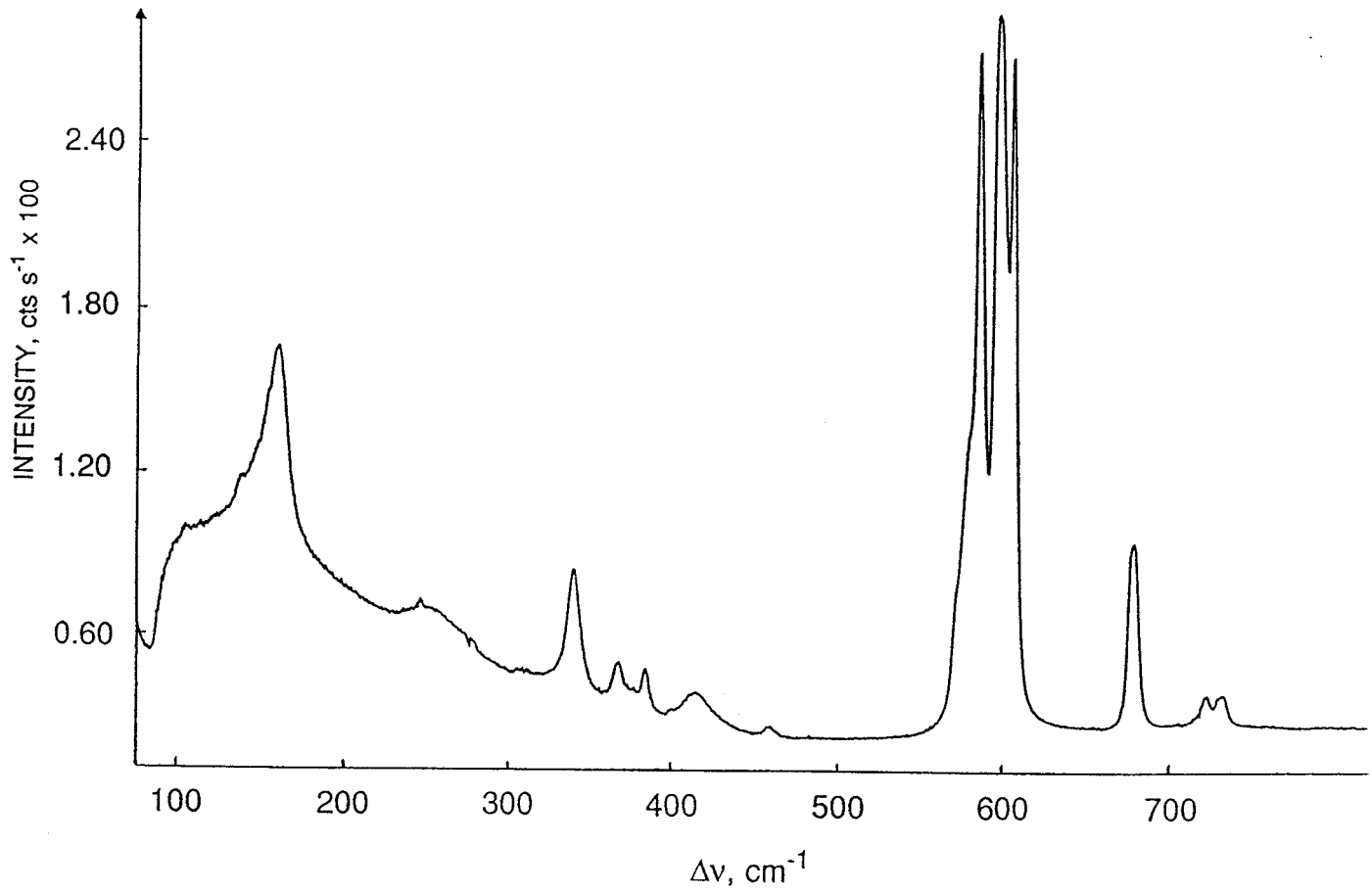
Table 4.4. ^{18}F Study of the Decomposition of $XeF^+AsF_6^-$ to $Xe_2F_3^+AsF_6^-$ Under Dynamic Vacuum

	% ^{18}F remaining on the $Xe_2F_3^+AsF_6^-$ salt	
	Actual[a]	Theoretical
After 1st pumping cycle	70	64
After 2nd pumping cycle	67	64

(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 $Xe_2F_3^+AsF_6^-$ (bottom)


3.00
2.40
1.80
1.20
0.60
INTENSITY, cts s-1 x 100
100
200
300
400
500
600
700
Δν, cm-1


2.40
1.80
1.20
0.60
INTENSITY, cts s-1 x 100
100
200
300
400
500
600
700
Δν, cm-1

was identified by the ν[Xe-F] stretching band at 607 cm^{-1} and the ν[Xe··F] bridging fluorine stretch at 345 cm^{-1}.[77] The salt, $Xe_2F_3^+AsF_6^-$, recovered after $XeF^+AsF_6^-$ was pumped on under high vacuum at room temperature, was identified by its three ν[$Xe_2F_3^+$] characteristic stretching bands at 586, 598, and 606 cm^{-1} (Figure 4.2).[77]

4.3 CONCLUSIONS

The ^{18}F studies of the Lewis acid enhanced oxidative fluorination of xenon have been studied by using [^{18}F]AsF_5 and [^{18}F]F_2 as radiotracer. The results are complicated by the exchange reactions that are found to occur between a newly formed [^{18}F]AsF_6^- anion and an unlabelled AsF_5 solvent. When the ^{18}F source is [^{18}F]AsF_5 these exchange reactions are "invisible" since the activity is transferred from the solvent to the salt directly through the reaction

$$Xe + F_2 + [^{18}F]AsF_5 \longrightarrow XeF^+[^{18}F]AsF_6^- \qquad (4.18)$$

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}F activity off of the solvent. Of primary importance, was the absence of [^{18}F]F_2 which precludes the possibility of a radical mechanism.[31]

Moreover, experiments that used [^{18}F]F_2 as an ^{18}F source provided direct observation of the fast exchange reactions that have been observed between the insoluble $XeF^+AsF_6^-$ salt and 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, F_2 and AsF_5, 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 AsF_5, 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_2 ACTIVATED COMPLEX

5.1 INTRODUCTION

5.1.1 Oxidative Fluorinators and the Oxidizer Strength Scale

The activated complex, F_5As--F-F, is an oxidative fluorinator as it has been shown that a formal "F^+" 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_5As--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_5, results in the formation of $Cl_2F^+AsF_6^-$,[71] a stable oxidative fluorinating salt capable of oxidizing xenon gas to $Xe_2F_3^+$.[70]

Recently, Christe, *et al.*[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^+ detachment energy (FPD). The FPD is expressed relative to that of the hypothetical free F^+ cation, which is assigned a value of 0 kcal mol^{-1}, and represents the amount of energy required for the reaction step

$$XF^+_{(oxid)} \longrightarrow X_{(prod)} + F^+ \quad \text{(for X = Kr, FPD = 115.9 kcal mol}^{-1}\text{)} \qquad (5.1)$$

For any oxidative fluorinator, there is a conjugate, non-oxidized form ($X_{(prod)}$, 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.

$$KrF^+ + Xe \longrightarrow XeF^+ + Kr \qquad (5.2)$$

With excess KrF^+, the reaction can proceed all the way to Xe(VI), namely the XeF_5^+ cation, which has an FPD of 158.9 kcal mol^{-1}, just above XeF^+ on the oxidizer strength scale. The $\Delta H^\circ_{reaction}$ for equation (4.2) can be calculated from the FPD values for KrF^+ and XeF^+ listed in the oxidizer scale.

$$\Delta H^\circ = FPD_{(oxid)} - FPD_{(prod)} \qquad (5.3)$$

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, ΔH° = -48.9 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.[3] 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_2 activated complexes, a series of experiments of the general form

$$A\text{--}F\text{-}F + D \longrightarrow AF^- DF^+ \qquad (5.4)$$

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_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,

$$MF_{n-1} + F\text{-}F \rightleftharpoons [MF_{n-1}\text{--}^{\delta-}F\text{--}^{\delta+}F] \qquad (5.5)$$

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

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

$$DF_m + MF_{n-1} \longrightarrow DF_{m-1}{}^+MF_n^- \qquad (5.6)$$

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,[78] the salts, $ArF^+SbF_6^-$ and $ArF^+AuF_6^-$, are predicted to be stable.[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^+ [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.[52] Alternatively, the oxidizer scale predicts that the reaction between KrF^+ and OF_2 should produce OF_3^+.

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

However, previous attempts at this reaction have not shown any evidence for the

formation of OF_3^+.[80]

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

$$AsF_5 + F_2 + OF_2 \longrightarrow OF_3^+AsF_6^- \qquad (5.8)$$

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^+.

$$Kr + F_2 + AsF_5 \longrightarrow KrF^+AsF_6^- \qquad (5.9)$$

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]

$$KrF^+AsF_6^- + BrF_5 \longrightarrow BrF_6^+AsF_6^- + Kr \qquad (5.10)$$

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}F NMR spectrum of BrF_6^+ at approximately 340 ppm relative to $CFCl_3$.[5] The ^{19}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}Br and ^{81}Br (50.69% and 49.31% natural abundances, respectively[9]), 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 inperceptible. No multiplet was observed in the ^{19}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 $[^{18}F]$-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}F activity transferred from the $[^{18}F]$-F_2 to the AsF_5 solvent in the binary system was less than the background error associated with the $[^{18}F]$-F_2 passivation of the reaction vessel. In the krypton system, however, a small percentage of the ^{18}F activity

Table 5.1. Comparative ^{18}F Exchange Values for the $Kr/[^{18}F]F_2/AsF_5$, $AsF_5/[^{18}F]F_2$, and $Xe/[^{18}F]F_2/BF_3$ Systems

Experiment	Initial ^{18}F, mCi	$\%^{18}F$ transferred	Reaction Time, hr
AsF_5/F_2	41.8	0.4 ± 0.4	1
AsF_5/F_2	66.4	0.6 ± 0.6	½
$Kr/F_2/AsF_5$	30.3	4.6 ± 1.9	1
$Kr/F_2/AsF_5$	24.9	2.4 ± 2.0	2
$Xe/F_2/BF_3$	42.3	0.8 ± 0.8	1

appeared to have been transferred off the $[^{18}F]F_2$. 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}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}F activity was exchanged.

In the absence of any chemical or physical evidence for the formation $KrF^+AsF_6^-$ salt, and, if the ^{18}F results are considered to be significant, an alternative explanation for the ^{18}F activity transfer must be sought. Possibly, a weak three bodied intermediate of the form $Kr\text{--}^{\delta+}F\text{-}F^{\delta-}\text{--}AsF_5$, 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}F results were real or an artifact of the $[^{18}F]F_2$ 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}F activity off of the $[^{18}F]$-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}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}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}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}F transfer between the $[^{18}F]F_2$ 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_2F^+ has an FPD energy of

139.3 kcal mol^{-1}, approximately half way between XeF^+ and KrF^+.

$$N_2 + F\text{-}F + AsF_5 \longrightarrow N_2F^+AsF_6^- \qquad (5.11)$$

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 $CsSO_4F$ AS AN ^{18}F 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 ^{18}F onto biologically active aromatic amino acids. For example, 3,4-dihydoxyphenlyalanine (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,[84] consequently, much effort has gone into the preparation of ^{18}F labelled biological tracers of this type.

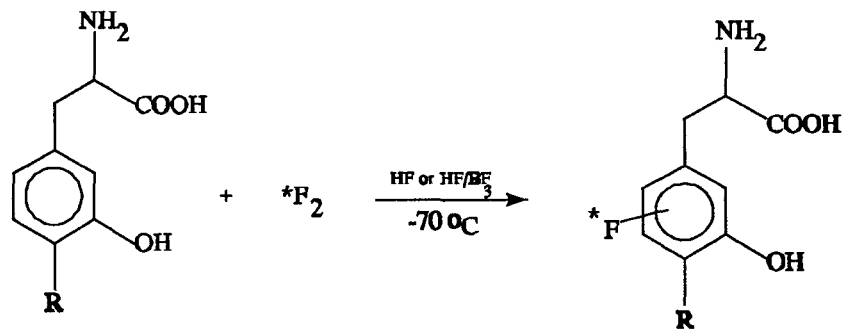
6.1.1 Cesium Fluoroxysulphate and Other Electrophilic Fluorinating Agents

Fluoroxysulphate was first noted by Fichter[85] 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.*[86] prepared and characterized $M^+SO_4F^-$ (M = Rb, Cs). The SO_4F^- ion was the first example of an ionic hypofluorite,[87] 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

$$MSO_4F \longrightarrow MSO_3F + \tfrac{1}{2}O_2 \qquad (6.1)$$

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_5^- at room temperature.[85] Later, it was determined that SO_4F^- was stable in CH_3CN for a period of hours, and consequently, this solvent provided a suitable media for the first reactions between SO_4F^- and aromatic compounds.[6] Other electrophilic fluorinating agents, including molecular

fluorine itself, will substitute fluorine for hydrogen on aromatic compounds under controlled reaction conditions.[89] The reactivity and selectivity of F_2 towards aromatic amino acids such as tyrosine, *m*-tyrosine and 3,4-dihydoxyphenylalanine have been studied using low specific activity [^{18}F]-F_2.[90] Successful ^{18}F substitution of fluorine onto the aromatic ring has been obtained by low temperature fluorinations with dilute fluorine (1% F_2 in Ne) in various acid media[90] (equation 6.2, fluorination of L-dopa in HF/BF_3, R = OH)



(6.2)

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

Trifluoromethyl hypofluorite, CF_3OF, has been shown to fluorinate activated aromatic systems[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_3OF.

The electrophilic fluorination chemistry of acetyl hypofluorite, CH_3COOF, has

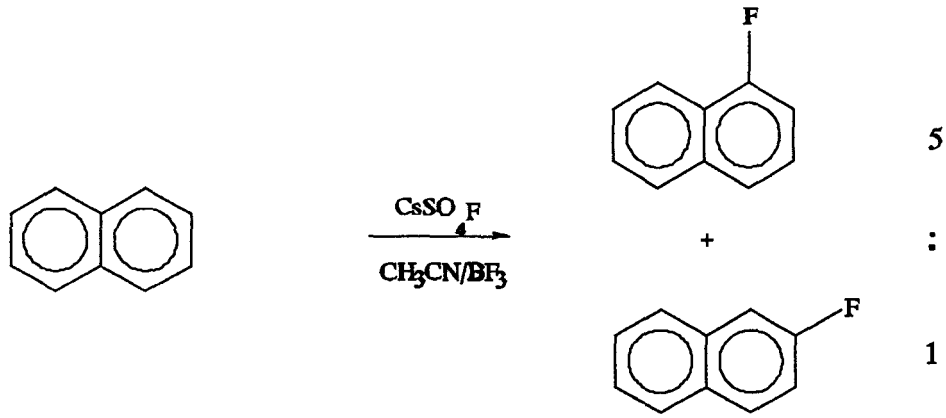
been well developed.[82] Also, its application to the field of nuclear medicine has been demonstrated by the successful preparation of [^{18}F]-CH_3COOF from [^{18}F]-F_2 and acetate salts,[92,93] and the subsequent production of ^{18}F-labelled aromatic amino acids.[8] Regiospecific production of [^{18}F]-6-fluorodopa was achieved from an aryl mercury derivative of L-dopa functionalized at the 6-position and [^{18}F]-CH_3COOF.[94]

The reaction chemistry of XeF_2 with organic compounds has been reviewed.[95] Xenon difluoride has been labelled with ^{18}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, XeF_2 has not been considered a viable electrophilic fluorinator for radiotracer work.

6.1.2 Regiospecific Nature of $Cs^+SO_4F^-$

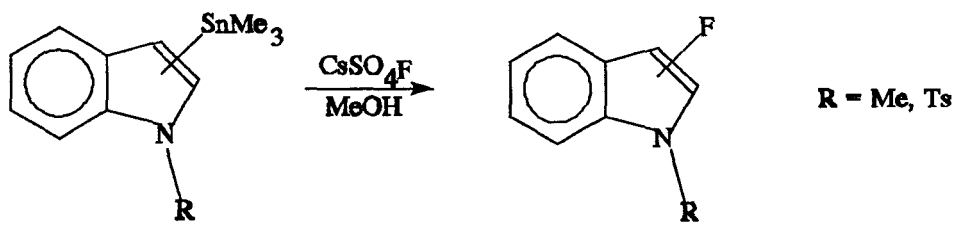
The first reports that $Cs^+SO_4F^-$ is a good candidate for the electrophilic fluorination of aromatic compounds were based on the results from BF_3 catalyzed reactions of SO_4F^- in CH_3CN with benzene, toluene, biphenyl and naphthalene.[6,98] All of the reactions gave monofluorinated compounds as 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 SO_4F^- *via* fluoro-destannylation of aryl[99] and heteroaryl



(6.3)

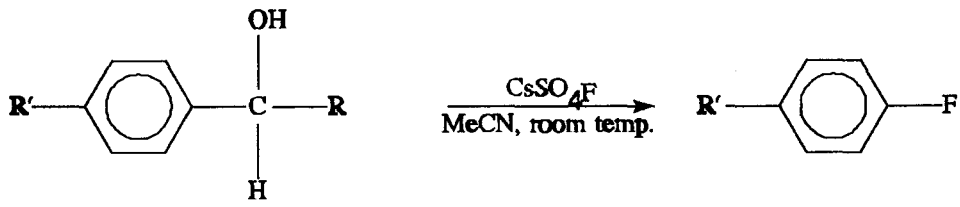
substrates.[100] Fluoro-substituted indoles were prepared by fluorination of trimethylstannyl indole derivatives with solutions of $CsSO_4F$ in methanol.



(6.4)

The most recent method for the selective fluorination of aromatics with $CsSO_4F$ has demonstrated that SO_4F^- in CH_3CN will displace hydroxyalkyl substituents on aromatic rings.[101]

For the reaction of $CsSO_4F$ with 4-methoxybenzyl alcohol, a 70 % yield of the



R' = H, OMe, NHCOMe, Ph

R = H, Me, Ph

(6.5)

monofuorinated 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 hydoxyalkyl leaving group. This was an excellent indication that the SO_4F^- 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 $Cs^+SO_4F^-$

Fluorine-19 NMR spectroscopy was used to identify $Cs^+SO_4F^-$ as the major product in the reaction. The ratio of the peaks arising from SO_4F^- 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 CH_3CN, the chemical shifts (Figure 6.1) of $Cs^+SO_4F^-$ and $Cs^+FSO_3^-$ were found to be 131.9 and 37.7 ppm, respectively (132.3 and 37.5, Appelman *et al.*).[86] Both of these signals appeared as singlets as a result of the unique fluorine environments. The chemical shifts in H_2O were 153.5 ppm for SO_4F^- and 37.3 ppm for FSO_3^-.

The ratio of the peak intensities for SO_4F^- to FSO_3^- 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,

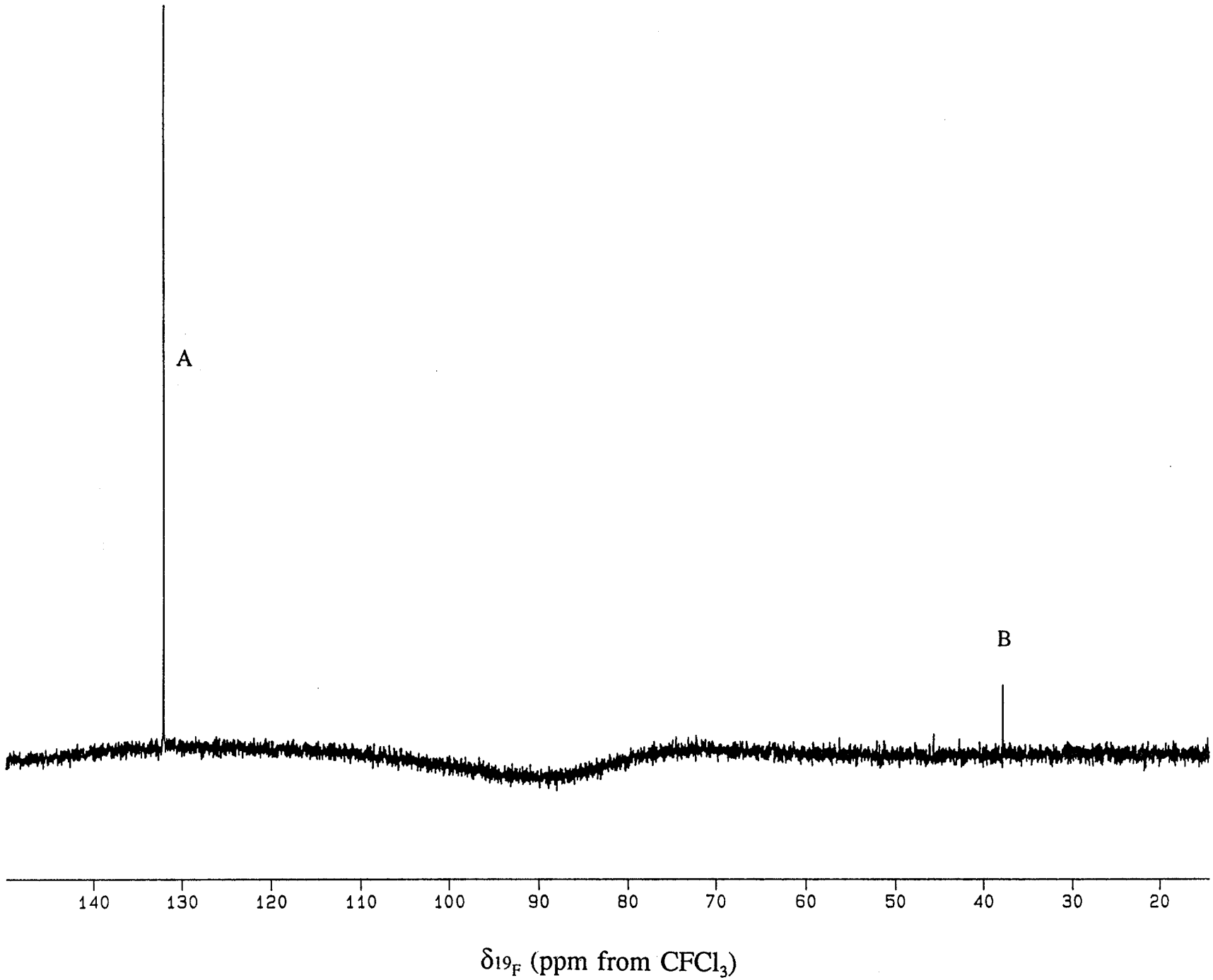
$$SO_4F^- \longrightarrow FSO_3^- + 1/2\ O_2 \qquad (6.6)$$

fluorosulphate is expected to be the only fluorine containing solid contaminant in a dried product. No other fluorine containing species were seen in the ^{19}F 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 ^{18}F Tracer Experiment

A ^{19}F NMR investigation into the decomposition of SO_4F^- in H_2O 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 $Cs^{+}SO_4F^{-}$ recorded at 30 °C in CH_3CN; (a) SO_4F^{-} and (b) FSO_3^{-}.


A
B
140
130
120
110
100
90
80
70
60
50
40
30
20
δ19F (ppm from CFCl3)

conditions. After ten minutes in water, the ratio of the peak intensities is 8.03 : 2.14 for SO_4F^- 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).

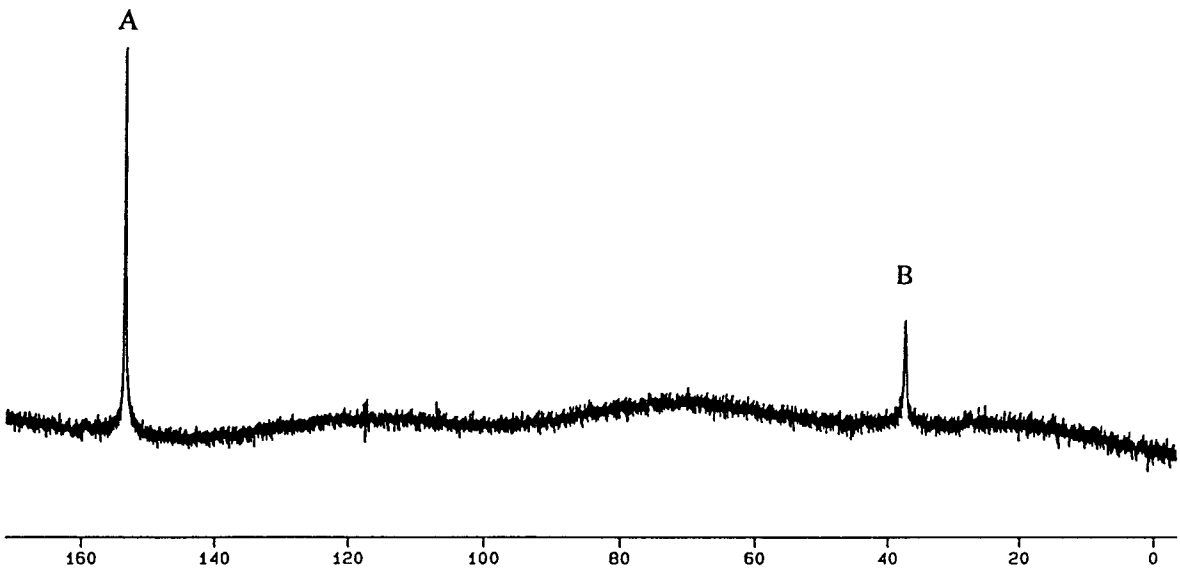
The results of these room temperature spectra emphasize the importance of consistently maintaining low temperatures throughout each step of the synthesis. In addition, the purification step, which attempts to remove the water soluble fluorosulphate from the fluoroxysulphate, will inherently induce slow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

Production of $[^{18}F]Cs^+SO_4F^-$ from the reaction of $[^{18}F]F_2$ with $CsSO_{4(aq)}$, followed directly by fluorination of the organic substrate with aqueous SO_4F^- may have been viable if the SO_4F^- ion was sufficiently stable in water. However, at room temperature, the decomposition of SO_4F^- 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.

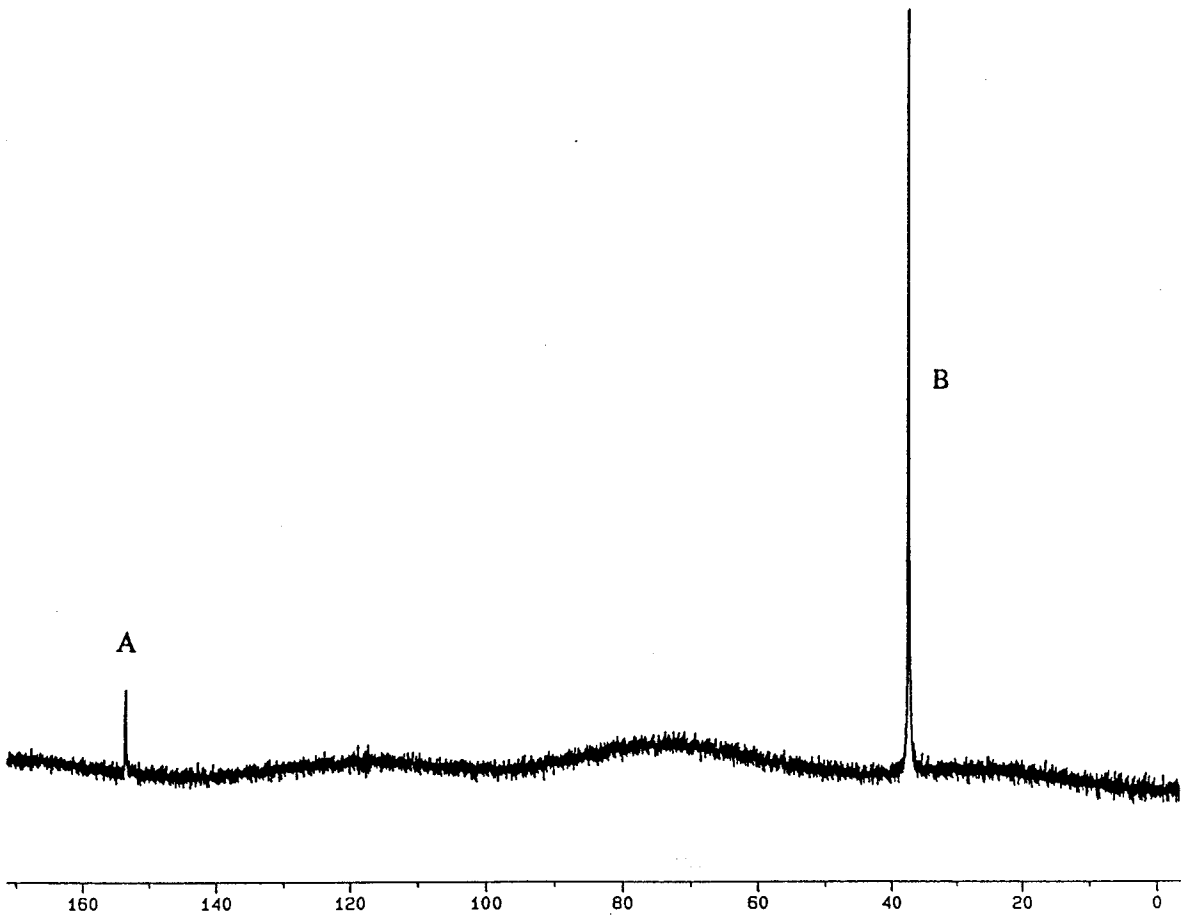
6.2.3 Separation and Identification of Fluorinated Products from Low Temperature Reactions

The desired product of the reaction between L-dopa and SO_4F^- 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 $Cs^+SO_4F^-$ recorded at 25 °C in H_2O solvent. The top spectrum was recorded 10 min. after dissolution of $Cs^+SO_4F^-$ in H_2O. The bottom spectrum was recorded 30 min. after dissolution of $Cs^+SO_4F^-$ in H_2O; (a) SO_4F^- and (b) FSO_3^-.



$\delta^{19}F$(ppm from $CFCl_3$)



$\delta^{19}F$(ppm from $CFCl_3$)

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.

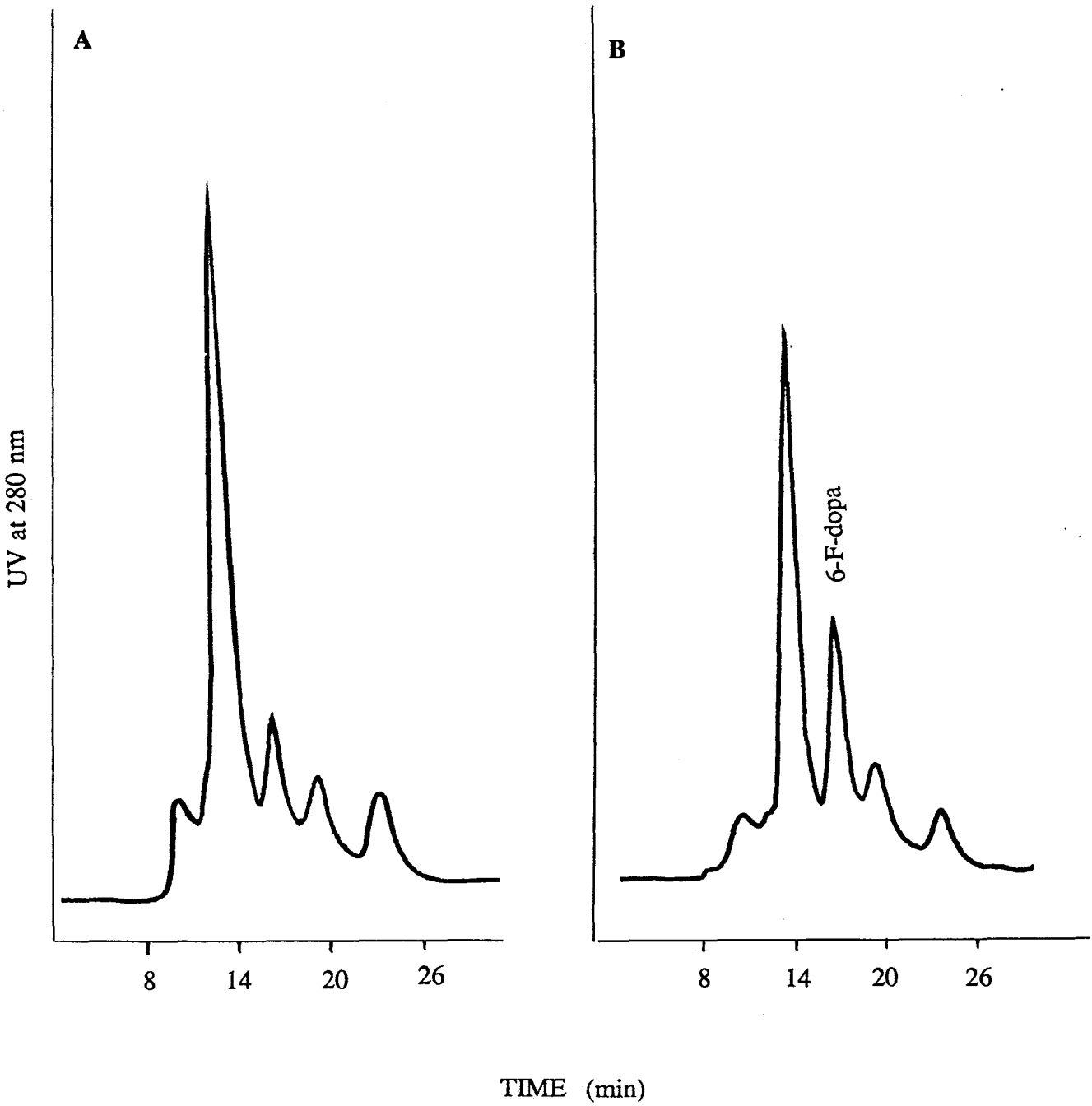
Chromatograms of the separated reaction mixture resulting from the fluorinations employing SO_4F^- in CH_3CN/BF_3 were compared to those obtained from a fluorination reaction employing molecular fluorine. The similarity of the traces provided encouraging evidence that the desired fluorinated products 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 CH_3CN 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}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_3CN solvent.

Chromatogram A - reaction mixture (0.2 ml)

Chromatogram B- reaction mixture plus 6-fluoro-L-dopa spike.


A
B
UV at 280 nm
6-F-dopa
8
14
20
26
8
14
20
26
TIME (min)

6.2.4 ^{19}F NMR of Fluoro-isomers of L-Dopa

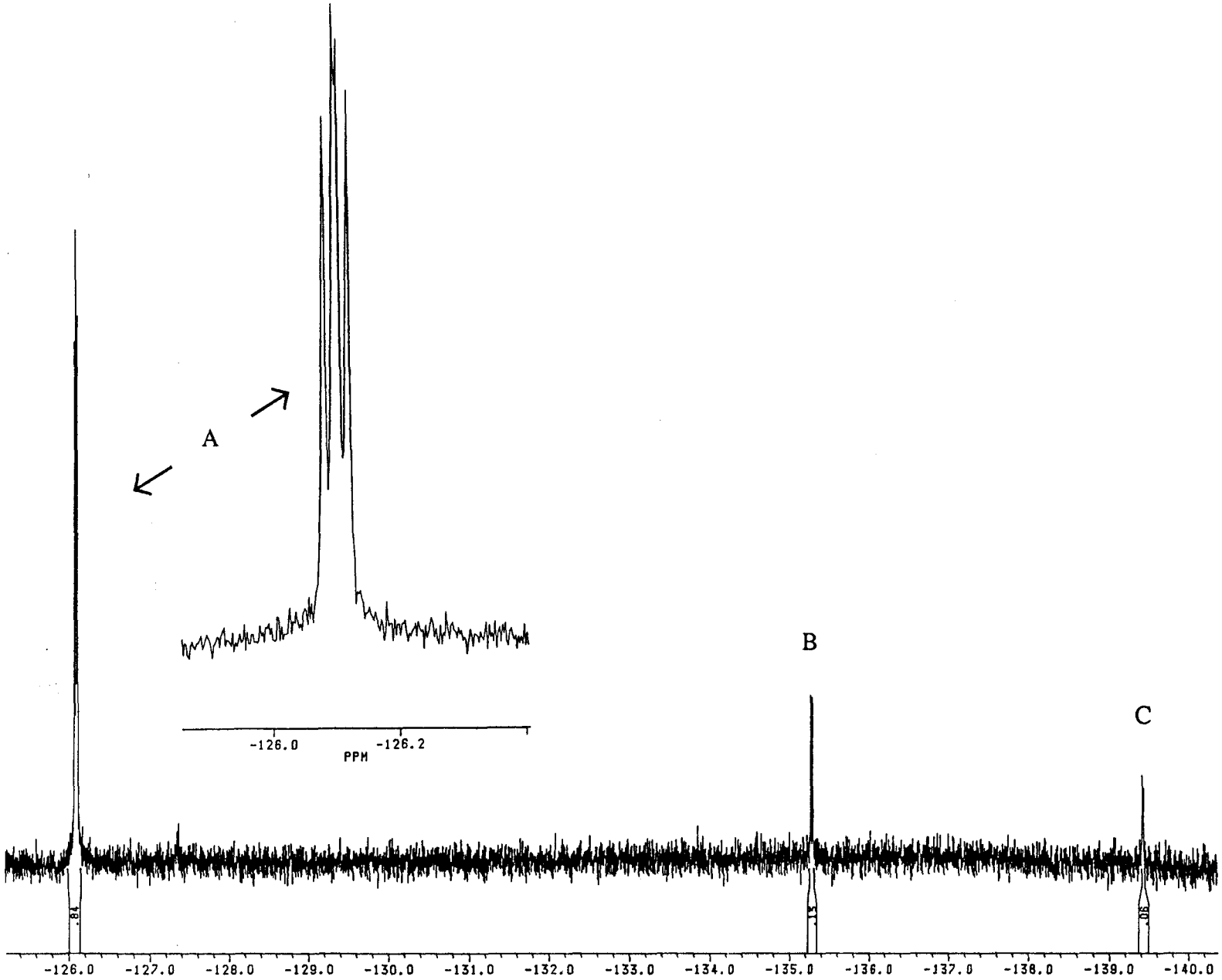
The ^{19}F NMR spectrum showed three resonances in the fluorinated aromatic region (Figure 6.4). Also a sharp singlet, a result of residual CF_3COOH, was seen at ($\delta(^{19}F)$ = -75 ppm). The doublet of doublets at -126.1 ppm was assigned to 6-fluoro-l-dopa [$^3J(^{19}F\text{-}^1H)$ = 10.4 Hz and $^4J(^{19}F\text{-}^1H)$ = 7.7 Hz]. The doublet at -135.3 has a 11.0 Hz coupling corresponding to $^3J(^{19}F\text{-}^1H)$ and was therefore assigned to 5-flouro-L-dopa. A doublet at -139.4 exhibited a 7.5 Hz coupling corresponding to $^4J(^{19}F\text{-}^1H)$ 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).[102] Therefore, these results have shown that the desired fluorinated product could be produced and separated from the product mixture of Cs^+SO_4F + 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 $Cs^+SO_4F^-$ 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 $Cs^{+}SO_4F^{-}$ plus L-dopa. Recorded at 25 °C in D_2O solvent; (a) 6-fluoro-L-dopa, (b) 5-fluoro-L-dopa and (c) 2-fluoro-L-dopa.



δ_{19_F} (ppm from $CFCl_3$)

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 SO_4F^-. The synthesis of $[^{18}F]Cs^+SO_4F^-$ with use of a stream of diluted $[^{18}F]F_2$ directly from the cyclotron has already been attempted. Though it was assumed the SO_4F^- ion was formed, subsequent reaction with an organic substrate did not result in ^{18}F-fluoro products.

The second possibility involves fluorine exchange reactions between an easily produced ^{18}F containing species and a lab bench source of high quality fluoroxysulphate. So far $[^{18}F]F^-$ 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}F by $[^{18}F]F^-$ may be plausible. Also, the possibility of inducing decomposition of the SO_4F^- to produce the more stable OF_2 species, must also be considered.

$$SO_4F^- + F^- \longrightarrow OF_2 + SO_3^{2-} \qquad (6.7)$$

Oxygen difluoride has already been identified as a viable alternative electrophilic fluorinating agent.[103] If indeed, a reaction were to occur between $CsSO_4F$ and F^-, to produce OF_2, then there is the possibility of producing $[^{18}F]OF_2$ from $^{18}F^-$ in CH_3CN with an CH_3CN solution saturated with $CsSO_4F$.

$$Cs^+SO_4F + K^+[^{18}F]F^- \xrightarrow[2,2,2\text{-crypt}]{CH_3CN} [^{18}F]OF_2 + (Cs^+)(K^+)SO_3^{2-} \qquad (6.8)$$

The reactivity and selectivity of OF_2 towards aromatic amino acids should also be considered.

REFERENCES

1. H. Moissan, *Compt. Rend.*, **1886**, 102, 1543.
2. A. L. Allred, E. G. Rochow, *J. Inorg. Nucl. Chem.*, **1958**, 5, 264.
3. K. O. Christe, D. A. Dixon, *J. Am. Chem. Soc.*, **1992**, 114, 2978.
4. R. J. Gillespie, G. J. Schrobilgen, *Inorg. Chem.*, **1976**, 15, 22.
5. R. J. Gillespie, G. J. Schrobilgen, *Inorg. Chem.*, **1974**, 13, 1230.
6. J. P. Dominic, C. D. Aurther, R. E. Winans, E. H. Appleman, *J. Am. Chem. Soc.*, **1981**, 103, 1964.
7. S. Rozen, O. Lerman, M. Kol, *J. Chem. Soc. Chem. Commun.*, **1981**, 443.
8. R. V. Chirakal, G. Firnau, J. Couse, E. S. Garnett, *Int. J. Appl. Radiat. Isot.*, **1984**, 35, 651.
9. Isotope tables, "CRC Handbook of Chemistry and Physics", 71st Ed., CRC Press, **1990**.
10. M. R. Kilbourn, "Fluorine-18 Labelling of Radiopharmacueticals", Nuclear Science Series, NAS-NS-3203, National Academy Press, Washington, 1990.
11. L. Lindner, T. H. G. A. Suer, G. A. Brinkman, J. Th. Veenboer, *Int. J. Appl. Radiat. Isot.*, **1973**, 24, 124.
12. I. Sheft, H. H. Hymen, R. M, Adams, J. J. Katz, *J. Am. Chem. Soc.*, **1961**, 83, 291.
13. J. M. Winfield, *J. Fluorine Chem.*, **1980**, 16, 1.

14. R. M. Lambrecht, R. Neirinckx, A. P. Wolf, *Int. J. Appl. Radiat. Isot.*, **1978**, 29, 175.

15. R. J. Nickles, M. E. Daube, T. J. Ruth, *Int. J. Appl. Radiat. Isot.*, **1984**, 35(2), 117.

16. H. W. Dodgen, W. F. Libby, *J. Chem. Phys.*, **1949**, 17, 951.

17. M. Azeem, M. Brownstein, R.J. Gillespie, *Can. J. Chem.*, **1969**, 47, 4159.

18. K. O. Christe, W. W. Wilson, G. J. Schrobilgen, R. V. Chirakal, *Inorg. Chem.*, **1988**, 27, 789.

19. K. O. Christe, W. W. Wilson, R. V. Chirakal, J. C. P. Sanders, G. J. Schrobilgen, *Inorg. Chem.*, **1990**, 28, 3506.

20. D. F. Shriver, P. W. Atkins and C. H. Langford, "Inorganic Chemistry", W. H. Freeman and Co., N.Y., 1990, 42.

21. C. T. Goetschel, V. A. Campanile, R. M. Curtis, K. R. Loose, C. D. Wagner, J. N. Wilson, *Inorg. Chem.*, **1972**, 11, 1696.

22. I. J. Solomon, J. N. Keith, A. Snelson, *J. Fluorine Chem.*, **1972/73**, 2, 129.

23. J. N. Keith, I. J. Solomon, I. Sheft, H. Hyman, *Inorg. Nucl. Chem. Suppl.*, **1976**, 143.

24. G. A. Olah, D. J. Donovan, J. Shen, G. J. Klopman, *J. Am. Chem. Soc.*, **1975**, 97, 3559.

25. R. W. Johnson, E. R. Holm, *J. Am. Chem. Soc.*, **1977**, 99, 8077.

26. C. S. Ewig, J. R. Van Wazer, *J. Am. Chem. Soc.*, **1989**, 111, 4172.

27. J. N. Murrel, C. E. Scollary, *J. Chem. Soc. Dalton Trans.*, **1976**, 818.

28. H. H. Michels, J. A. Montgomery, Abstracts of Air Force High Energy, Low Density Materials Contractors' Conference; Long Beach, California, Feb. 1990.

29. E. H. Appelman, R. C. Thompson, *J. Am. Chem. Soc.*, **1984**, 106, 4167.

30. E. H. Appelman, A. W. Jache, *J. Am. Chem. Soc.*, **1987**, 109, 1754.

31. R. M. Adams, B.Sc. Thesis, McMaster University, 1992.

32. L. Stein, *J. Fluorine Chem.*, **1982**, 20, 65.

33. C. Shen, R. Hagiwara, T. E. Mallouk, N. Bartlett, unpublished work.

34. C. J. Hoffman, *Inorg. Synth.*, **1953**, 4, 150.

35. R. J. Gillespie, A. Netzer, G. J. Schrobilgen, *Inorg. Chem.*, **1974**, 13, 1455.

36. G. Firnau, R. V. Chirakal, D. deWitte, W. Moore, E. S. Garnett, G. T. Bida, 1991, IVth International Workshop on Targetry and Target Chemistry, PSI, Villigen, Switzerland, R. Weinreich Ed., 134.

37. D. R. Strull, *Ind. Eng. Chem.*, **1947**, 39, 517.

38. R. V. Chirakal, unpublished results.

39. G. T. Bida, R. Ehrenkaufer, A. P. Wolf, J. S. Fowler, R. R. MacGregor, T. J. Ruth, *J. Nucl. Med.*, **1980**, 21, 758.

40. V. Casella, T. Ido, A. P. Wolf, J. S. Fowler, R. R. MacGregor, T. J. Ruth, *J. Nucl. Med.*, **1980**, 21, 750.

41. J. J. Sunderland, O. T. DeJesus, O. Solin, R. J. Nickles, VIIIth International Symposium on Radiopharmaceutical Chemistry, Princeton, New Jersey, U.S.A., **1990**, 89.

42. T. J. Ruth, A. P. Wolf, *Radiochemica Acta*, **1979**, 26, 175.

43. G. T. Bida, G. O. Henry, A. J. Bishop, N. Satgamurthy, "Proc. IVth International Worshop on targetry and Target Chemistry" PSI, Villigan, Switzerland, **1991**, 130.

44. R. V. Chirakal, R. M. Adams, G. Firnau, G. J. Schrobilgen, G. Coates, E. S. Garnett., *Nucl. Med. Biol.*, In press.

45. W. A. Cannon, S. K. Asunmaa, W. D. English, N. A. Tiner, *Trans. Metall. Soc. AIME*, **1968**, 242, 1635.

46. E. Ghibandi, A. J. Colussi, K. O. Christe, *Inorg. Chem.*, **1985**, 24, 2869.

47. G. H. Cady, *J. Am. Chem. Soc.*, **1934**, 56, 2635.

48. H. Moissan, *Ann. chim. phys.*, **1891**, 24, 224.

49. R. Schmutzler, *Angew. Chem. Int. Ed. Engl.*, **1968**, 7(6), 440.

50. E. R. Staricco, J. E. Sicre, H. J. Schumacher, *Z. physik. Chem. N.F.*, **1963**, 39, 337.

51. R. A. Ogg, J. D. Ray, *J. Chem. Phys.*, **1956**, 25, 797.

52. J. J. Turner, *Endeavour*, **1968**, 27, 42.

53. A. G. Streng, *Chem. Rev.*, **1963**, 63, 607.

54. J. F. Liebman, *J. Fluorine Chem.*, **1977**, 9, 153.

55. J. W. Nebgen, W. B. Rose, F. I. Metz, *J. Mol, Spectrosc.*, **1966**, 20, 72.

56. J. W. Nebgen, F. I. Metz, W. B. Rose, *J. Am. Chem. Soc.*, **1967**, 89, 3118.

57. A. J. Bishop, N. Satymurthy, G. Bida, M. E. Phelps, J. R. Barrio, *J. Nucl. Med.*, **1991**, 32, 1010.

58. J. H. Holloway, L. V. Streng, A. G. Streng, *Inorg. Chem.*, **1965**, 4, 1370.

59. F. Schreiner, J. G. Malm, J. C. Hindman, *J. Am. Chem. Soc.*, 87, 25.

60. J. J. Turner, G. C. Pimentel, *Science*, **1963**, 140, 974.

61. "JANAF Tables", Dow Chemical Co., Midland, Mi., **1977**.

62. J. Binenboym, H. Selig, J. Shamir, *J. Inorg. Nucl. Chem.*, **1968**, 30, 2863.

63. N. Bartlett, P. L. Robinson, *J. Chem. Soc.*, **1961**, 3417.

64. F. Seel, O. Detmer, *Z. Anorg. Allg. Chem.*, **1959**, 301, 113.

65. H. Selig, J. H. Holloway, "Cationoc and Anionic Complexes of the Noble-Gases" in F. L. Boschke, ed., *Topics in Current Chemistry*, 124, Springer-Verlag, Berlin, **1984**, pp. 33-90.

66. W. E. Tolberg, R. T. Renwick, R. S. Stringham, M. E. Hill, *Inorg. Chem.*, **1967**, 6, 1156.

67. J. P. Guertin, K. O. Christe, A. E. Pavlath, *Inorg. Chem.*, **1966**, 5, 1921.

68. K. O. Christe, R. D. Wilson, A. E. Axworthy, *Inorg. Chem.*, **1973**, 12, 2478.

69. K. O. Christe, C. J. Schack, R. D. Wilson, *Inorg. Chem.*, **1976**, 15, 1275.

70. K. O. Christe, R. D. Wilson, *Inorg. Nucl. Chem. Lett.*, **1973**, 9, 845.

71. K. O. Christe, R. D. Wilson, I. B. Goldberg, *Inorg. Chem.*, **1979**, 18, 2572.

72. D. R. Brown, M. J. Clegg, A. J. Downs, R. C. Fowler, A. R. Minihon, J. R. Norris, L. Stein, *Inorg Chem.*, **1992**, 31, 5041.

73. J. Shamir, J. Binenboym, *Inorg. Chim. Acta.*, **1968**, 2, 37.

74. J. B. Beal, C. Pupp, W. E. White, *Inorg. Chem.*, **1969**, 8, 828.

75. N. Bartlett, F. Okino, T. E. Mallouk, R. Hagiwara, M. Lerner, G. L. Rosenthal, K. Kourtakis, in "Advances in Chemistry", Series No. 226, **1990**, 391.

76. N. Bartlett, D. H. Lohmann, *Proc. Chem. Soc.*, **1962**, 277;

77. F. O. Sladky, P. A. Bulliner, N. Bartlett, *J. Chem. Soc. A*, **1969**, 2179.

78. N. Bartlett, *Proc. R.A. Welch Foundation Conf. on Chem. Research XXXII Valency*, **1988**, 259.

79. G. Frenking, W. Koch, C. A. Deakyne, J. F. Liebman, N. Bartlett, *J. Am. Chem. Soc.*, **1989**, 111, 31.

80. G. J. Schrobilgen, personal communication.

81. R. D. Chambers, Fluorine in Organic Chemistry; Wiley: New York, **1973**, pp. 391.

82. J. A. Wilkinson, *Chem. Rev.* **1992**, 92, 505.

83. R. Filler, *J. Fluorine Chem.*, **1986**, 33, 361.

84. G. Firnau, *J. Neurochem.*, **1987**, 48, 1077.

85. F. Fichter, K. Humpert, *Helv. Chim. Acta.*, **1926**, 9, 602.

86. E. H. Appelman, L. J. Basile, R. C. Thompson, *J. Am. Chem. Soc.*, **1979**, 101, 3384.

87. J. M. Shreeve, *Adv. Inorg. Chem. Radiochem.*, **1983**, 26, 132.

88. R. C. Thompson, E. H. Appleman, *Inorg. Chem.*, **1980**, 19, 3248.

89. F. Cacace, P. Giacomello, A. P. Wolf, *J. Am. Chem. Soc.*, **1980**, 102, 3511.

90. R. V. Chirakal, Ph.D Thesis, McMaster University, Hamilton, 1991.

91. D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, M. M. Pechet, *J. Chem. Soc. Chem. Commun.*, **1968**, 806.

92. D. M. Jewett, J. F. Potocki, R. E. J. Ehrenkaufer, *J. Fluorine Chem.*, **1984**, 24, 477.

93. C. Y. Shiue, P. A. Salvadori, A. P. Wolf, J. S. Fowler, R. R. MacGregor, *J. Nucl. Ned.*, **1982**, 23, 899.

94. A. L. Luxen, *J. Label. Comp. Radiopharm.*, **1986**, 24, 1623.

95. R. Filler, *Israel. J. Chem.*, **1978**, 17, 71.

96. R. V. Chirakal, G. Firnau, G. J. Schrobilgen, J. M. McKay, E. S. Garnett, *J. Appl. Radiat. Isot.*, **1984**, 35, 401.

97. G. Firnau, R. V. Chirakal, S. Sood, *J. Label. Compound. Radiopharm.*, **1981**, 18, 7.

98. S. Stavber, M. Zupan, *J. Fluorine Chem.*, **1981**, 17, 597.

99. M. R. Bryce, R. D. Chambers, S. T. Mullins, A. Parkin, *J. Chem. Soc. Chem. Commun.*, **1986**, 1623.

100. H. F. Hodson, D. J. Madge, D. A. Widdowson, *Synlett*, **1982**, 831.

101. S. Stavber, I. Košir, M. Zupan, *J. Chem. Soc. Chem. Commun.*, **1992**, 274.

102. R. V. Chirakal, G. Firnau, E. S. Garnett, *J. Nucl. Med.*, **1986**, 27, 417.

103. A. J. Bishop, N. Satyamurthy, G. Bida, M. E. Phelps, J. R. Barrios, *J. Nucl. Med.*, **1991**, 32, 1010.

APPENDIX 1 Abosolute Oxidizer Strength Scale and Formation Enthalpies for Oxidative Fluorinators

oxidative fluroniator[a] XF^+	F^+ detachment energy (kcal mol^{-1})[b] FPD (XF_g^+)	formation enthalpy (kcal mol^{-1}) $\Delta H_f°$ (XF_g^+)
(HeF^+) ($^3\pi$)	-1.6	423.6
(HeF^+) ($^1\Sigma^+$)	(-16.2)	(438.2)
(F^+)	0	422.0
(NeF^+) ($^3\pi$)	0.6	421.4
(NeF^+) ($^1\Sigma^-$)	(-19.6)	(441.6)
(F_3^+)	60.0	362.0
(ArF^+)	84.3	337.7
KrF^+	115.9	306.1
(XeF_7^+)	116.7	222.2
(OF_3^+)	122.2	305.7
(BrF_4O^+)	131.1	
(O_2F^+)	133.8	288.2
(ClF_4O^+)	135.6	251.0
N_2F^+	139.3	283.7
(XeF^5O^+)	139.8	276.2
BrF_6^+	140.8	178.7
($XeF_3O_2^+$)	141.7	336.3
ClF_6^+	147.3	215.5
XeF_3^+	152.4	243.7
ClF_4^+	158.7	224.3
XeF_5^+	158.9	200.6
$ClF_2O_2^+$	161.0	228.4
(IF_4O^+)	164.0	

XeF^+	164.8	257.2
ClF_2^+	167.1	241.9
XeF_3O^+	173.1	
BrF_4^+	174.0	187.0
IF_6^+	175.0	40.4
NF_2O^+	175.3	230.8
Cl_2F^+	179.1	242.9
NF_4^+	180.1	210.5
$(XeFO^+)$	182.4	290.1
BrF_2^+	182.4	217.2
ClF_2O^+	193.0	
$XeFO_2^+$	195.3	
BrF_2O^+	200.5	
IF_4^+	212.1	93.9
IF_2^+	213.5	185.7
(IF_2O^+)	230.0	

[a]The cations listed in parenthesis have so far not been isolated in the form of stable salts. [b]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.