FLUORIDE ION COMPLEXATION BY STIBONIUM LEWIS ACIDS-

TOWARD APPLICATION IN BIOIMAGING

A Senior Scholars Thesis

by

MERID HAILE

Submitted to the Office of Undergraduate Research
Texas A&M University
in partial fulfillment of the requirements for the designation as

UNDERGRADUATE RESEARCH SCHOLAR

April 2011

Major: Chemistry

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Approved by:

Research Advisor: François P. Gabbai
Director for Honors and Undergraduate Research: Sumana Datta

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ABSTRACT

Fluoride Ion Complexation by Stibonium Lewis Acids – Toward Application in Bioimaging. (April 2011)

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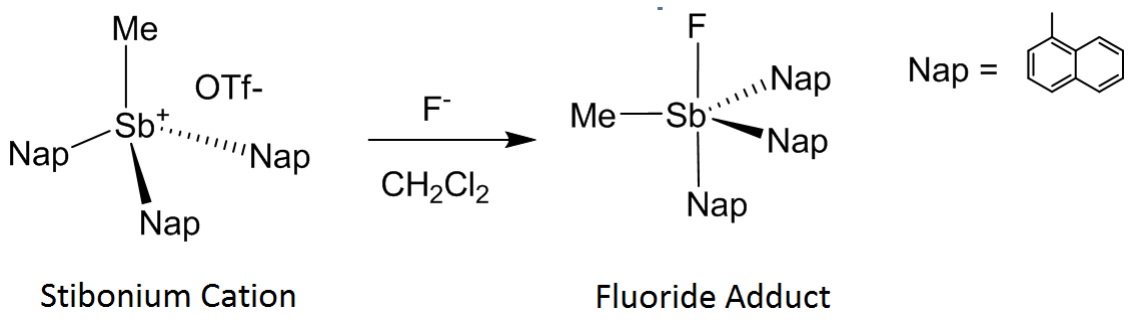
Fluoride has proven to be a helpful anion in improving dental health when added to drinking water and toothpaste but extremely detrimental to the body at higher concentrations. Its isotope ^{18}F is useful as a labeling agent in PET imaging. Due to these applications, much effort has been devoted to the development of methods allowing to sense this anion in aqueous solution. In this thesis, I will discuss the results that I have obtained on the use of stibonium cations as anion receptors. Remarkably, these antimony species react with fluoride ions in organic solvents and sometimes in aqueous solutions to form the corresponding fluorostiboranes. Formation of these fluoride species can be conveniently monitored by a variety of techniques such as UV-vis and NMR spectroscopy.



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CHAPTER I

INTRODUCTION

Positron Emission Tomography (PET) is a valuable imaging technique that can allow us to noninvasively observe the physiology of living organisms. In order to use the technology, positron emitting nuclides must be injected into the tissue of question.[1,2] ^{18}F is an excellent radioisotope for this purpose due to a relatively long half-life and ease of preparation in comparison with other positron-emitting nuclides. The half-life of ^{18}F is 110 minutes which necessitates a quick method of fixating the isotopic ion onto a biomolecule.[1-3] Finding a receptor than can easily bind the $[^{18}F]^-$ ion would be beneficial and expedient as an alternative to nucleophilically fluorinating peptides in water. Research has shown that stibonium cations are able to bond covalently to small anions in water.[4] Compounds incorporating stibonium could be used to incorporate ^{18}F ions into biomolecules for use in the introduction of the radioisotope into organisms for PET.

Stibonium compounds contain a 4-coordinate stibonium center with aryl/alkyl substituents arranged tetrahedrally. When the compound binds fluoride it becomes neutral in charge and the substituents arrange in a trigonal pyramidal structure. Such a change can be seen in UV-Vis and NMR.

This thesis follows the style of *Inorganic Chemistry.*

CHAPTER II

METHODS

Figure 1 shows the schemes used to synthesize the three target compounds of the study.

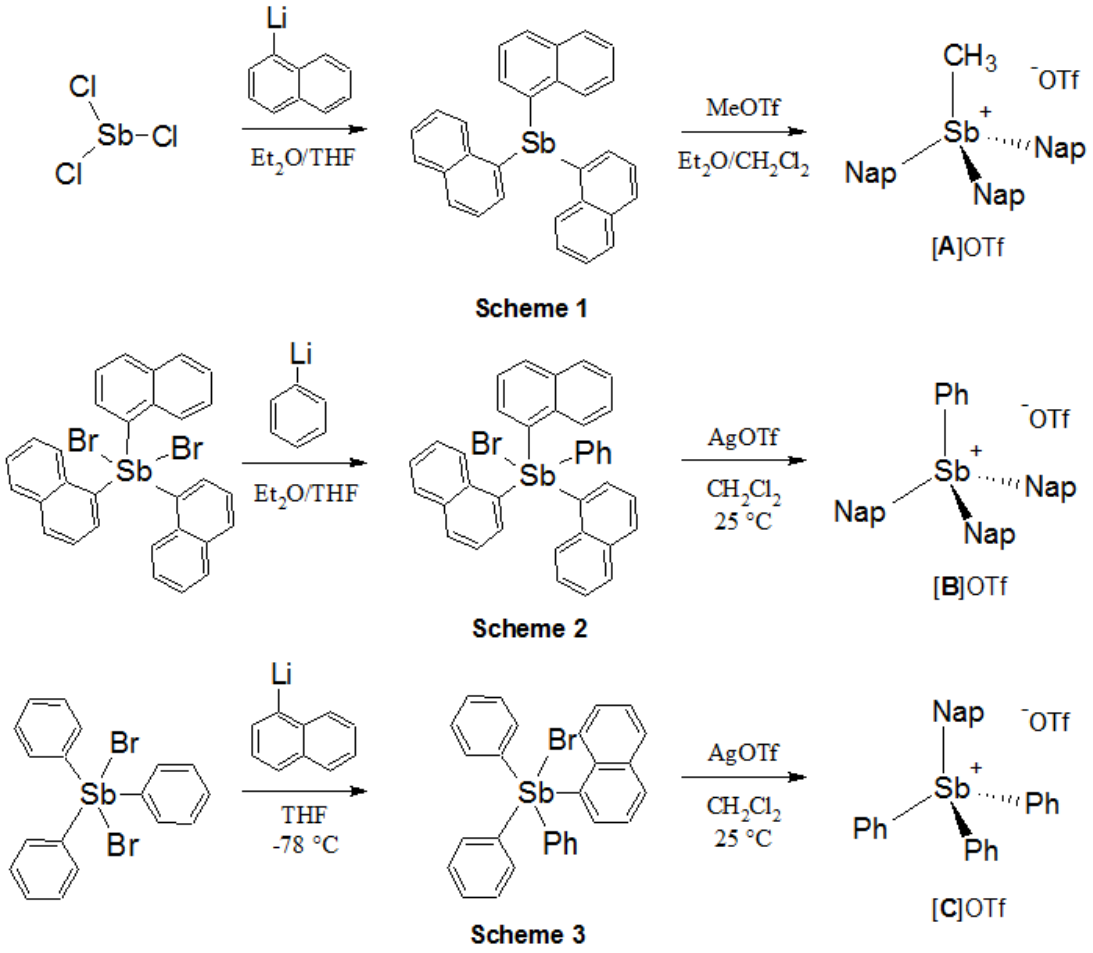

Figure 1. Schemes of synthesis of the compounds. **[A]**OTf is the stibonium cation with three naphthyl and one methyl substituent. [**B]**OTf is similar with the methyl group replaced with a phenyl group. [**C]**OTf has three phenyl groups and one naphthyl group. All compounds have triflate as the corresponding anion.

The synthetic route employed for the preparation of target compound [**A**]OTf is illustrated in Scheme 1. The starting material, $SbCl_3$ was used to quench three equivalents of naphthyl lithium to yield the intermediate trinaphthyl antimony. This was subsequently methylated with methyl triflate to yield [**A**]OTf. The yield after workup was 53% and ^{1}H NMR and ^{13}C NMR were taken to confirm the product's identity. Mass spectrometry and X-ray crystallography were also used to confirm the identity of the product [**A**]OTf.

We also attempted the synthesis of [**B**]OTf by allowing one equivalent of phenyllithium to react with di(bromo)tri(naphthyl)antimony folloed by the treatment of the putative bromotri(naphthyl)phenylantimony intermediate with silver triflate. However, ^{1}H NMR spectroscopy of the resulting mixture showed no evidence for the formation of the product. Presumably, the unsuccesful synthesis of [**B**]OTf can be explained by the bulk of the naphythyl groups, which hinder the addition of the phenyl group to the antimony center.

For the synthesis of [**C**]OTf, one equivalent of naphthyllithium was added to di(bromo)tri(phenyl)antimony to yield bromonaphthyltri(phenyl)antimony. The latter was allowed to react with silver triflate to eliminate the bromide anion to afford [**C**]OTf at 3% yield. The identity of this stibonium salt has been confirmed by ^{1}H NMR spectroscopy, elemental analysis, and X-ray.

CHAPTER III

RESULTS

[**A**]Otf has been characterized by ^{1}H NMR spectroscopy in $CDCl_3$. The following resonances are observed in the spectrum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (s, 3H, -CH_3), 7.51-7.66 (m, 12 H), 7.90 (d, 3H, , J_{H-H}=3 Hz), 7.92 (d, 3H, J_{H-H}=2 Hz), 8.23 (d, 3H, , J_{H-H}=3 Hz). Figure 2 shows the numbered hydrogen assignments.

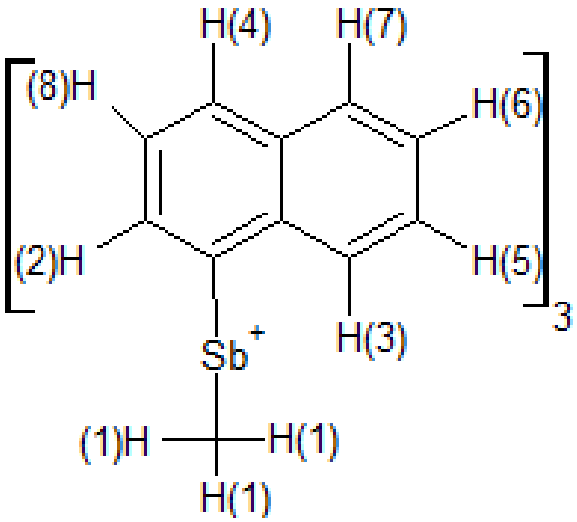

Figure 2. Hydrogen peak assignments of [**A**]OTf.

The methyl hydrogen nuclei H(1) give rise to a singlet at 2.98 ppm which integrates to an intensity of 3. The three naphthyl groups' H(2) hydrogen nucleus *ortho* to the antimony atom appears as a doublet at 8.23 ppm. The three hydrogen nuclei H(3) give rise to a doublet at 7.90 ppm. The doublet at 7.92 ppm arises from the hydrogen nuclei H(7) or H(4). All other C_{nap}-H nuclei are assigned to a series of multiplets obseved in the 7.51-7.66 ppm range. In total, there are 21 hydrogen nuclei integrated in the aromatic region to the aliphatic region's 3 hydrogen nuclei as expected from the structure of [**A**]OTf.

The ^{13}C NMR spectrum of [A]OTf displays the following resonances: ^{13}C NMR (300 MHz, $CDCl_3$) δ 4.670, 121.1, 126.1, 126.5, 126.7, 127.7, 129.3, 130.2, 134.7, 137.2. The methyl carbon appears at 4.670 ppm as expected of the aliphatic group. For the naphthyl carbon nuclei, definitive assignment is more complicated. We simply note there are seven intense signals at 126.1, 126.7, 127.7, 129.3, 130.2, 134.7, 137.2 ppm which are assigned to the C_{nap}-H carbon nuclei. The signals for the three quartenary carbon nuclei could not be observed due to the proton decoupling.

X-ray crystallography of [**A**]OTf showed the expected tetrahedral geometry as shown in Figure 4. The bond angles at antimony are all close to the expected tetrahedral angle of 109.5°. The carbon-antimony bond lengths range at 2.095-2.120 Å, similar to the lengths for aryl carbon-antimony bonds reported in the literature.[5] Elemental analysis revealed proper carbon and hydrogen percentages in the compound (Calculated: 57.59% C,

3.62% H; Obtained: 57.43% C, 3.58% H). Mass spectometry showed the proper molecular weight of the cation at *m/z*=518 amu.

The compound [**B**]OTf could not be succesfully synthesized. ^{1}H NMR of the product showed only starting material from the reaction.

[**C**]OTf has been characterized by ^{1}H NMR spectroscopy in $CDCl_3$. The following resonances are observed in the spectrum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, 1 H, J_{H-H}=3 Hz) 7.60-7.80 (m, 18 H), 7.82 (d, 1H, , J_{H-H}=3 Hz), 8.06 (d, 1H, J_{H-H}=2 Hz), 8.24 (d, 1H, , J_{H-H}=3 Hz). Figure 3 shows the numbered hydrogen assignments for [**C**]OTf.

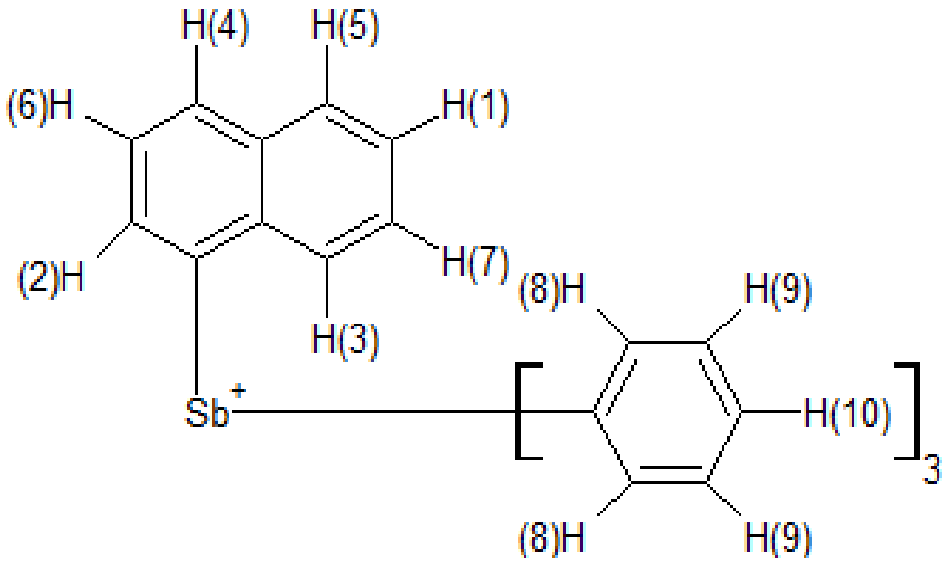

Figure 3. Hydrogen peak assignments of [**C**]OTf.

The hydrogen nucleus H(1) on the naphthyl group produces a triplet at 7.51 ppm integrated to an intensity of 1. The hydrogen nuclei H(2) and H(3) on naphthyl are assigned to the doublets at 8.24 ppm and 8.06 ppm, respectively. The doublet at 7.82 ppm arises from H(4) or H(5). All other C_{nap}-H nuclei on the naphythyl group and the C_{ph}-H hydrogen nuclei on the three phenyl groups are assigned to the series of multiplets in the 7.60-7.80 ppm range.

The ^{13}C NMR spectra of [A]OTf display the following resonances:. ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.6, 135.6, 134.7, 133.8, 131.4, 130.2, 128.9, 127.7, 126.8, 126.6. We will note that these resonances of seven peaks of medium intensity at 137.6, 134.7, 130.2, 128.9, 127.7, 126.8, 126.6 ppm arise from the C_{nap}-H nuclei. The three peaks of strong intensity at 135.6, 133.8, and 131.4 arise from the C_{ph}-H carbon nuclei. The quartenary carbon nuclei were not observed.

Elemental analysis revealed proper carbon and hydrogen percentages in the compound **[C]**OTf (Calculated: 55.35% C, 3.52% H; Obtained: 55.63% C, 3.43% H).

X-ray crystallography of [**C**]OTf showed the expected tetrahedral geometry as shown in Figure 4. The bond angles at antimony are all close to the expected tetrahedral angle of 109.5°. The carbon-antimony bond lengths range expectedly at 2.081-2.138 Å.

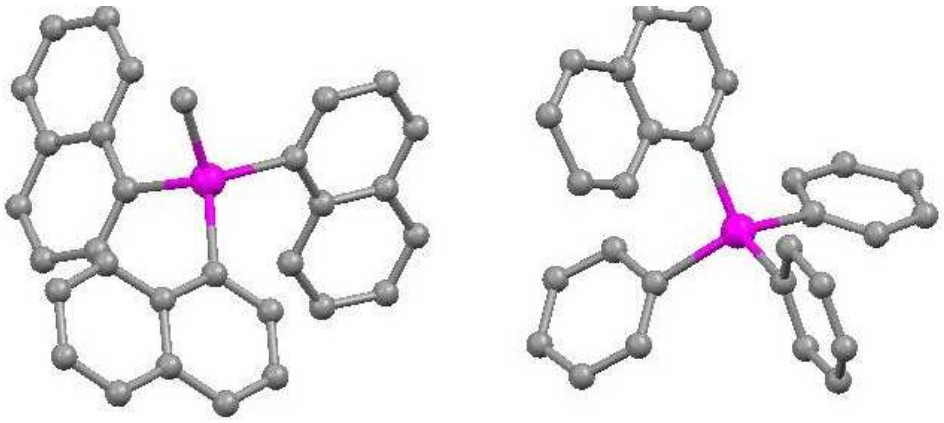

Figure 4. Crystal structure of [**A**]OTf (left) and [**C**]OTf (right). Both structures have C-Sb-C bond angles all ranging from 108°-110°. In **[A]**OTf, the bond length from Sb to the methyl group is 2.107 Å and the bond length from Sb to the naphthyl groups is 2.095-2.120 Å. In **[C]**OTf, the bond length from Sb to the phenyl groups is 2.110-2.138 Å and from Sb to naphthyl is 2.081 Å.

The UV-Vis absorption spectrum of [**A**]OTf in dichloromethane shows a maximum absorption at 296 nm corresponding to electronic transitions of the naphthalene groups. This absorption is quenched by the addition of tetrabutylammonium fluoride, indicating fluoride binding (Figure 5). The spectrum of the compound is blue-shifted as more fluoride is added. The 1:1 binding constant $K=[\text{adduct}]/[A]^{-1}[F^-]^{-1}$ was calculated by fitting the data to a calculated binding curve shown in Figure 5. The binding constant was determined to be larger than 10^7 M^{-1}.

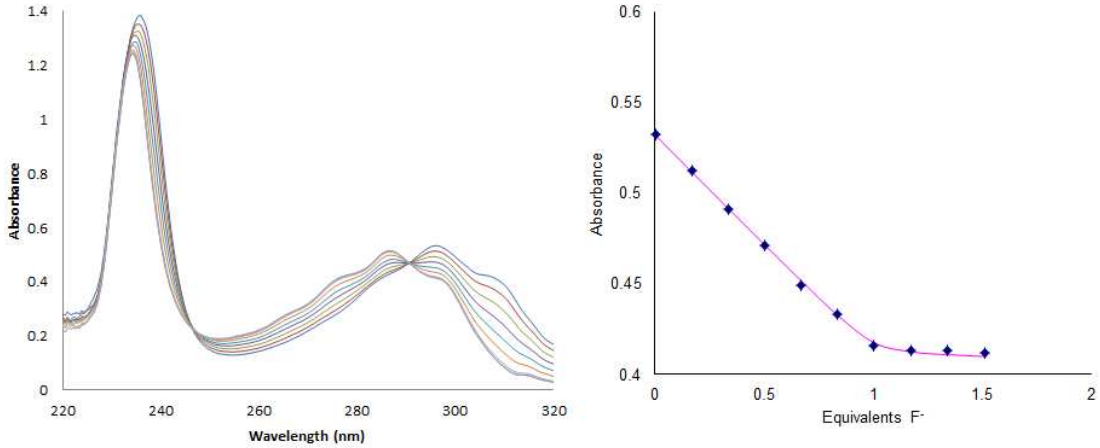

Figure 5. UV-Vis titration of **[A]**OTf. Left: Absorption spectra of [**A**]OTf by addition of fluoride ions in dichloromethane. Right: Experimental and calculated 1:1 fluoride binding isotherms for [**A**] For [**A**]OTf, the data was measured at 296.18 nm and fitted with $K = 10^7$ M^{-1} using ε[**A**]OTf) = 17674 M^{-1} cm^{-1} and ε(**A**-F) = 13800 M^{-1} cm^{-1}.

Titration of [**A**]OTf with fluoride in water and methanol resulted in no change in absorbance, indicating the compound does not bind fluoride in protonated solvents. ^{1}H NMR spectroscopy in deuterated methanol showed no change in the spectrum of [**A**]OTf before and after addition of potassium fluoride, confirming its inability to bind the anion. The compound cannot capture fluoride in these protic solvents due to the high solvation energy of the fluoride anion in methanol and water. [**A**]OTf cannot serve as a good fluoride sensor in water and cannot be used for the biological imaging applications we originally seeked.

The absorbance of [**C**]OTf at wavelength 296 nm was quenched with fluoride in dichloromethane. It had a similar binding constant as [**A**]OTf in these conditions. When titrated with potassium fluoride in methanol, the compound showed a much lower binding constant of 4500 M^{-1}, as calculated by the fitting on the spectroscopic data to a binding curve shown in Figure 6. The final titration was done in water with the surfactant CTABr (10 mM) acting to solvate the compound and adduct. A phosphate buffer was used to keep the pH acidic (~pH 5) so [**C**] could maintain its cationic form, unbound to hydroxide. Fluoride quenched the absorbance of [**C**] in water at 289 nm. The binding constant was weak at 200 M^{-1} in the water/methanol (90/10, v/v) solution.

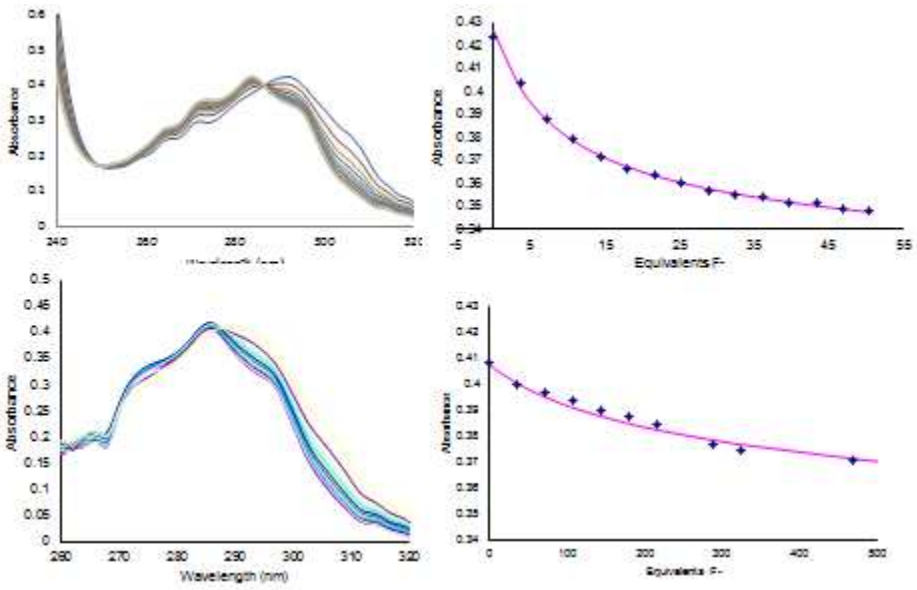

Figure 6. UV-Vis titration of **[C]**OTf. Left: Absorption spectra of [**C**]OTf in methanol (top) and [**C**]OTf in water (bottom). Right: Experimental and calculated 1:1 fluoride binding isotherms for [**C**]OTf in methanol (top) and water (bottom). In methanol, the data was measured at 291 nm and fitted with K = 4500 M^{-1} using ε[**C**]OTf) = 15400 M^{-1} cm^{-1} and ε(**C**-F) = 12400 M^{-1} cm^{-1}. For [**C**]OTf in water, the data was measured at 289 nm and fitted with K = 200 M^{-1} using □[**C**]OTf) = 14700 M^{-1} cm^{-1} and □(**C**-F) = 13300 M^{-1} cm^{-1}.

Main group compounds with carbon π-conjugated systems for substituents, like the aryl antimony compounds we are using, allow for through-space interaction between the ligands.[6] When the antimony compounds are the cationic unbound species, there is a strong through-space interaction between the tetrahedrally-arranged aryl ligands. When the antimony center is hypercoordinated by the binding of fluoride, the substituents rearrange to a trigonal bipyramidal structure, resulting in a weaker through-space interaction between the ligands. This change in interligand through-space interaction results in the blue-shift seen in the UV-Vis absorption spectra for the fluoride-binding species (Figures 5 and 6).

CHAPTER IV

SUMMARY AND CONCLUSIONS

The only compounds sucessfully synthesized were [**A**]OTf and [**C**]OTf**.** Compound [**A**]OTf had a very strong binding constant to fluoride in dichloromethane but could not bind fluoride in the protonated solvents methanol and water.

The compound [**C**]OTf proved to succesfully bind fluoride in not only methanol but water as shown by its titration with potassium fluoride monitored by UV-Vis spectroscopy. This could be due to the high Lewis acidity of the stibonium center caused by the three electron-withdrawing phenyl groups and one naphthyl group. The compound could only bind fluoride in water when the surfactant CTABr acted to keep the the molecule soluble in the 10% methanol, 90% water solution.

[**C**]OTf proved to be a better fluoride captor then [**A**]OTf, especially in methanol and water. This is likely because the substituents on the stibonium center of [**C**]OTf are less bulky overall so that it can arrange in a trigonal bipyramidal structure more readily when binding fluoride than [**A**]OTf whose three bulky naphythyl substituents prevent this rearrangement. This allows [**C**]OTf to capture fluoride in those protic solvents, whose high solvation energies for the anion would usually prohibit such binding.

We could not accomplish incorporating the cation [**C]** into a polypeptide or other biomolecule, but it is likely that such a compound can act as an excellent agent for

capturing fluoride in water and bringing the necessary anion to the aqueous environment of tissues for PET imaging. Later studies can focus on this approach.

REFERENCES

1. Sun, Y; Yu, M.; Liang, S.; Zhang, Y.; Li, C.; Mou, T.; Yang, W.; Zhang X.; Li, B,; Huang, C.; Li, F. *Biomaterials*. **2011**, *32,* 2999-3007.

2. Lasne, M; Perrio, C.; Rouden, J; Barré, L; Roeda, D.; Dolle, F.; Crouzel, C. *Topics in Current Chemistry.* **2002**, *222,* 203-251.

3. Bourdier, T Bourdier, T; Sheperd, R; Berghofer, P.; Jackson, T.; Fookes, C.; Denoyer, D.; Dorow, D.; Greguric, I.; Gregoire, M.; Hicks, R. J.; Kastifis, A. *J. Med. Chem.* **2011,** *54*, 1860-1870.

4. Bordner, J; Anderews, B. *Cryst. Struct. Commun.* **1976**, *5*, 801.

5. Brabant, C; Hubert, J; Beauchamp, A.L. *Can. J. Chem.* **1973**, *51*, 2952-2957.

6. Yamaguchi, S.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc*. **2000**, *122*, 6793– 6794

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