

Hydrolysis and Atmospheric Oxidation Reactions of Perfluorinated Carboxylic Acid Precursors

by

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Abstract

This dissertation explores a number of different environmentally relevant reactions that lead to the production of perfluorocarboxylic acids (PFCAs), a family of environmental pollutants that does not undergo any further degradation pathways.

The compound perfluoro-2-methyl-3-pentanone (PFMP) is a new fire fighting fluid developed by 3M that is designed as a Halon replacement. The environment fate of PFMP with regards to direct photolysis, abiotic hydrolysis and hydration was determined using a combination of laboratory experiments and computational modeling. PFMP was found to undergo direct photolysis giving a lifetime of 4-14 days depending on latitude and time of year. Offline samples confirmed PFCA products and a mechanism was proposed.

Polyfluorinated amides (PFAMs) are a class of chemicals produced as byproducts of polyfluorinated sulfonamide synthesis via electrochemical fluorination (ECF). Using synthesized standards of four model compounds, PFAMs were detected and quantified in a variety of legacy commercial materials synthesized by ECF. PFAMs were hypothesized to undergo biological hydrolysis reactions, suggesting their importance as historical PFOA precursors.

The PFAMs were also investigated with regards to their environmental fate upon atmospheric oxidation. Using a smog chamber, the kinetics and degradation mechanisms of *N*-ethylperfluorobutyramide (EtFBA) were elucidated. The lifetime of EtFBA to oxidation by OH was found to be approximately 4 days. Using offline sampling, PFAMs were shown to give PFCAs upon atmospheric oxidation and a plausible mechanism was proposed involving an initial *N*-dealkylation step followed by loss of isocyanic acid to give a perfluorinated radical. The perfluorinated radical then produces PFCAs by a series of known atmospheric reactions.

Finally, the biological hydrolysis of the polyfluoroalkyl phosphate monoesters (monoPAPs) were studied *in vitro* using a bovine alkaline phosphatase enzyme. Michaelis-Menten kinetic parameters were measured and compared to hexyl phosphate. It was discovered that monoPAPs hydrolyzed on average 100 times faster than hexyl phosphate due to the electron withdrawing fluorine substituents. The results were also used to rationalize the results of a previous *in vivo* study which suggested monoPAPs were rapidly hydrolyzed in the small intestines of rats following a high dose by oral gavage.

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Preface

This thesis is organized as a series of manuscripts that have been published or are in preparation for submission to be published in peer-reviewed scientific journals. As such, repetition of introductory materials and methodology was inevitable. All manuscripts were written by Derek Jackson with critical comments provided by Scott Mabury and all other co-authors. Contributions of all co-authors are provided in detail below.

Chapter One – Environmental Physical and Chemical Properties of the Carbon-Fluorine Bond

Contributions – Prepared by Derek Jackson with guidance from Scott Mabury.

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List of Acronyms

This page provides a list of acronyms for the most commonly mentioned fluorinated compounds in this dissertation. Other fluorinated species will be specifically defined within each of the following chapters.

diPAP	Polyfluorinated alkyl phosphate diester
ECF	Electrochemical fluorination
EtFOA	<i>N</i> -ethylperfluorooctanamide
EtFOSA	<i>N</i> -ethylperfluorooctanesulfonamide
EtFOSE	<i>N</i> -ethyl- <i>N</i> -(2-hydroxyethyl)perfluorooctanesulfonamide
FTAc	Fluorotelomer acrylate
FTAL	Fluorotelomer aldehyde
FTCA	Fluorotelomer carboxylic acid
FTI	Fluorotelomer iodide
FTOH	Fluorotelomer alcohol
FTUAL	Fluorotelomer unsaturated aldehyde
FTUCA	Fluorotelomer unsaturated carboxylic acid
MeFOA	<i>N</i> -methylperfluorooctanamide
MeFOSA	<i>N</i> -methylperfluorooctanesulfonamide
MeFOSE	<i>N</i> -methyl- <i>N</i> -(2-hydroxyethyl)perfluorooctanesulfonamide
monoPAP	Polyfluorinated alkyl phosphate monoester

PBSF	Perfluorobutanesulfonyl fluoride
PFAI	Perfluorinated alkyl iodide
PFAL	Perfluorinated aldehyde
PFAM	Polyfluorinated amide
PFCA	Perfluorocarboxylic acid
PFOA	Perfluorooctanoic acid
PFOAF	Perfluorooctanoyl fluoride
PFOH	Perfluorinated alcohol
PFPA	Perfluorinated phosphonic acid
PFPiA	Perfluorinated phosphinic acid
PFPrA	Perfluoropropionic acid
POSF	Perfluorooctanesulfonyl fluoride
TFA	Trifluoroacetic acid

CHAPTER ONE

Environmental Physical and Chemical Properties of the Carbon-Fluorine Bond

Derek A. Jackson and Scott A. Mabury

To be submitted – as a review paper to a journal specializing in environmental chemistry

Contributions – Prepared by Derek Jackson with guidance from Scott Mabury.

1.1 Overview

The main focus of this dissertation is the chemical processes in the environment that produce perfluorinated carboxylic acids (PFCAs) from a variety of polyfluorinated precursor compounds that are used commercially. A wide variety of fluorinated compounds is used for many different industrial purposes; those take advantage of the physical and chemical properties imparted by the C-F bonds therein. Polymers and surfactants containing C-F bonds within their structure are used extensively as coatings for carpets and food packaging, fire fighting fluids, heat transfer fluids, pesticides and formulation additives.¹ In certain applications, the C-F bond is introduced to impart both hydrophobic and lipophobic properties to the molecule to prevent staining. Other fluorinated compounds that are produced take advantage of the high C-F bond stability in high temperature applications, increased volatility or resistance to atmospheric oxidation.

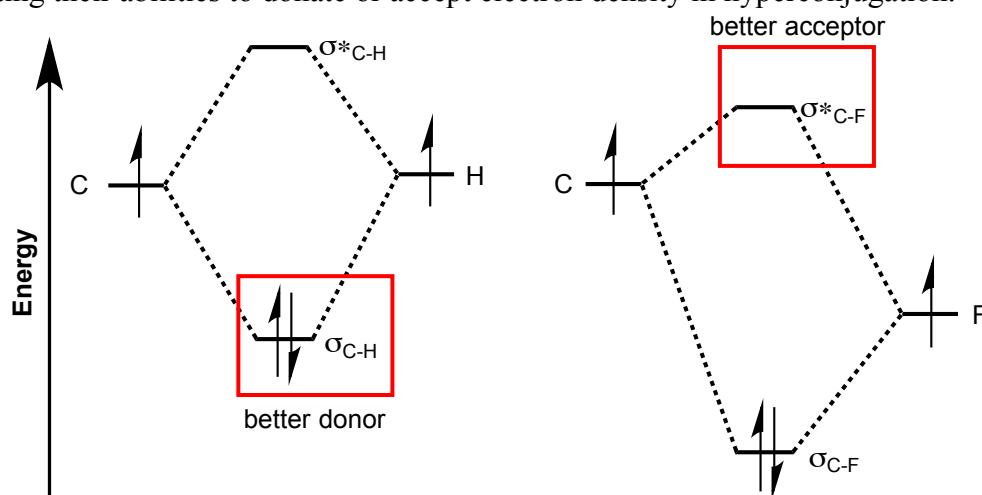
There are a number of chemical reactions that degrade organic pollutants under environmental conditions including atmospheric oxidation, hydrolysis and biodegradation. The reactions that will take place on any given compound depend not only on its chemical structure but also into which environmental compartment the compound partitions into. One goal of this dissertation is to explore a variety of previously unexplored reactions that can degrade precursor compounds into the highly persistent PFCAs. Another major objective is to probe the effects that C-F bonds within a compound have on the rates and mechanisms of degradation of that molecule in the environment.

The purpose of this introductory chapter is to provide an overview of the molecular properties the C-F bond imparts within a structure with respect to physical properties such as aqueous solubility, vapour pressure, acidity constants, electron withdrawal and donation, as well as chemical properties such as reaction rates and mechanisms. Next, the two major synthetic families of fluorinated surfactants, electrochemically fluorinated surfactants and fluorotelomers, will be reviewed with respect to their environmental chemistry. Finally a brief overview of ^{19}F NMR as it pertains to environmental analysis will be provided along with examples of spectra.

1.2 The carbon-fluorine covalent bond

The C-F bond is the strongest single bond in all organic chemistry². It is a polar covalent bond that possesses significant ionic character due to fluorine, being the most electronegative of all the chemical elements. This results in C-F bonds having bond dissociation energies up to 544 kJ mol^{-1} .² In terms of molecular orbital theory, the $\sigma_{\text{C-F}}$ bond is very low in energy, making it a poor electron donor for hyperconjugation as shown in Figure 1.1.

Figure 1.1: Simplified MO diagram showing energy levels for the C-H and C-F bonds indicating their abilities to donate or accept electron density in hyperconjugation.

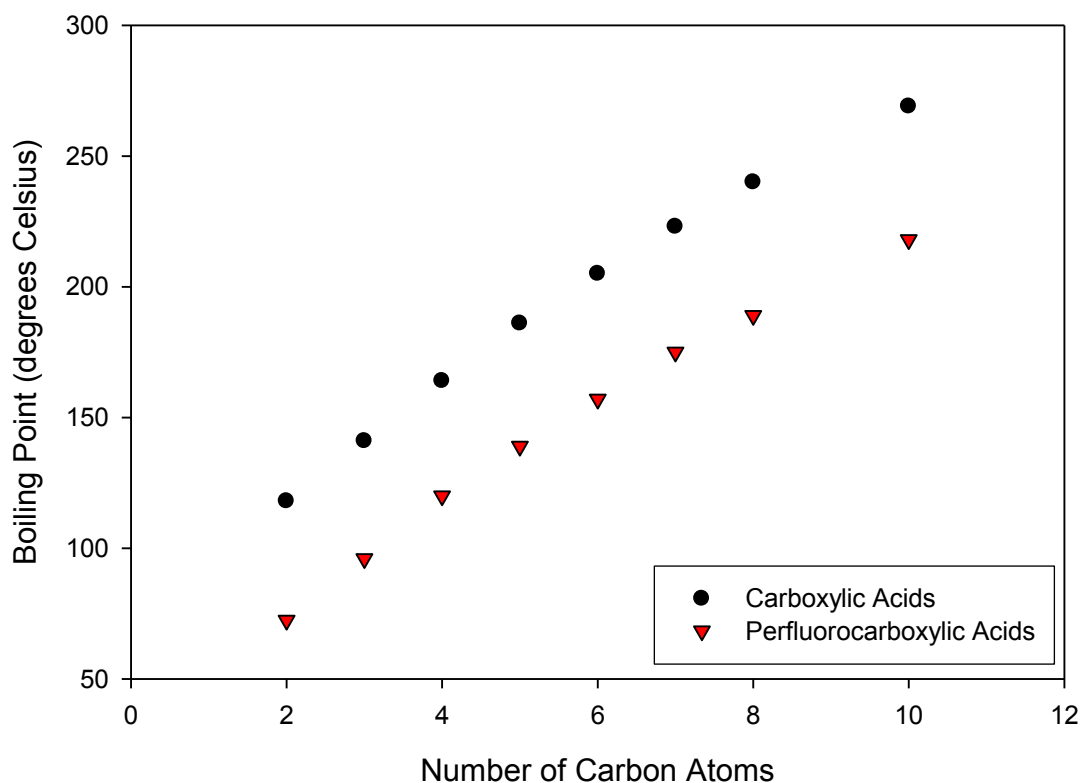


As a result of fluorine's high electronegativity, the three lone pairs on the fluorine atom are held at a lower energy level compared to nitrogen and oxygen. Fluorine atoms within an organic molecule therefore have comparatively low nucleophilicity and basicity. Fluorine atoms in C-F bonds make poor hydrogen bond acceptors³ for this reason; their average hydrogen bond strength is $2 - 3 \text{ kcal mol}^{-1}$ compared with an O-H hydrogen bond strength of $5 - 10 \text{ kcal mol}^{-1}$.⁴

The inability of C-F bonds to participate in significant hydrogen bonding results in organofluorines having low water solubilities. As a result of the hydrophobic effect, the interactions between water molecules are stronger than between water molecules and the organofluorine leading to exclusion of the organofluorine from the aqueous phase. Certainly the presence of a hydrophilic functional group on the organofluorine (such as a carboxylate or sulfonate) will increase water solubility. Fluorine is approximately isosteric with oxygen (van der Waals radii of F and O are $1.47 \text{ \AA}$ and $1.52 \text{ \AA}$ respectively).⁵

Organofluorine compounds have low polarizabilities, resulting from the high electronegativity of the fluorine atom combined with its relatively small size.² The low polarizability of the C-F bond leads to minimal London dispersion forces. This results in decreased solubilities of organofluorines in organic solvents as well as increased vapour pressures which correspond to decreased boiling points. This is evident when examining the boiling points of homologous series of carboxylic⁶ and perfluorocarboxylic⁷ acids, as shown in Figure 1.2.

Figure 1.2: Boiling points for carboxylic acids ($C_nH_{2n+1}COOH$) and perfluorocarboxylic acids ($C_nF_{2n+1}COOH$).

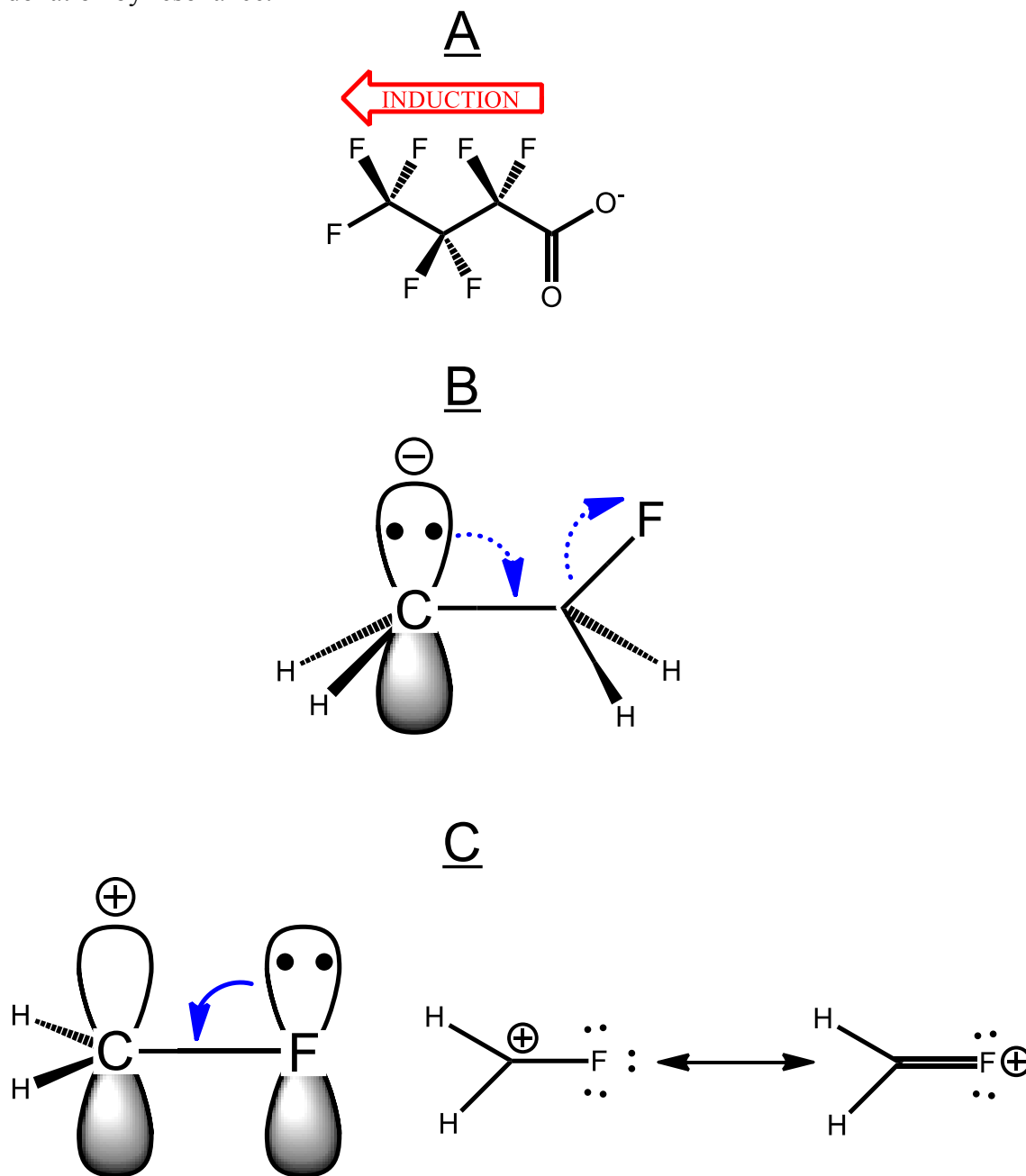


1.2.1 Electronic properties – electron withdrawal and electron donation

A fluorine atom within an organic structure is capable of three main electronic effects on the rest of the structure: electron withdrawal by induction, electron withdrawal by hyperconjugation and electron donation by resonance. These three effects are summarized in Figure 1.3.

Carbon-fluorine bonds are capable of withdrawing electron density by both hyperconjugation as well as induction through sigma bonds due to the high electronegativity of the fluorine atom. These effects lead to many physical and chemical properties that are observed with organofluorines, some of which will be described in greater detail.

Figure 1.3: Summary of the three major electronic effects of C-F bonds discussed in this introduction: A) withdrawal by induction, B) withdrawal by hyperconjugation, C) donation by resonance.



The inductive electron withdrawing effect of a fluorine atom diminishes with distance throughout a molecule but its effects can still be felt more than four carbons away. For example, 5,5,5-trifluoropentanoic acid has a pK_a of 4.5 compared to pentanoic acid which has a pK_a of

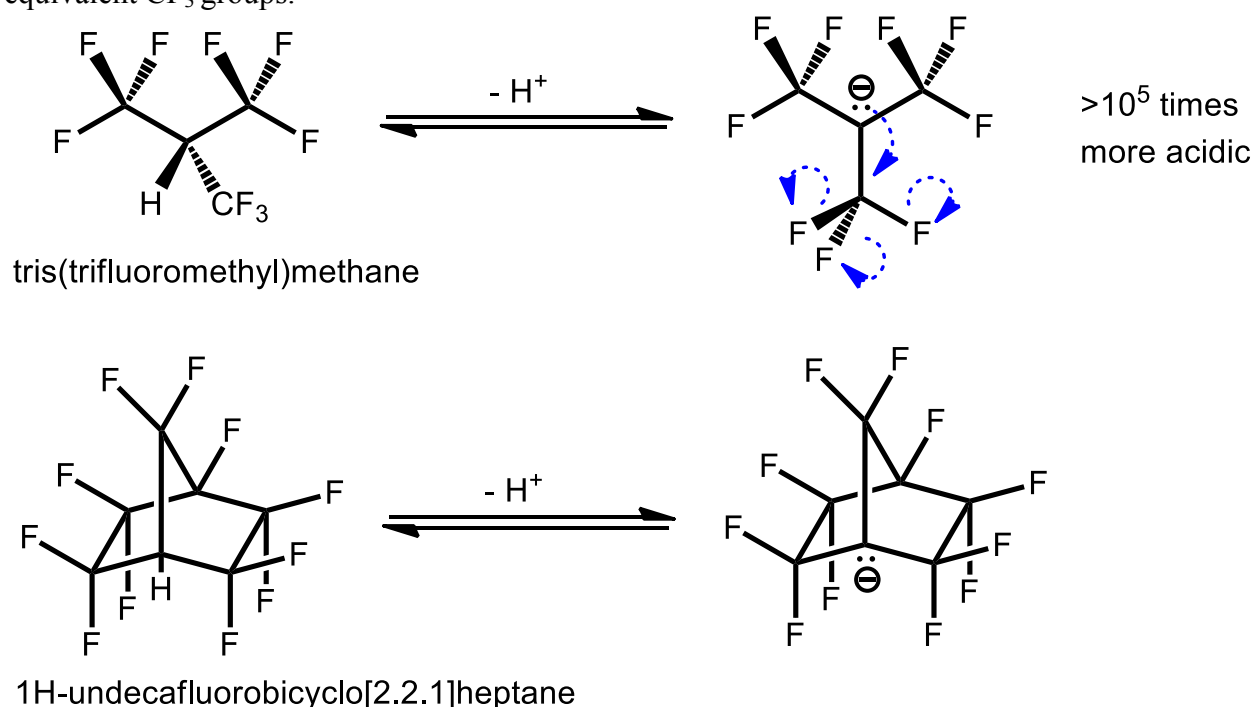
4.8.⁸ The effects of fluorination are additive with an increasing degree of fluorination further increasing its acidity as can be seen when comparing pK_a values for fluoroacetic acid (2.66), difluoroacetic acid (1.24) and trifluoroacetic acid (0.5).⁹ In contrast to these well defined values, longer chained perfluorinated acids such as perfluorooctanoic acid (PFOA) have pK_a values that are not well characterized as discussed later.

During an atmospheric oxidation reaction with hydroxyl radical (OH), C-H bonds that are more electron dense react faster since OH is a very strong electrophile. The presence of C-F bonds in aliphatic compounds, particularly the CF₃ group, withdraws electron density from nearby C-H bonds and aromatic rings making them slower to react. This effect causes atmospheric lifetimes of volatile fluorinated compounds such as hydrofluorocarbons (HFCs) to be on the order of years.¹⁰ Since most HFCs have high radiative efficiencies, their long lifetimes impart them with very high global warming potentials relative to carbon dioxide.¹⁰

In addition to the inductive effect, C-F bonds can also withdraw electron density by a process called negative hyperconjugation with a nearby negative charge or lone pair, such as an aliphatic carbanion.^{11,12} The electron donor is the lone pair (n_F) and the electron acceptor is the C-F antibonding orbital (σ^*_{C-F}). The effect is strongest when the two groups are periplanar, ensuring maximal orbital overlap. An example of negative hyperconjugation is when comparing the acidities of two polyfluorinated compounds with relatively acidic C-H bonds, one of which is capable of delocalizing the conjugate base by hyperconjugation and the other is not (Figure 1.4).¹³ The compound capable of negative hyperconjugation between the resultant carbanion and neighboring C-F bonds was found to be more than 10^5 times more acidic than the compound only

capable of electron withdrawal through induction. The enormous difference in acidity between these two compounds was ascribed to negative hyperconjugation.¹³

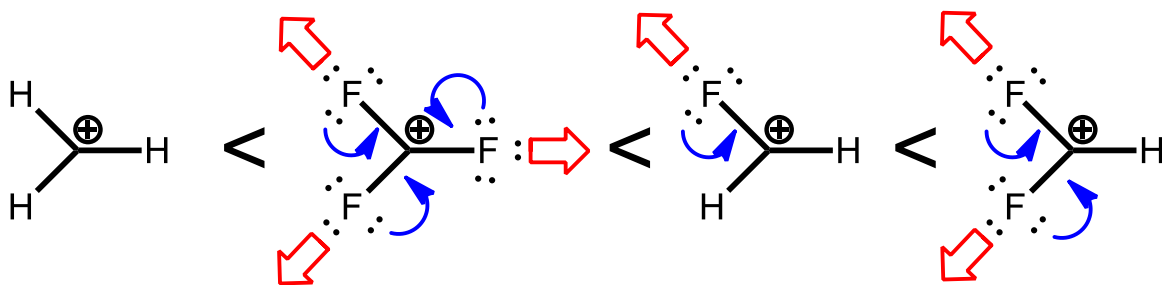
Figure 1.4: Effects of negative hyperconjugation in stabilizing a conjugate base (ref. 12). The bottom compound is not capable of hyperconjugation due to dihedral angle restrictions and therefore the carbanion is less delocalized and less stable. For clarity, the inductive effects are not shown and hyperconjugation in the top compound is only shown for one out of three equivalent CF₃ groups.



Fluorine is also capable of acting as an electron donating group (EDG), a property that had it once referred to as the “schizoid substituent”.² As a halogen, fluorine has three lone pairs in three orthogonal 2p orbitals. These are capable of participating in electronic resonance forms to stabilize electron deficiencies on directly bonded groups such as carbocations and radicals (Figure 1.3C). Since fluorine is in the same row of the periodic table as carbon, the ability of fluorine’s lone pairs to interact with orbitals on carbon atoms is enhanced greatly over other halogens.¹⁴

Carbocations are important reaction intermediates in certain substitution mechanisms for both aliphatic and aromatic compounds. Any functional group stabilizing the carbocation intermediate will increase the rate of the reaction by the Hammond Postulate.¹⁵ A lone pair on a fluorine atom can donate its electron density to the empty p orbital on the carbocation forming a resonance structure in which all the atoms obey the octet rule. This stabilization effect is much more pronounced for fluorine compared to the other halogens because fluorine is a second row element and therefore closer in energy and spatial overlap to carbon.¹⁴ In the specific case of methyl carbocations, the experimental order of stability¹⁶ is $\text{CH}_3^+ < \text{CF}_3^+ < \text{CH}_2\text{F}^+ < \text{CHF}_2^+$ which illustrates the ability of the fluorine atom to both withdraw and donate electron density, as illustrated in Figure 1.5.

Figure 1.5: Relative stabilities of fluorinated methyl carbocations showing the competing electronic effects of each fluorine atom.



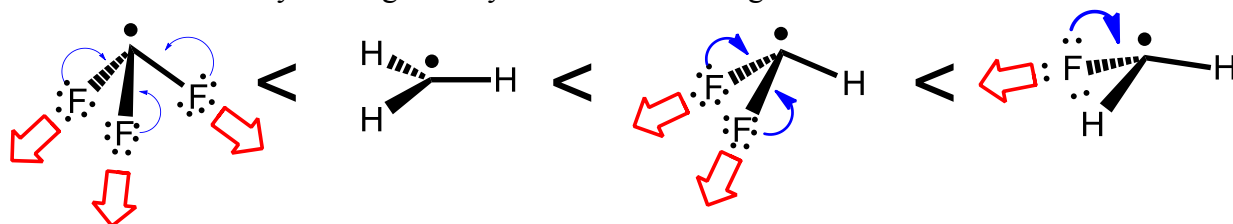
This resonance effect can stabilize arenium ions during electrophilic aromatic substitutions with the fluorine substituent being an ortho/para director that is very slightly activating.¹⁷ A quantitative measurement of an aryl substituent's ability to donate or withdraw electron density uses Hammett substituent constants, represented by the Greek letter sigma (σ), derived from the acidity constants of substituted benzoic acids as a reference.¹⁸ For substituents that can interact with the benzene ring through resonance as well as induction, modified Hammett constants have

been developed. The ability to donate electron density by resonance at the para position is given by σ_p^+ and is based on the S_N1 hydrolysis reaction of substituted cumyl chlorides.¹⁹ The intermediate formed during this reaction is a benzylic carbocation. The ability of a substituent to withdraw electron density by resonance at the para position is given by σ_p^- and is based on the acidity constants of substituted phenols.

The fluorine atom has modified Hammett substituent constants in the para position of $\sigma_p^+ = -0.07$ ¹⁷ and $\sigma_p^- = -0.03$.¹⁷ For the meta position $\sigma = +0.34$ ¹⁷ since electron withdrawal due to induction is the only electronic effect of fluorine at that position.

Since carbon-centred radicals are electron deficient, they are stabilized by electron donating groups through resonance with heteroatoms. For nitrogen and oxygen, their stabilization effect through resonance outcompetes their destabilization effects through induction but fluorine is not as good an electron donor because its lone pairs are in comparatively lower energy HOMOs (lower basicity). In addition, carbon radicals become less trigonal planar and more tetrahedral by Bent's rule, as the degree of fluorination increases.²⁰ This decreases the degree of overlap between the lone pairs and the radical centre since the hybridization of the radical carbon becomes closer to sp^3 than sp^2 . Therefore, as more fluorines are bonded to the radical centre the inductive withdrawing effect increases and will overcome the resonance donation. In the case of methyl radicals, the order of stability is $CF_3 < CH_3 < CF_2H < CFH_2$ which shows one fluorine atom provides the greatest stabilization effect²¹ as illustrated in Figure 1.6. Any fluorine atoms not directly bonded to the radical centre will also destabilize the radical by the inductive effect.

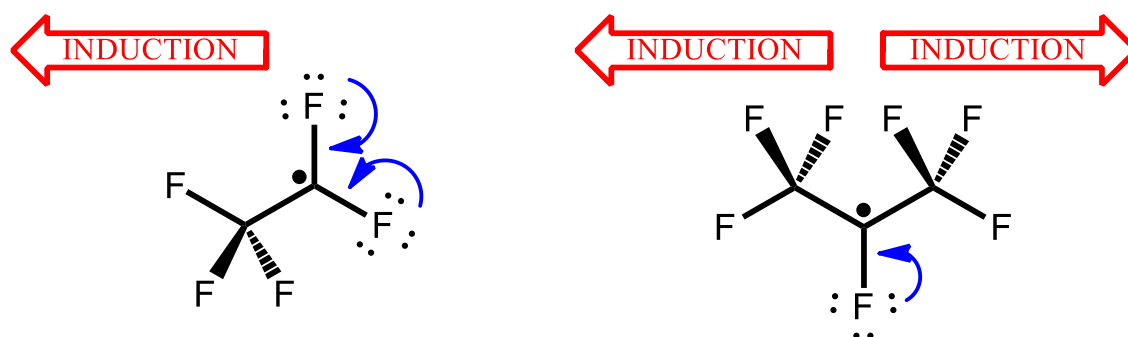
Figure 1.6: Relative stabilities of fluorinated methyl radicals showing the competing electronic effects of each fluorine atom and the relative magnitudes of the ability of each fluorine atom to donate electron density as the geometry of the radical changes.



Perfluorinated radicals are species that contain aliphatic carbon chains containing no hydrogen atoms and an unpaired electron present on a carbon atom. They are very important intermediates in atmospheric oxidation reactions because they can undergo a series of reactions to produce PFCAs. Young and Mabury have published a comprehensive review which details all the known atmospheric reaction pathways of perfluorinated radicals.²² The stability of a perfluorinated radical is a tradeoff between electron donation from fluorines bonded directly to the radical carbon and electron withdrawal by induction from all other fluorine atoms. The net effect from these interactions can be probed using the published lifetimes of HFCs with one hydrogen atom since they will form a perfluorinated radical upon reaction with OH. As the stability of the perfluorinated radical increases, the atmospheric lifetime of the parent HFC will decrease as its reaction with OH will be faster. As expected from the radical stability trends mentioned earlier, fluoroform (CHF_3) has an atmospheric lifetime of 260 years²³, compared to 10 years for methane (CH_4). The lifetimes of difluoromethane (CH_2F_2) and fluoromethane (CH_3F) are 6 and 4 years respectively²⁴ and demonstrate the stabilizing effects of the fluorine atom on the radical centre. The perfluorinated radical formed from HFC-125 ($\text{CF}_3\text{CF}_2\text{H}$) is destabilized by one CF_3 group, giving an atmospheric lifetime of 31 years for this HFC.²⁵ Another greenhouse gas, HFC-227ea ($\text{CF}_3\text{CFHCF}_3$), has a comparable lifetime of 42 years.²⁶ Its corresponding radical ($\text{CF}_3\text{C}\cdot(\text{F})\text{CF}_3$) is overall stabilized by one fluorine atom while being highly destabilized

by two adjacent CF_3 groups, as shown in Figure 1.7. Due to these competing effects, the relative stabilities of isomeric perfluorinated radicals are difficult to predict.

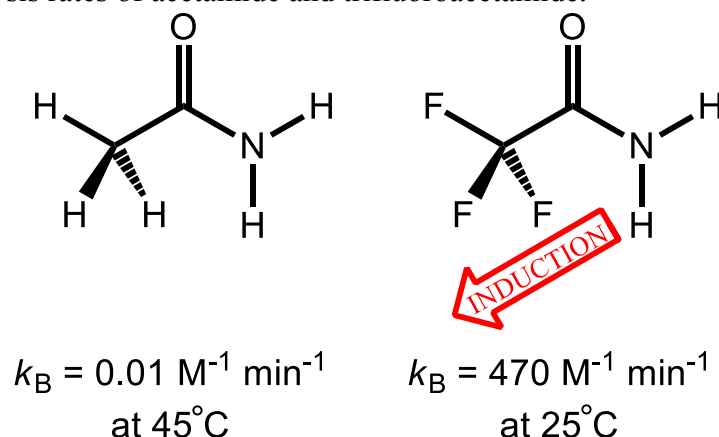
Figure 1.7: Electronic effects affecting the stabilities of the CF_3CF_2 radical and the CF_3CFCF_3 radical.



1.2.2 Hydrolysis of esters and amides

As most C-F bonds are recalcitrant to chemical transformation under aqueous conditions, hydrolysis reactions of fluorinated compounds usually occur on functional groups that are also present in the molecule such as esters and amides. Since hydrolysis reactions of most acid derivatives proceeds through an addition-elimination mechanism and are acid or base catalyzed, the presence of an electron withdrawing group will enhance the reaction rate. Meresaar and Bratt measured the hydrolysis rates of various acetamides and reported base catalyzed rate constants (k_B) of $0.01 \text{ M}^{-1} \text{ min}^{-1}$ for acetamide at 45°C and $470 \text{ M}^{-1} \text{ min}^{-1}$ for trifluoroacetamide at 25°C ²⁷ as shown in Figure 1.8. This enormous rate enhancement is due to the electron withdrawing CF_3 group stabilizing the negative charge that develops in the transition state of the rate determining step under alkaline conditions. The trifluoroacetyl group can be used as a protecting group for amines since it can be hydrolyzed under relatively mild conditions to restore the original compound.^{28,29}

Figure 1.8: Hydrolysis rates of acetamide and trifluoroacetamide.



The same rate enhancement effect seen for these amides should also apply for esters. Although very little experimental work has been performed on fluorinated esters, evidence suggests they are unstable in water. Kimura et al. reported that ester derivatives of perfluorooctanoic acid are impractical as commercial surfactants due to their ease of hydrolysis and suggested amides as a more stable alternative.³⁰

1.2.3 Breaking C-F bonds under environmental conditions

Although C-F bonds are the strongest in organic chemistry, there are a limited number of reactions that occur under environmental conditions whereby C-F bonds may be cleaved.

1.2.3.1 Hydrolysis of acyl fluorides

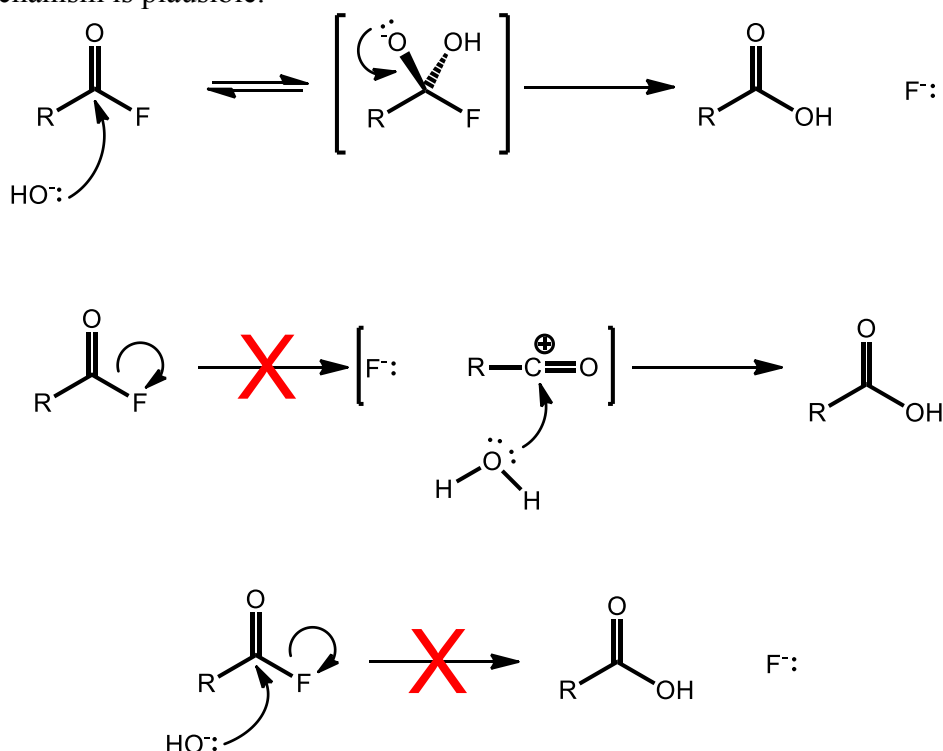
Organic compounds with the structure $\text{RC}(\text{O})\text{F}$ are known as acyl fluorides or acid fluorides and belong to the acid halide family which includes acyl chlorides, bromides and iodides.

Acyl chlorides (RC(O)Cl) are widely used as synthons in organic chemistry for their ability to be transformed into a wide variety of carboxylic acid derivatives such as esters, anhydrides and amides. Acyl chlorides are highly reactive electrophiles and will undergo exothermic hydrolysis in moist air to produce a carboxylic acid and hydrogen chloride. There are a few potential mechanisms for the hydrolysis of an acyl chloride depending on its structure that have been proposed in the literature. The first is an addition-elimination mechanism ($\text{B}_{\text{AC}}2$) that is common with other carboxylic acid derivatives whereby water or hydroxide attacks the C=O first to form a tetrahedral intermediate which then reforms the C=O bond and expels chloride as the leaving group.³¹ The second possibility is an elimination-addition mechanism similar to $\text{S}_{\text{N}}1$ whereby the C-Cl bond breaks first expelling chloride and leaving an acyl cation which rapidly reacts with water in a separate step.³² This mechanism will likely occur with benzylic acyl chlorides depending on the solvent and similar substrates that are able to stabilize a carbocation intermediate. A third possible mechanism is a concerted mechanism similar to $\text{S}_{\text{N}}2$ by which unhindered substrates such as acetyl chloride can hydrolyze in one step without forming a discrete intermediate.³³ These three mechanisms are shown in Figure 1.9.

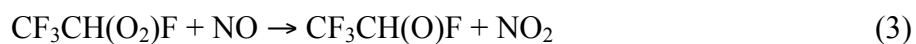
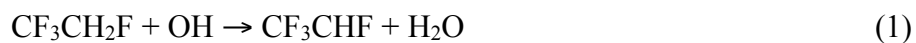
Of these three postulated mechanisms for acyl chlorides, only the addition-elimination pathway seems plausible for the hydrolysis of an acyl fluoride. This is because the other two options would involve the breaking of the very strong C-F bond in the rate determining step. The hydrolysis of acetyl fluoride has been studied and the proposed mechanism is an addition-elimination pathway whereby water (or hydroxide) adds to the C=O bond to form a tetrahedral intermediate which then eliminates fluoride.³⁴ The breaking of the C-F bond is therefore not in

the rate determining step. Overall, the hydrolysis reaction is slower than for acyl chlorides but should still be rapid under environmental conditions.

Figure 1.9: Three potential mechanisms for the hydrolysis of an acyl fluoride. Only the first mechanism is plausible.



Acyl fluorides can be produced in the environment from the degradation of many different polyfluorinated compounds in the atmosphere.²² One example is the atmospheric oxidation of CF_3CH_2F (HFC-134a)³⁵, a commonly used refrigerant, as shown in reactions 1 - 4.



Once produced, the major fate of acyl fluorides in the environment is rapid hydrolysis to the carboxylic acid, making this reaction a very important area of study.

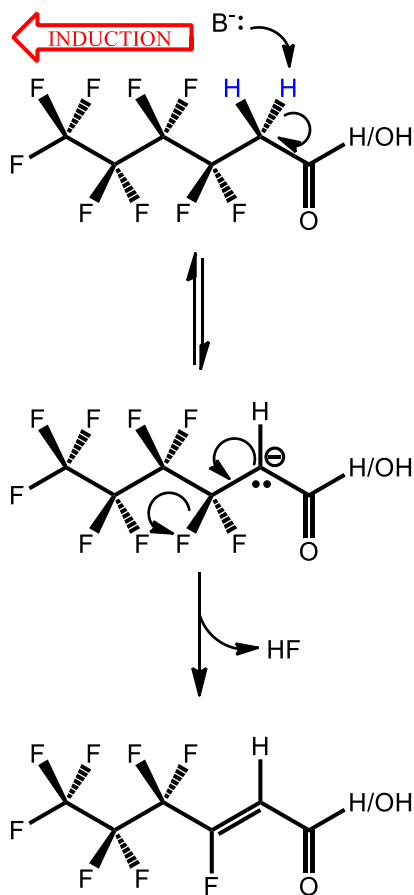
1.2.3.2 Dehydrohalogenation

Structures of the general form $R_1R_2(H)C-C(X)R_3R_4$ where X is a leaving group are capable of undergoing an elimination reaction in the presence of a base to produce an alkene with the structure $R_1R_2C=C-R_3R_4$ by one of three mechanisms: E1, E2 and E1cB. The prevailing mechanism will depend on many factors such as nature of the leaving group, the base used and solvent. Normally, organofluorines do not readily undergo elimination reactions since the C-F bond is very strong and fluoride is a poor leaving group.³⁶ However, in certain situations the elimination reaction will proceed under environmental conditions. When considering the chemistry of fluorinated pollutants, the most relevant example of a C-F elimination reaction is the degradation pathway of fluorotelomer carboxylic acids (FTCAs) and fluorotelomer aldehydes (FTALs). These two classes of compounds (subsequently discussed in greater depth) have the general structures $C_xF_{2x+1}CH_2C(O)OH$ and $C_xF_{2x+1}CH_2C(O)H$ respectively. They are both reactive intermediates produced during the biological degradation of many fluorinated precursors. Both FTCAs and FTALs have been shown to lose HF under aqueous conditions to form fluorotelomer unsaturated carboxylic acids (FTUCAs) and aldehydes (FTUALs) of the general structures $C_xF_{2x}=CHC(O)OH$ and $C_xF_{2x}=CH_2C(O)H$.³⁷ Clearly a dehydrofluorination reaction has taken place to form an α,β unsaturated system that is stabilized by extended conjugation. Presumably, the formation of this product provides the thermodynamic driving force that allows the reaction to proceed. Characterization of the FTUCA and FTUAL products

allows a mechanism to be proposed for this process. Analysis by ^{19}F NMR shows that only the *Z* isomer is formed that places the bulkier groups *trans* across the double bond.³⁸

The most likely mechanism for this dehydrofluorination reaction is E1cB, as shown in Figure 1.10. The proton on the CH_2 group vicinal to the CF_2 group is slightly acidic as a result of the inductively withdrawing fluorine atoms and can be removed by a base to form a carbanion intermediate. The carbanion then eliminates fluoride to give the unsaturated product as observed. The FTUCAs and FTUALs are both electrophilic as a result of this α,β unsaturated system, an attribute with important toxicological consequences that will be discussed later.

Figure 1.10: E1cB mechanism for the dehydrofluorination of 4:2 FTCA or FTAL to form 4:2 FTUCA or FTUAL.



1.2.3.3 Decomposition of perfluorinated alcohols

The perfluorinated alcohols (PFOHs) are important intermediates in the atmospheric degradation of many fluorinated surfactants and have the general structure $C_xF_{2x+1}OH$.²² These compounds are unstable and eliminate HF to form acyl fluorides as per reaction 5:



Although the mechanism of this process is not completely understood, recent computational studies have suggested vibrational overtone degradation as a likely process.³⁹

The perfluorinated acyl fluoride formed as a product can undergo rapid hydrolysis to produce the corresponding PFCA, making the degradation of PFOHs a very important environmental pathway whereby C-F bonds are cleaved.

1.2.3.4 Direct photolysis reactions

Although aliphatic fluorinated surfactants do not absorb sufficient actinic radiation to undergo direct photolysis reactions, the power of sunlight in breaking a C-F bond is well documented.⁴⁰ In order for a photolysis reaction to proceed, the organic molecule in question must have an absorption cross-section in the actinic region of the solar incidence spectrum (>290 nm at Earth's surface). Such a requirement is achieved in many aromatic compounds. The trifluoromethyl (CF_3) functional group is often substituted onto a benzene ring, usually to impart stability toward oxidation although it sometimes plays a role in the binding of a molecule to a substrate such as an enzyme. Although aryl CF_3 groups are normally extremely stable, they can

degrade completely to a COOH group in the presence of sunlight. This reaction has been demonstrated for fluoxetine (Prozac™).⁴¹ The mechanism is thought to be a multiple step process whereby each C-F bond is broken in turn rather than simultaneously.⁴²

1.2.4 Perfluorinated carboxylic acids (PFCAs)

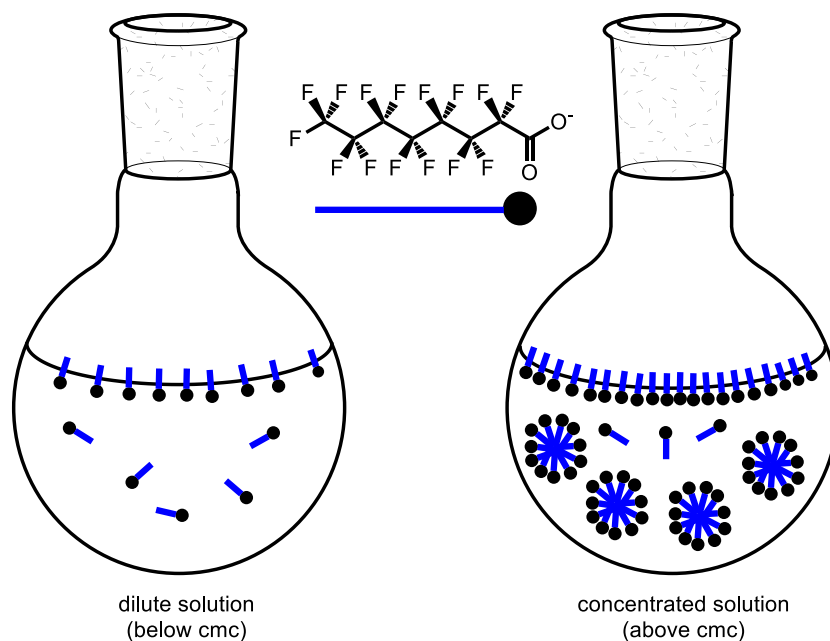
The perfluorinated carboxylic acids (PFCAs) have the general structure $C_xF_{2x+1}C(O)OH$ where the value of “x” determines its chain length. The most studied PFCA is perfluorooctanoic acid (PFOA, x = 7) however PFCAs of all chain lengths from 1 (trifluoroacetic acid, TFA) to higher than 10 (perfluorodecanoic acid, PFDA) are now routinely analyzed in environmental samples. Historically, the major use of PFOA was as a processing aid for fluoropolymer production and in that capacity, 3M was the world’s major manufacturer of PFOA from 1947-2002.⁴³ Aside from this main commercial use, PFCAs are considered waste products resulting from the environmental degradation of polyfluorinated polymers and surfactants that have commercial uses. The catalyst for driving analytical research into perfluorinated acids began when these compounds were detected ubiquitously in many environmental matrices including human blood.^{44,45,46} Answering the question of how these compounds were transported throughout the environment sparked years of fruitful research.

In a PFCA, each C-F and C-C bond is strengthened relative to an isolated bond which contributes to their high thermal and chemical stabilities.² It has been suggested that both hyperconjugation ($n_F \rightarrow \sigma^*_{C-F}$) and greater partial positive charge on carbon with successive fluorine substitution are the causes for the increase in C-F bond strengths.²

The PFCAs are so recalcitrant in the environment that they “redefine” persistence and have no clearly defined lifetimes as a result. From a biological standpoint, PFCAs longer than PFOA are bioaccumulative due to their hydrophobicity.⁴⁷ Shorter chained PFCAs such as TFA, perfluoropropanoic acid (PFPrA) and perfluorobutanoic acid (PFBA) are not considered as biologically malignant due to their much lower hydrophobicities, although pathways leading to their formation may result in harmful intermediate compounds, as will be discussed later.

As surfactants, PFCAs form micelles when dissolved in water with their hydrophobic fluorinated chains pointing inwards and the hydrophilic COO^- groups interacting with the H_2O molecules. A parameter known as the critical micelle concentration (cmc) describes the minimum concentration of surfactant required to form micelles in aqueous solution, after which the solubility of the surfactant increases dramatically¹. The Krafft point is the minimum temperature required in solution to reach the cmc before the solubility threshold of the surfactant is exceeded.¹ Micelles therefore can not form below the Krafft point and solubility remains low at that temperature. A schematic showing micelle formation for PFOA is illustrated in Figure 1.11.

Figure 1.11: Schematic showing micelle formation above the cmc for PFOA.



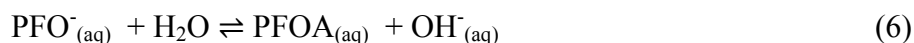
The Krafft points and cmc values have been measured using conductivity experiments for many PFCAs. For the sodium salt of PFOA, the Krafft point is 283 K (10 °C) and the cmc at 303 K (30 °C) is 0.03 M.⁴⁸ This can be compared with sodium octanoate, which has a Krafft point below 273 K (0 °C) and a cmc at 303 K (25 °C) of 0.37 M, an order of magnitude greater than PFOA.⁴⁸ These results elegantly illustrate the effect of a perfluorinated chain on the hydrophobicity of a compound as well as its potency as a surfactant. In comparing PFCAs, the cmc values decrease with perfluorinated chain length indicating greater surfactant activity.⁴⁹ As the chain length increases, the Krafft point temperature also increases.⁴⁹

1.2.4.1 Acidity constants of perfluorinated acids

As alluded to earlier, fluorine substituents increase the acidity of carboxylic acid groups by withdrawing negative charge through induction and stabilizing the conjugate base. For simple structures such as trifluoroacetic acid (TFA), the pK_a values of fluorinated acids have well-

defined values, for example $pK_a(\text{TFA}) = 0.5$.⁹ However, the pK_a values of longer chained PFCA's such as PFOA have long been under dispute. It is not the purpose of this review to enter the controversy with a firm statement of opinion but it is necessary to recount previous work and explain why it is difficult to define a pK_a for these compounds.

At first, determining the pK_a of a PFCA such as PFOA might seem completely academic since all PFCA's will essentially be completely deprotonated at environmental pH. There is, however, at least one important environmental consequence. If the pK_a of PFOA is higher than might be expected from its structure, then PFOA might be subjected to transport through aerosol particles above the surface of the oceans.⁵⁰ This process is governed by the following two equilibria:



Since elucidating the mechanisms of transport of PFOA and its precursors from mid-latitudes to the Arctic is an area of intensive study, this mode of transport has important consequences provided the pK_a is large enough for PFOA encountered in the protonated form to any significant extent.

To determine the pK_a of an organic acid, a titration experiment with a strong base is often performed. This requires appreciable quantities in solution to obtain accurate pH measurements. As the perfluorinated chain length increases, the solubility of a PFCA in water decreases due to

increased hydrophobicity. Early conductivity measurements suggested PFCAs were completely ionized in aqueous solution.⁷

Burns et al. reported a pK_a for PFOA of 3.8 based on measurements using ^{19}F NMR spectroscopy.⁹ The authors also mentioned PFOA aggregation in solution above concentrations of 4.6 μM will artificially lower its pK_a and not make the study environmentally relevant. The reported pK_a value of 3.8 was obtained by extrapolating results obtained using different percentages of methanol added to the aqueous solution of PFOA to improve solubility.⁹ The results of this study aroused controversy in the environmental community since it implied the acidity of PFOA is approximately 1000 times less than that of TFA despite having a homologous structure.

Other research groups suggest much lower pK_a values for PFOA. For example, Goss calculated a pK_a for PFOA of ~ 0 ⁵¹ and this value was supported by an *ab initio* computational study by Rayne and Forest.⁵²

Cheng et al. reported a pK_a for PFOA of ~ 0 using an electrospray ionization method combined with mass spectrometry to obtain a titration curve.⁵³ The method used was validated by measuring the pK_a values of a series of hydrogenated acids with known literature values. No features were observed in the titration curve for PFOA, suggesting that at the pH values used in the experiment, PFOA did not appreciably protonate.⁵³ The reported pK_a value of 0 is therefore an extrapolation based on the limits of the experimental design.

It is clear that fluorinated surfactants with low water solubilities do not lend themselves to simple experiments and a well-defined pK_a . Further experimental work will need to be performed before a true pK_a for PFOA can be accepted by the entire environmental chemistry community.

1.2.5 Polyfluorinated surfactants

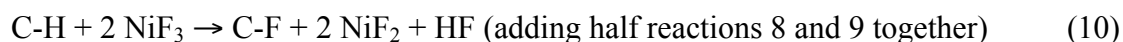
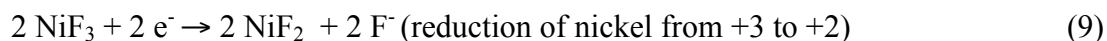
As mentioned, the PFCAs are ultimate degradation products of commercially used polyfluorinated compounds, which can be divided into two major categories: the polymers and the surfactants. The fluorinated polymers (such as ScotchGard™) will not be elaborated on in this introduction although they comprise the majority of the fluorinated compounds synthesized today.^{54,55} The polyfluorinated surfactants are lower molecular weight derivatives of perfluorinated acids, with the compounds synthesized by one of two major routes: electrochemical fluorination (ECF) and telomerization.

The surfactants synthesized by ECF are mostly structural derivatives of perfluorinated sulfonic acids (PFSAs) which have very similar environmental characteristics to PFCAs. Surfactants synthesized by the telomerization process are mainly derivatives of PFCAs usually containing a mixture of homologous compounds containing fluorinated chains of varying lengths. The next section of this introduction will review the salient synthetic chemistry and environmental reactions for each class of fluorinated surfactant.

1.3 Electrochemical fluorination and polyfluorinated sulfonamides

The first mass production method for perfluorinated surfactant synthesis was electrochemical fluorination (ECF) as developed by Simons.⁵⁶ This method uses an electrolytic cell to replace C-H bonds in a substrate with C-F bonds using anhydrous HF as the fluorine source. In this process the carbon atoms in the substrate are oxidized and the protons are reduced to elemental hydrogen. Nickel (III) fluoride acts as a catalyst during the reaction. Voltages typically range from 5-6 V which is sufficient to allow the reaction to proceed without oxidizing HF to fluorine gas and anhydrous conditions are strictly required to avoid the formation of explosive OF₂.¹ The ECF process was used by the 3M Company to synthesize the starting materials for their commercial fluorinated polymer and surfactant products.⁵⁴ The typical starting materials (feedstocks) used by 3M were linear aliphatic acyl fluorides (RC(O)F) and sulfonyl fluorides (RS(O)₂F), typically eight carbons in length.⁵⁴

The ECF reaction is a good example of a redox reaction by which electron transfer is part of the reaction mechanism. It has been determined the nickel fluoride acts as a catalyst for fluorine transfer and the ultimate fluorine source is HF. By breaking down the reaction into simple steps, this concept can be more easily seen. Disregarding the mechanism of the reaction, the steps can be written out as follows:



The above three reactions accomplish the replacement of a C-H bond with a C-F bond with the concurrent reduction of nickel (III) fluoride. Since NiF_3 is a catalyst, the next series of reactions serve to regenerate the catalyst using HF.



Adding equations 11 and 12 gives:



which is the regeneration of the nickel (III) fluoride catalyst. Equation 13 can be added to equation 10 to give the overall ECF balanced reaction as equation 10.

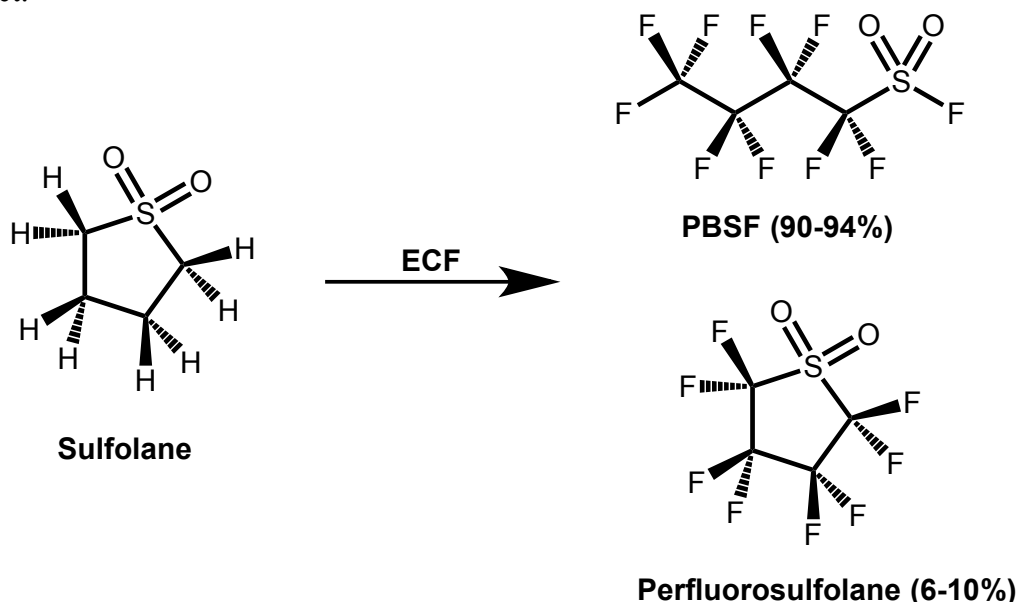


While these equations properly describe the stoichiometry of the ECF reaction, they do not reveal any details about the reaction mechanism. The ECF mechanism has not been determined with absolute certainty. Gambaretto et al. proposed the EC_bEC_N mechanism for electrochemical fluorination.⁵⁷ In this mechanism, a carbocation is the reactive intermediate. More recently, Ignat'ev et al. stated that while the EC_bEC_N may be occurring to some extent in the ECF process, a mechanism involving radicals is more likely to dominate.⁵⁸ In this scheme, the reaction takes place with the organic substrate adsorbed to the NiF_3 anode. After the first

electron transfer, a carbon centred radical is formed which is then fluorinated. It is from these radical intermediates that branched and cyclic byproducts are formed.⁵⁸ The branched constitutional isomers of the desired linear sulfonyl or acyl fluoride are characteristic of ECF reactions. A great deal of research has been performed to characterize the environmental properties of these isomeric products.⁵⁹

The ECF reaction was used predominantly by 3M to synthesize two important compounds: perfluorooctanoyl fluoride (PFOAF) and perfluorooctanesulfonyl fluoride (POSF).⁵⁴ The only intended fate of PFOAF was hydrolysis to give perfluorooctanoic acid (PFOA), a compound used as a processing aid in fluoropolymer synthesis. The other product, POSF, was the starting material for all 3M polymer and surfactant commercial products based on the sulfonamide linkage.⁵⁴ In 2000-2001, 3M voluntarily phased out production of both POSF-based materials and PFOA manufactured from PFOAF.⁶⁰ Analogous compounds based on perfluorobutanesulfonyl fluoride (PBSF) were chosen as suitable replacements.⁶¹ PBSF can be synthesized by electrochemical fluorination of either butanesulfonyl fluoride or 2,5-dihydrothiophene 1,1-dioxide (sulfolane).⁶² During the fluorination of sulfolane, PBSF is the major product with 6-10% perfluorosulfolane being synthesized as an impurity⁶² as shown in Figure 1.12. It is not known which synthetic method for PBSF is used by 3M today. Hence, perfluorosulfolane may be an unappreciated long lived greenhouse gas if present in the atmosphere. Commercially available PBSF (Sigma-Aldrich) is about 96% pure with the main impurity being perfluorosulfolane, as determined in our lab by ¹⁹F NMR peak matching to published spectra.⁶³

Figure 1.12: Electrochemical fluorination of sulfolane gives PBSF and perfluorosulfolane as a byproduct.



1.3.1 Sulfonyl fluorides

Sulfonyl fluorides are a class of compounds with the general structure $\text{RS(O)}_2\text{F}$ known to be hydrolytically stable in distilled water although the presence of a strong base will hydrolyze them to sulfonic acid salts.⁶⁴ Aberlin and Bunton measured hydrolysis rate constants for aromatic sulfonyl fluorides and found electron withdrawing groups enhanced the reaction rate suggesting developing negative charge in the transition state of the rate determining step.⁶⁵ These results could suggest either a concerted $\text{S}_{\text{N}}2$ -like mechanism or an addition-elimination mechanism but rules out the $\text{S}_{\text{N}}1$ mechanism. Gramstad and Haszeldine reported $\text{C}_8\text{F}_{17}\text{S(O)}_2\text{F}$ (POSF) being stable for days in water at 180°C with reactivity increasing as fluorinated chain length decreased, presumably due to increased solubility.⁶⁴ The four carbon analog $\text{C}_4\text{F}_9\text{S(O)}_2\text{F}$ (PBSF), was found to be stable for four days at room temperature at pH 12.⁶² These results for sulfonyl fluorides are in stark contrast to the lack of hydrolytic stability displayed for perfluorinated acyl fluorides discussed earlier. The hydrolytic stability of sulfonyl fluorides has important environmental

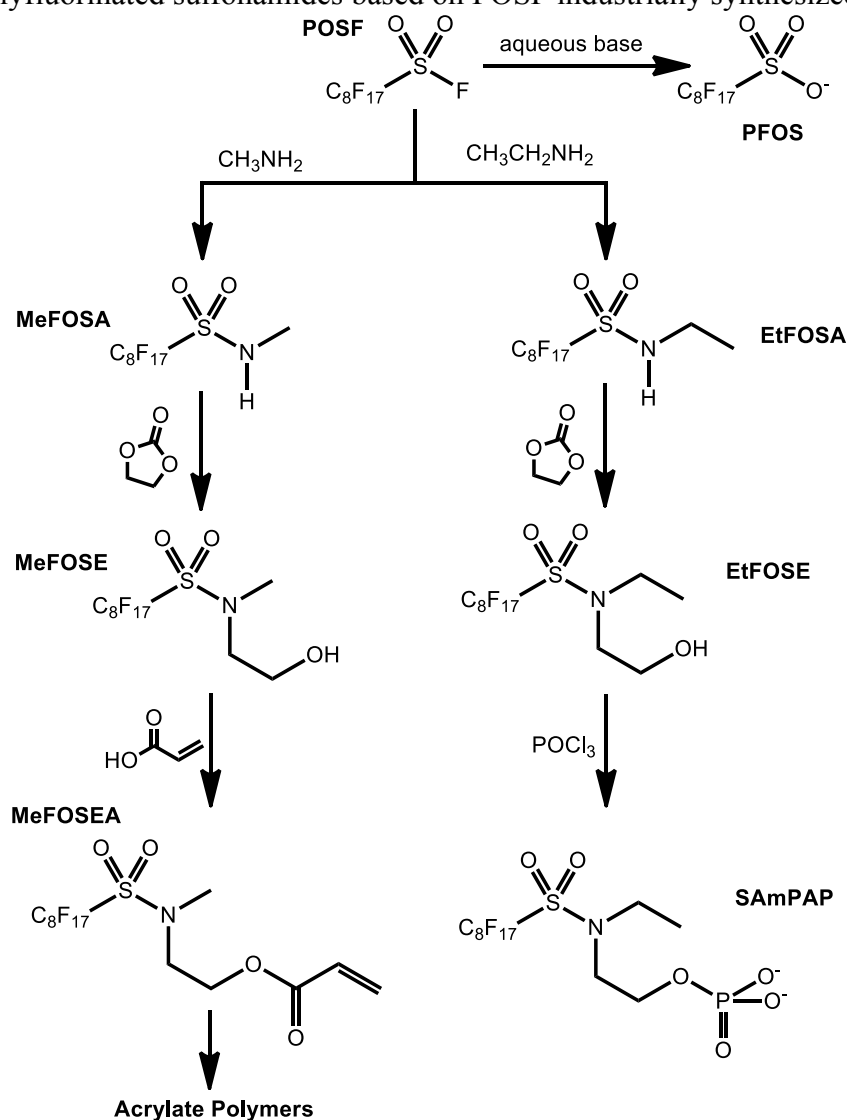
consequences because the sulfonyl fluorides POSF and PBSF are likely unappreciated long lived atmospheric contaminants, provided they are largely unreactive, as we would suggest, to atmospheric oxidants.

There is only one analytical method published for the detection of POSF; an LC-MS/MS method requiring derivatization with benzamide.⁶⁶ This method has not yet been applied to monitoring environmental samples. A previous attempts to detect POSF using GC-MS with a chemical ionization source failed to give a signal.⁶⁷ The development of a robust analytical method for the detection of sulfonyl fluorides such as POSF and PBSF would be of great benefit to environmental research.

1.3.2 Polyfluorinated sulfonamides

Polyfluorinated sulfonamides ($R_F\text{S(O)}_2\text{N(R}_1\text{)(R}_2\text{)}$, where R_F is a perfluorinated alkyl chain) served as the backbone for the 3M polymer and surfactant product lines.⁵⁴ A summary of the various chemical structures based on POSF that were historically synthesized by ECF are shown in Figure 1.13.

Figure 1.13 Polyfluorinated sulfonamides based on POSF industrially synthesized by ECF.



Sulfonamides are synthesized by reacting a sulfonyl fluoride synthesized by ECF (POSF prior to 2001, PBSF post-2001) with a monosubstituted amine such as ammonia, methylamine or ethylamine. The reaction mechanism is a nucleophilic substitution with expulsion of a fluoride ion and produced FOSA, MeFOSA and EtFOSA respectively. The compound EtFOSA was marketed as an insecticide called Sulfluramid™ which worked by uncoupling oxidative phosphorylation.⁶⁸

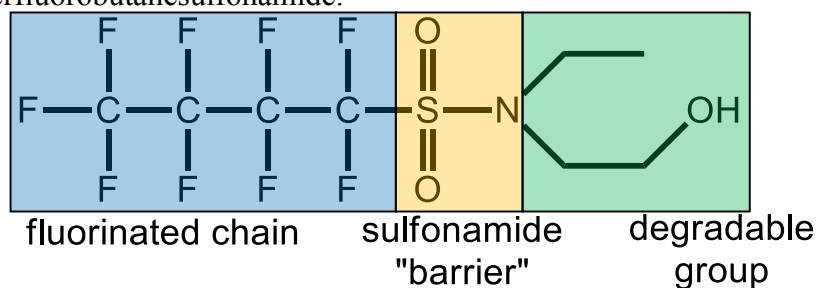
Monosubstituted sulfonamides such as MeFOSA and EtFOSA can be reacted with ethylene carbonate to produce sulfonamidoethanols (*N*-2-hydroxyethanol derivatives) whereby a CH₂CH₂OH moiety has substituted onto the sulfonamide group. Although the reaction mechanism is not well known, it presumably involves an initial deprotonation step on the nitrogen atom of the monosubstituted sulfonamide since the reaction is base catalyzed. This amide anion can then attack the electrophilic carbon atom α to the carbonate group on ethylene carbonate to open the five membered ring. With heat added during the reaction, the end group can be decarboxylated to give the alcohol functionality. The 2-hydroxyethyl derivatives of MeFOSA and EtFOSA are referred to as MeFOSE and EtFOSE respectively and are synthons for commercially useful materials produced by 3M.⁵⁴

The sulfonamidoethanol MeFOSE is reacted with either acrylic acid or acryloyl chloride⁶⁹ to produce the acrylate ester derivative *N*-methylperfluorooctanesulfonamidoethyl acrylate (MeFOSEA). This compound can then be co-polymerized to produce a side-chain fluorinated polymer that comprises the active ingredient of historical ScotchGard™. After their voluntary phaseout of POSF-based materials, 3M has switched to fluorinated chains four carbons long for their polymers instead of eight to reduce the environmental impacts of their products.⁶¹

Other polyfluorinated sulfonamide products were historically used as components of aqueous film forming foams (AFFF), notably perfluorinated sulfonates and amphoteric surfactants.⁷⁰

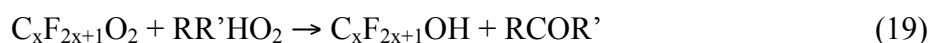
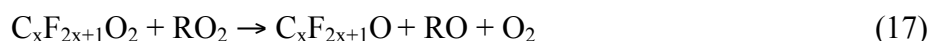
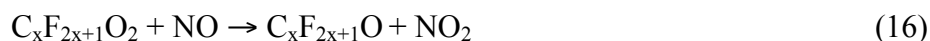
The sulfonamide group is highly stable to hydrolysis and therefore serves as an unreactive “barrier” or “wall” between the perfluorinated component and the functionalized component of the compounds as illustrated in Figure 1.14. An internal 3M study showed that EtFOSE will hydrolyze to form PFOS but that it requires very strongly basic conditions (20% alcoholic KOH) and elevated temperatures for the reaction to proceed.⁷¹ Under milder conditions, the sulfonamide bond can be regarded as almost inert in the abiotic environment.

Figure 1.14: Sulfonamide “barrier” as illustrated for *N*-ethyl-*N*-(2-hydroxyethyl)perfluorobutanesulfonamide.



This implies the ultimate degradation product of an eight perfluorinated carbon sulfonamide will be perfluorooctane sulfonate (PFOS), only if hydrolysis occurs. Once PFOS itself is formed, it has not been shown to degrade further under any known environmental conditions. The only environmental process known to break a sulfonamide linkage is atmospheric oxidation by hydroxyl radical (OH). The atmospheric oxidation of *N*-methyl-*N*-(2-hydroxyethyl)perfluorobutanesulfonamide (MeFBSE) produced a homologous series of short-chain perfluorinated carboxylic acids (PFCAs).⁷² The authors proposed a mechanism whereby the OH radical adds to the S=O bond followed by departure of a perfluorinated radical leaving group.⁷² Under low-NO_x conditions, perfluorinated radicals are capable of forming PFCAs of varying chain lengths by an “unzipping” mechanism in the presence of alkylperoxy radicals⁷³ as

shown in the reactions below. Reactions 16 and 18 unzip the perfluorinated radical, eliminating COF₂ units with each iteration while reactions 17 and 19-21 generate PFCAs from perfluorinated radicals.



Under biological conditions, only PFOS is known to be formed during degradation of perfluorinated sulfonamide compounds. Since the sulfonamide functionality remains intact during metabolic reactions, no intermediates containing a reactive site in the fluorinated chain are formed in vivo. The consequences of this will be discussed later.

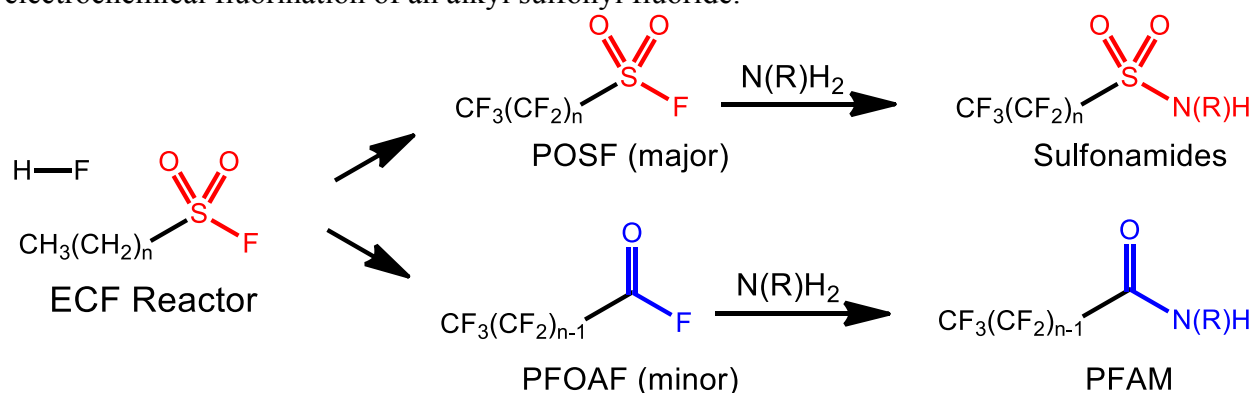
When quantification of the branched isomers of an ECF compound is required, chromatography can be used to achieve separation. Although it is difficult to separate all isomers, the presence of multiple peaks surrounding one dominant peak (normally the linear isomer) confirms a compound was likely synthesized by ECF. New analytical methods have recently been developed that allow quantitation of most, if not all, isomers in an eight carbon perfluorinated chain.^{74,75} There is a direct relationship between fluorinated chain length and the

number of isomers synthesized.⁵⁹ For example, PFBS manufactured from ECF does not show any branched isomers whereas PFDS shows many branched isomeric peaks in an LC-MS/MS chromatogram.⁵⁹

During electrochemical fluorination, unintentional byproducts can be formed that may have had important environmental consequences. Gramstad and Haszeldine electrochemically fluorinated octanesulfonyl fluoride and obtained POSF as the desired product along with perfluorooctane (19% yield) and perfluorinated carboxylic acids (PFCAs, 1% yield) as two of the byproducts along with sulfonyl fluorides of varying chain lengths.⁶⁴ The formation of PFCAs likely results from the initial synthesis of perfluorinated acyl fluorides such as perfluorooctanoyl fluoride (PFOAF) which are then hydrolyzed to form PFCAs.⁶⁴

Since perfluorinated acyl fluorides are a known byproduct of sulfonyl fluoride production by ECF, it was postulated recently by us that during sulfonamide synthesis, acyl fluorides can react with an amine to produce a polyfluorinated amide (PFAM) with the general structure $C_xF_{2x-1}C(O)N(H)R$ where $R = CH_3$ or CH_2CH_3 ⁷⁶ as shown in Figure 1.15. Since eight fluorocarbon materials were the most common ECF materials produced historically, the PFAM compounds expected are MeFOA ($C_7F_{15}C(O)N(H)CH_3$) and EtFOA ($C_7F_{15}C(O)N(H)CH_2CH_3$). These two compounds were detected in a wide variety of commercial ECF materials tested using GC-MS;⁷⁶ described in chapter 3 in this dissertation.

Figure 1.15: Unintentional synthesis of polyfluorinated amides (PFAMs) from the electrochemical fluorination of an alkyl sulfonyl fluoride.



1.3.3 Sulfonamide based phosphate esters

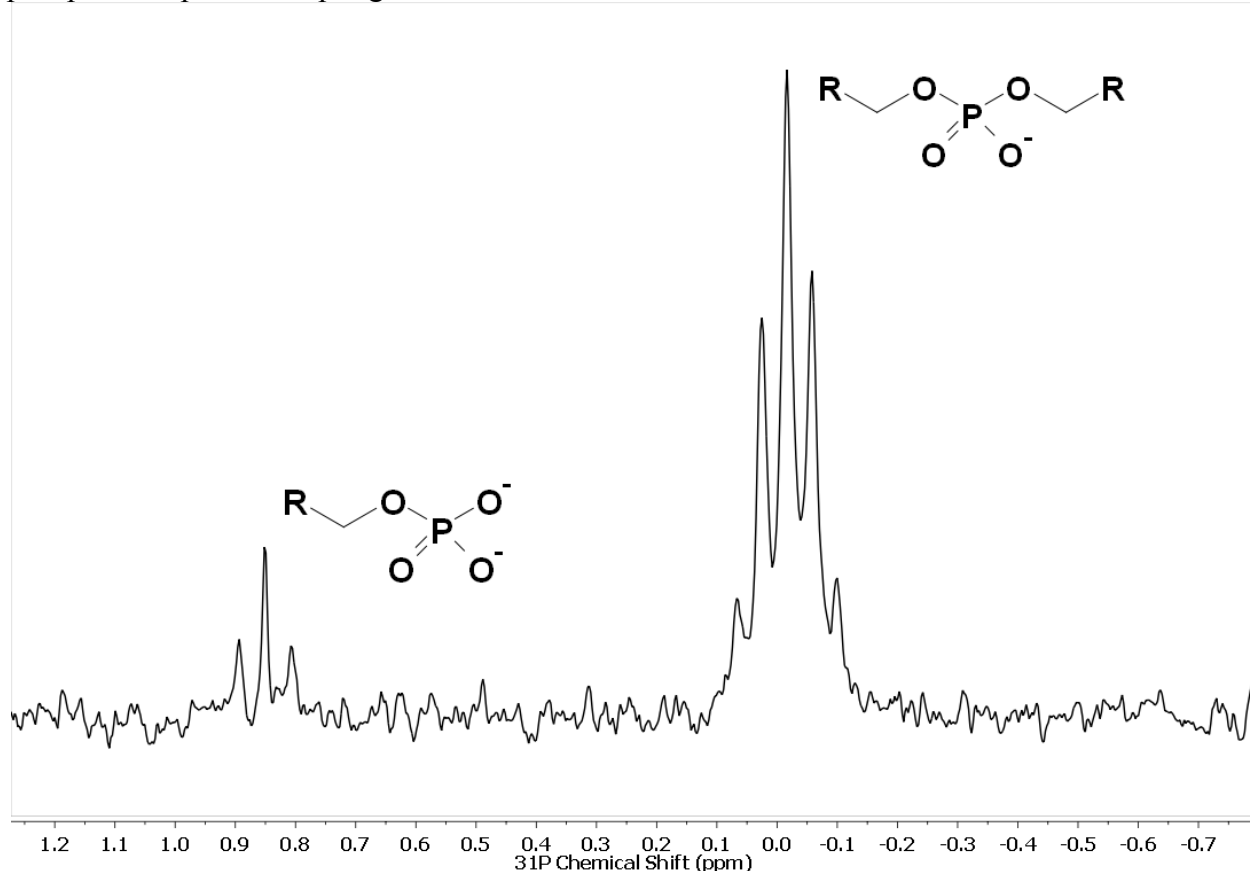
One of the major products from the 3M surfactant line was the EtFOSE-based phosphate mono and diester (SAmPAP, CAS# 2965-52-8). These compounds were historically used in food contact packaging to impart water and oil repellency until the phase-out of POSF-based products in 2000-2001.⁵⁴ The EtFOSE-based phosphate triester was not commercially useful but still might have been present in some formulations as a byproduct during the synthesis of the mono and diesters. The central structural unit in SAmPAPs is the phosphodiester group, negatively charged at environmental pH. To synthesize a SAmPAP, EtFOSE can be reacted with POCl_3 in a nucleophilic substitution reaction and the chlorine atoms are replaced by the fluorinated groups.⁷⁷ Adjusting the ratio of EtFOSE: POCl_3 should allow some control over the distribution of degrees of substitution at phosphorus. A more recent synthetic method uses polyphosphoric acid instead of POCl_3 to obtain specifically the monoester product in yields of almost 97%.⁷⁸

Recently, Benskin et al. subjected a model SAmPAP formulation to a biodegradation experiment using marine sediment and found no evidence of transformation of the starting material after 120 days.⁷⁹ Under the same conditions, EtFOSE degraded as expected and formed

PFOS as the final degradation product. The authors proposed lack of bioavailability due to sorption as the reason for lack of SAmPAP biodegradation.⁷⁹

A useful tool for the characterization of SAmPAP formulations is ^{31}P NMR spectroscopy. If a ^{31}P spectrum is acquired without any decoupling to ^1H , then the phosphorus atoms within the sample will show spin-spin splitting with any nearby protons and give information on the level of organic substitution at the phosphorous centre. As an example, the ^{31}P NMR of a typical SAmPAP formulation, ScotchbanTM FC-807A, is given in Figure 1.16. Two signals are seen at different chemical shifts: a pentet at 0.0 ppm and a triplet at 0.9 ppm. The triplet results from ^3J coupling to one CH_2 group and indicates the presence of a phosphate monoester. The pentet results from ^3J coupling to two CH_2 groups, indicative of a phosphate diester. By integrating the two signals, the relative proportions of the two species can be found. In the case of FC-807A, roughly 90% of the formulation is comprised of the diester, with the monoester being a residual from the synthetic process assuming excess POCl_3 was used.

Figure 1.16: ^{31}P NMR of ScotchbanTM FC-807A obtained by our research group showing phosphorous-proton coupling of both monoesters and diesters.



1.4 Telomerization and fluorotelomer compounds

A major industrial route used for the production of the majority of fluorochemical compounds used today is telomerization, first described by DuPont in 1942.⁸⁰ Typically, the fluorinated chain is built up using radical reactions of two carbon units, leading to an even number of carbon atoms in the final product, if any only if the starting material (the *telogen*) contains two carbon atoms, typically pentafluoroethyl iodide ($\text{CF}_3\text{CF}_2\text{I}$) is used. The reagent used to extend the fluorocarbon chain during the telomerization process is called the *taxogen* and is usually tetrafluoroethylene (C_2F_4). Fluorotelomers are named using the x:y nomenclature where

“x” refers to the number of perfluorinated carbons and “y” refers to the number of hydrogenated carbons in the chain (usually $y = 2$).

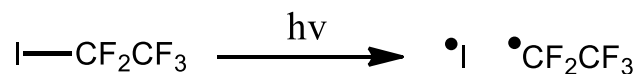
1.4.1 Synthesis of fluorotelomer compounds

Overall, the telomerization reaction is a polymerization process with initiation, propagation and termination steps. Typically, synthesis begins with the telogen perfluoroethyl iodide, $\text{CF}_3\text{CF}_2\text{I}$. Carbon-iodide bonds are fairly weak and can be homolytically cleaved using ultraviolet light or heat to give an iodine atom and the perfluoroethyl radical, CF_3CF_2 in the initiation phase.

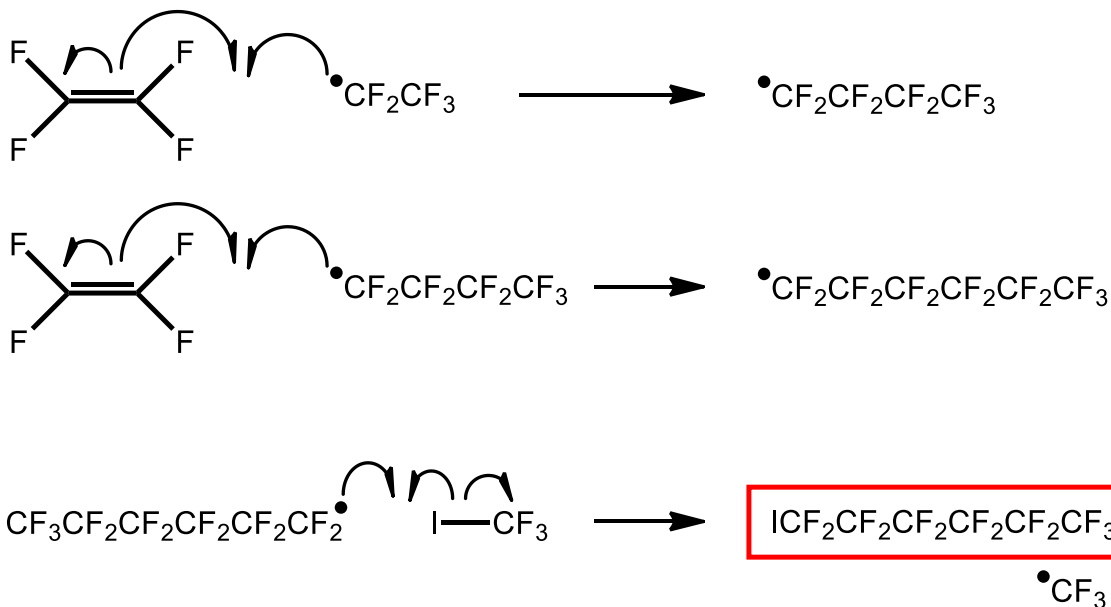
The propagation step consists of reactions between perfluorinated radicals beginning with CF_3CF_2 , and the typical taxogen tetrafluoroethylene, C_2F_4 . The π bond in C_2F_4 is homolytically cleaved to form a new C-C bond and the product is a perfluorinated radical two carbons longer. This process repeats until a perfluorinated chain of an appropriate length is synthesized as shown in Figure 1.17. For most practical uses, the chain is usually no longer than ten carbons long however on occasion longer telomer chains have been found in commercial products. The termination of the telomerization reaction using trifluoromethyl iodide gives a perfluorinated iodide (PFAI) of the general structure $\text{C}_x\text{F}_{2x+1}\text{I}$. Due to the nature of the reaction mechanism, the PFAI contains a linear perfluorinated chain and is free from any branched isomers. The major byproducts of a telomerization reaction are PFAIs of different chain lengths.

Figure 1.17: Synthetic pathway for the synthesis of perfluorohexyl iodide (C₆-PFAI) by telomerization. All other PFAIs can be synthesized by repeating a different number of propagation steps.

INITIATION



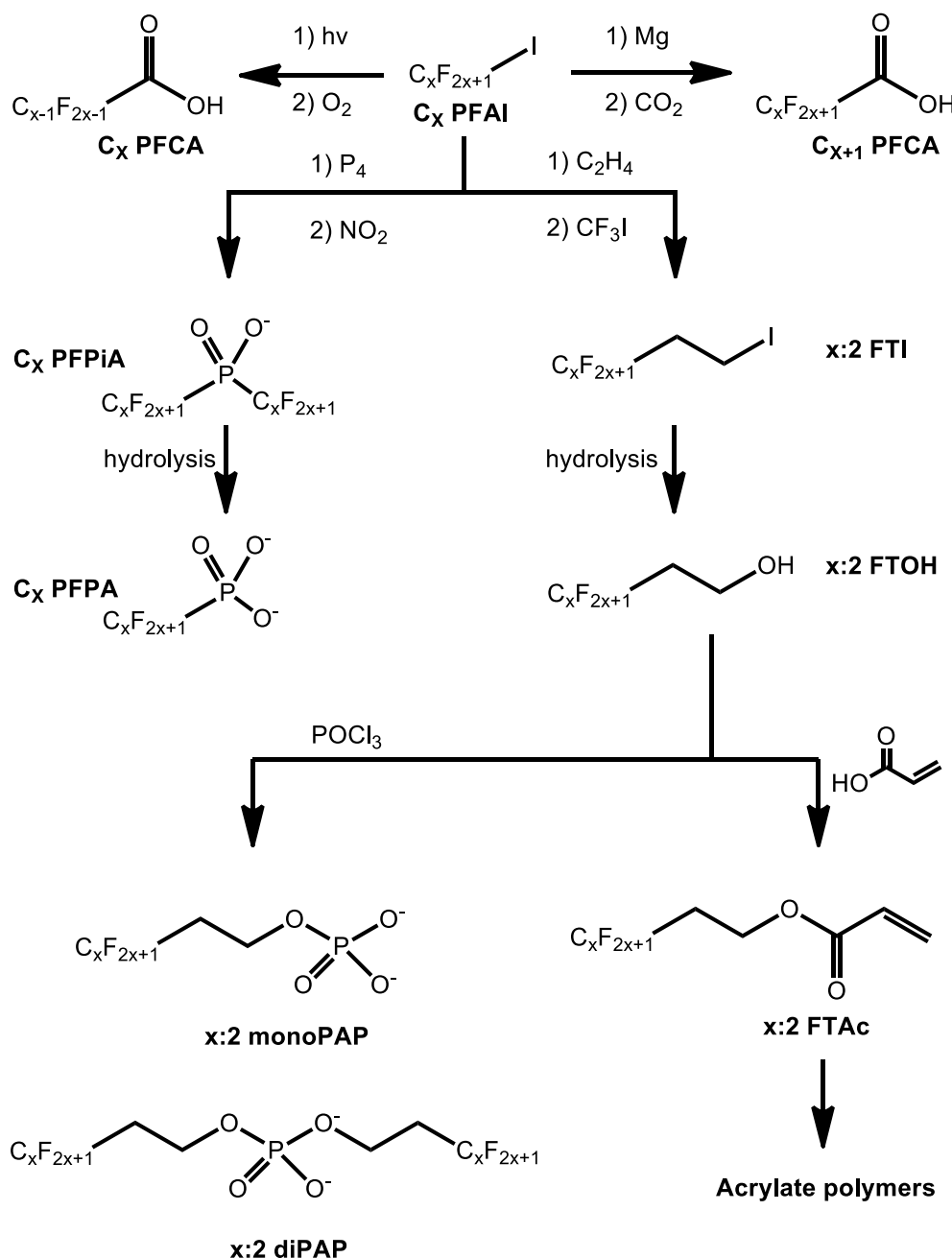
PROPAGATION



Once the PFAI products are synthesized, additional reactions functionalize this initial product into a myriad of polyfluorinated compounds with their own specific uses. Some of the more common synthetic pathways for producing derivatives of PFAIs are shown in figure 1.18.

Figure 1.18: General synthetic overview of some commercially used fluorotelomer compounds

where “x” is an even number, typically 4, 6, 8, 10.



1.4.2 Perfluorinated iodides

There are four major synthetic uses of PFAIs. For the C_8 PFAl, perfluorooctanoic acid (PFOA) can be produced by an oxidation reaction and perfluorononanoic acid (PFNA) can be

produced by a carboxylation reaction of perfluorooctyl iodide. The oxidation reaction is initiated by UV light (250-310 nm) to dissociate perfluorooctyl iodide, $C_8F_{17}I$, into an iodine atom and the perfluorooctyl radical $C_8F_{17}\cdot$.⁸¹ This radical then reacts with oxygen in the presence of an alcohol (typically methanol or ethanol) to initially form an ester of PFOA, which can then be hydrolyzed to form PFOA.⁸¹ The reaction of $C_8F_{17}I$ to produce PFNA is a Grignard reaction whereby a carbanion reacts with carbon dioxide to form a carboxylic acid extended by one carbon.⁸² Initially, magnesium metal is used to form the Grignard reagent which then reacts with CO_2 to form the desired carboxylate product.

A third synthetic use for PFAIs is their reaction with phosphorous to produce perfluorinated phosphonates and phosphinates,⁸³ an emerging group of environmental contaminants discussed later. Finally, PFAIs can be converted to fluorotelomer iodides (FTIs), which are important building blocks for many commercial products.

1.4.3 Fluorotelomer iodides (FTIs)

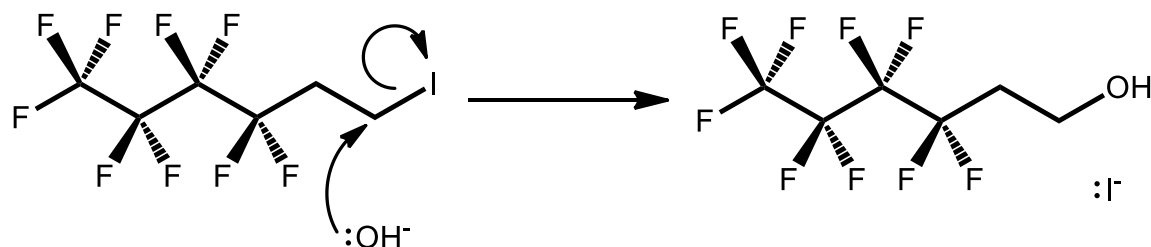
Most fluorotelomer compounds are derivatives of FTIs which have the general structure $C_xF_{2x-1}CH_2CH_2I$. They are synthesized by a radical reaction between the corresponding PFAI and ethylene. The iodide group in an FTI facilitates nucleophilic substitution reactions to build up more complex structures. The ethylene “bridge” between the fluorinated chain and the iodine atom is used because perfluorinated iodides (PFAIs) of the structure $C_xF_{2x-1}I$ do not easily react by the S_N2 mechanism to displace the iodine atom by a nucleophile such as hydroxide.¹ From the fluorotelomer iodides an eclectic variety of commercially useful compounds can be synthesized.

Since FTIs are high production volume compounds, their environmental fate is of great interest. They are highly volatile compounds due to their inability to participate in hydrogen bonding and will partition into the atmosphere where they can undergo either reactions with hydroxyl radicals or direct photolysis.⁸⁴ As determined by smog chamber experiments, the major product of atmospheric degradation by either pathway is a fluorotelomer aldehyde (FTAL) of the structure $C_xF_{2x+1}CH_2CHO$.⁸⁴

One major industrial use of FTIs is serving as precursors by hydrolysis for the production of fluorotelomer alcohols (FTOHs) that have the general structure $C_xF_{2x-1}CH_2CH_2OH$. Since FTIs are likely environmental contaminants, this hydrolysis reaction might also be environmentally relevant. The hydrolysis of FTIs to FTOHs was modeled by Rayne and Forest,⁸⁵ and assumed the reaction mechanism was the same as iodomethane, being S_N2 at $pH > 9$ and S_N1 at all other pH values, including environmental pH. However, methyl halides are not known to participate in S_N1 reactions since the formation of the unstable methyl carbocation would be prohibitively slow.^{86,87} The hydrolysis of iodomethane was studied by Adachi et al. who reported unimolecular reaction kinetics (independent of $[OH^-]$) at $pH < 9$.⁸⁸ From this observation, an S_N1 mechanism for the hydrolysis of iodomethane has unfortunately been erroneously implied.⁸⁵ It is far more likely that unimolecular kinetics are seen due to H_2O serving as the nucleophile in the S_N2 reaction. Since water as the solvent is present in large excess, the observed rate law becomes pseudo-first order. It is possible that FTIs will also undergo S_N2 hydrolysis reactions to produce FTOHs in the environment as seen in Figure 1.19. The rate of this reaction will likely be decreased compared to a simple hydrogenated iodide. Previous studies by Hine and Brader⁸⁹ as well as Shaik⁹⁰ have established that halogen atoms at the β carbon to the leaving group will

reduce the rate of an S_N2 reaction. Since FTIs probably have high Henry's Law constants, their major environmental fate will likely be atmospheric oxidation as described earlier,⁸⁴ rather than aqueous hydrolysis.

Figure 1.19: Hydrolysis of 4:2 FTI to produce 4:2 FTOH by the S_N2 mechanism.

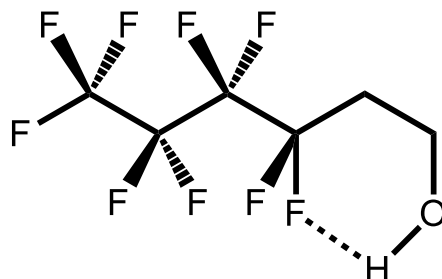


1.4.4 Fluorotelomer alcohols

The FTOHs themselves are not used commercially but are intermediates in the syntheses of useful products, as well as degradation products of more complex fluorinated products. On an industrial scale, they can be synthesized from FTIs using several different methods such as treatment with oleum and water⁹¹ as well as treatment with hot 10% KOH.⁹² They have been the focus of a multitude of environmental studies as they have been ubiquitously detected in the atmosphere.⁹³ Despite having an OH group capable of intermolecular hydrogen bonding, FTOHs are moderately volatile compounds, more so than their hydrogenated analogs,⁹⁴ and can partition into the atmosphere. Once in the gas phase they can be transported to remote areas such as the Canadian Arctic⁷³ and subsequently degrade either biotically or atmospherically⁹⁵ to produce PFCAs. The original hypothesis for the moderate volatility of the FTOHs is an intramolecular hydrogen bond between the O-H proton and the C-F bonds closest to the CH_2CH_2 group.⁹⁴ In this model, a six-membered ring is formed when the hydrogen bond is included in the molecular geometry as shown in Figure 1.20. Due to this bond, the intermolecular hydrogen bonding

between different FTOH molecules was proposed to be weakened as a result, increasing its vapour pressure.⁹⁴

Figure 1.20: Proposed intramolecular hydrogen bonding in FTOHs using the 4:2 FTOH as an example.



More recent work has suggested the importance of this intramolecular hydrogen bond to be minimal and not the primary reason for the high vapour pressure of FTOHs. As stated earlier, C-F bonds make poor hydrogen bond acceptors. Krusic et al. used gas-phase NMR and FTIR techniques and suggested that the intramolecular hydrogen bonding of FTOHs to be insignificant.⁹⁶ In particular, the vapour phase FTIR spectrum of 8:2 FTOH showed only one peak resulting from an O-H stretch and did not resemble other compounds known to have an intramolecular hydrogen bond.⁹⁶ Arp et al. used computational methods and concluded that a significant intramolecular hydrogen bond would result in vapour pressures for the FTOHs at least one order of magnitude greater than determined experimentally.⁹⁷

The FTOHs are extremely important environmental contaminants since they represent a common intermediary “funnel” that link the degradation of more complex fluorinated compounds to their PFCA ultimate degradation products. Consequently, much work has already gone into elucidating the degradation pathways of FTOHs.⁹⁸ Atmospherically, FTOHs are known to either directly degrade to PFCAs or to undergo an “unzipping” process by which the

fluorinated chain iteratively releases COF_2 as described earlier.⁹⁵ The resultant pathway will largely depend on the amount of NO_x ($\text{NO} + \text{NO}_2$) in the atmosphere. Biotically, the FTOHs are enzymatically oxidized through a series of reactions that resemble the β -oxidation catabolic pathway to produce PFCAs as end degradation products.^{99,100}

1.4.5 Fluorotelomer aldehydes and perfluorinated aldehydes

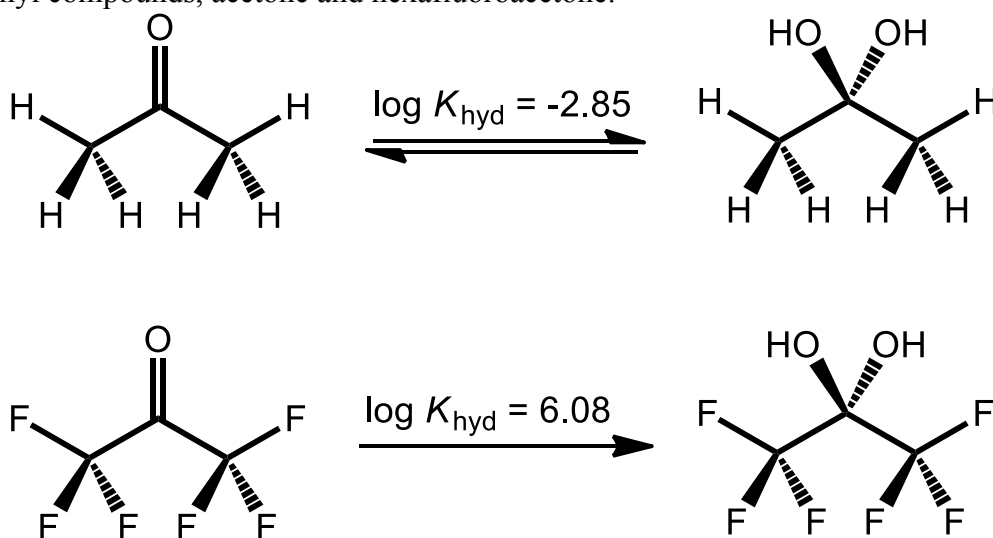
The fluorotelomer aldehydes (FTALs) with the general structure $\text{C}_x\text{F}_{2x+1}\text{CH}_2\text{CHO}$ are primary degradation products from the oxidation of the OH group in FTOHs.⁹⁹ In common with simpler aldehydes, FTALs can be oxidized further to the corresponding fluorotelomer carboxylic acid (FTCA), $\text{C}_x\text{F}_{2x+1}\text{CH}_2\text{C}(\text{O})\text{OH}$ in biological systems. Atmospherically, FTALs are degraded by either hydroxyl radicals¹⁰¹ or direct photolysis¹⁰² to produce perfluorinated aldehydes (PFALs) with the structure $\text{C}_x\text{F}_{2x+1}\text{CHO}$. Both FTALs and PFALs degrade to form PFCAs by known atmospheric oxidation reactions.⁷³

Both FTALs and PFALs are capable of undergoing a hydration reaction to form a gem-diol compound which is common to all aldehydes and ketones. This reaction can be acid or base catalyzed and is a reversible equilibrium in most cases. The propensity of a carbonyl compound to form its corresponding gem-diol is governed by the equilibrium constant K_{hyd} which varies by many orders of magnitude depending on the structure of the parent carbonyl.



This equilibrium usually favours the carbonyl structure for simple aliphatic compounds. For example, $\log K_{\text{hyd}}(\text{acetone}) = -2.85$.¹⁰³ In certain structures however, the gem-diol may be favoured. The most common reason is halogenation; for example $\log K_{\text{hyd}}(\text{hexafluoroacetone}) = 6.08$.¹⁰³ A compound with such a high K_{hyd} value is essentially always in its hydrated state and can not be reversed easily as shown in Figure 1.21.

Figure 1.21: Hydration reactions and equilibrium constants for two representative carbonyl compounds, acetone and hexafluoroacetone.



The PFALs are known to possess very high K_{hyd} values and are commercially sold as their hydrates. Under environmental conditions, a PFAL formed in the atmosphere will rapidly form a hydrate upon reaction with water but may be dehydrated back to the parent carbonyl structure in a heterogeneous process.¹⁰⁴

The FTALs may have appreciable K_{hyd} values that would affect their partitioning behaviour in the environment however they will not favour the hydrate structure as much as the

PFALs since the perfluorinated chain in FTALs is separated from the carbonyl by a CH_2 group. No experiments have currently been done to determine the hydration equilibrium constants for any FTAL however it is possible to make a hypothesis on what environmental implications of hydration might be for a typical FTAL. It is reasonable to assume that hydrate formation will be favoured more than acetaldehyde itself but less so than formaldehyde, which strongly favours the gem-diol form. The $\log K_{\text{hyd}}$ values of acetaldehyde and formaldehyde are 0.03 and 3.36 respectively.¹⁰⁵ Since formaldehyde predominantly exists as the gem-diol in aqueous solutions yet still reacts rapidly as a carbonyl compound, it is likely that FTALs will as well.

1.4.6 Fluorotelomer carboxylic acids and aldehydes

The fluorotelomer carboxylic acids ($\text{C}_x\text{F}_{2x+1}\text{CH}_2\text{C}(\text{O})\text{OH}$, FTCAs) and fluorotelomer aldehydes ($\text{C}_x\text{F}_{2x+1}\text{CH}_2\text{C}(\text{O})\text{H}$, FTALs) are intermediates produced during the atmospheric and biological degradation of fluorotelomer precursors to PFCAs.¹⁰⁶ Studies carried out using *Daphnia magna* show FTCAs to be 5 orders of magnitude more toxic than their corresponding PFCA degradation products.¹⁰⁷ There are two prevailing hypotheses for this observation, neither of which are mutually exclusive. As stated previously, FTCAs (and FTALs) can undergo an E1cB reaction to eliminate HF and form the corresponding fluorotelomer unsaturated acid ($\text{C}_{x-1}\text{F}_{2x-1}\text{C}(\text{F})=\text{C}(\text{H})\text{C}(\text{O})\text{OH}$, FTUCA) or aldehyde ($\text{C}_{x-1}\text{F}_{2x-1}\text{C}(\text{F})=\text{C}(\text{H})\text{C}(\text{O})\text{H}$, FTUAL). The HF produced in this reaction is highly toxic and can contribute to the observed ill-effects in *Daphnia*.¹⁰⁷

The FTUCAs and FTUALs contain an α,β unsaturated system and as such, are reactive electrophiles in Michael reactions with endogenous nucleophiles such as glutathione, amino

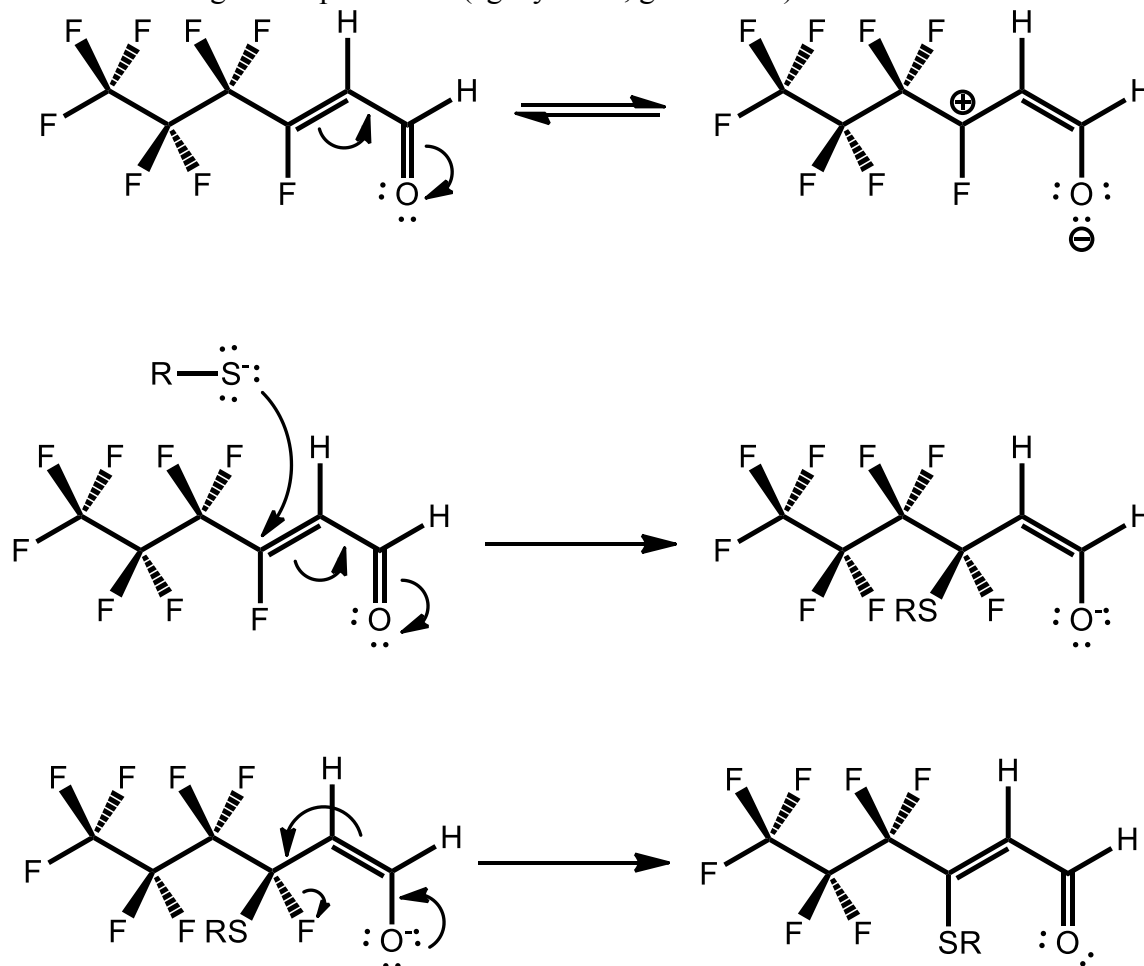
acids, proteins and DNA.¹⁰⁸ The reactive site is present on the β carbon and can be visualized by drawing the appropriate resonance structure for the FTUCA or FTUAL. A resonance form with a positive charge on the β carbon can be drawn indicating that site should be electrophilic as shown in Figure 1.23.

The first study showing that these intermediates are electrophilic was performed by Martin et al. by dosing rat hepatocytes with the 8:2 FTOH.³⁷ Two of the products identified included the glutathione (GSH) conjugates of 8:2 FTUCA and 8:2 FTUAL. In these structures, GSH has reacted with the α,β -unsaturated system at the β carbon to form the 1,4-Michael addition product.³⁷ Since GSH acts as a cellular antioxidant, its reaction with endogenous electrophiles is a symptom of oxidative stress.¹⁰⁹

A more extensive study using GSH as a nucleophilic probe by Rand and Mabury investigated the extent of the reaction between GSH and FTUCAs and FTUALs of various chain lengths in vitro.¹¹⁰ The FTUALs were found to be more reactive than the FTUCAs and that a chain length effect may be present, with the shorter chained compounds being more reactive to GSH.¹¹⁰ Further work has demonstrated the reactivity of these important intermediates to the nucleophilic amino acids cysteine, lysine, histidine and arginine using NMR spectroscopy.¹¹¹ The most reactive amino acid towards FTUALs and the only amino acid to react with FTUCAs was cysteine which contains the SH nucleophilic group. Since the site of attack on the Michael acceptor is the β carbon atom,¹¹² it is a relatively soft electrophile compared to the carbonyl carbon using the Pearson Lewis acid/base concept¹¹³ and therefore is more reactive toward soft nucleophiles such as sulfur. The FTUALs were found to be more electrophilic than FTUCAs and

reacted with harder nucleophiles such as the nitrogen-containing amino acids histidine, lysine and arginine.¹¹¹ The complete mechanism of a Michael reaction with 4:2 FTUAL as a representative electrophile is shown in Figure 1.22.

Figure 1.22: Mechanistic scheme of the Michael reaction between 4:2 FTUAL and a sulfur-containing nucleophile RSH (eg. cysteine, glutathione).



1.4.7 Polyfluoroalkyl phosphate esters

An FTOH can be reacted with phosphorous oxychloride (POCl_3) to produce polyfluorinated alkyl phosphate surfactants (PAPs), an extremely important class of fluorinated pollutants.¹¹⁴ Three levels of phosphate ester substitution are possible: monoesters (monoPAPs),

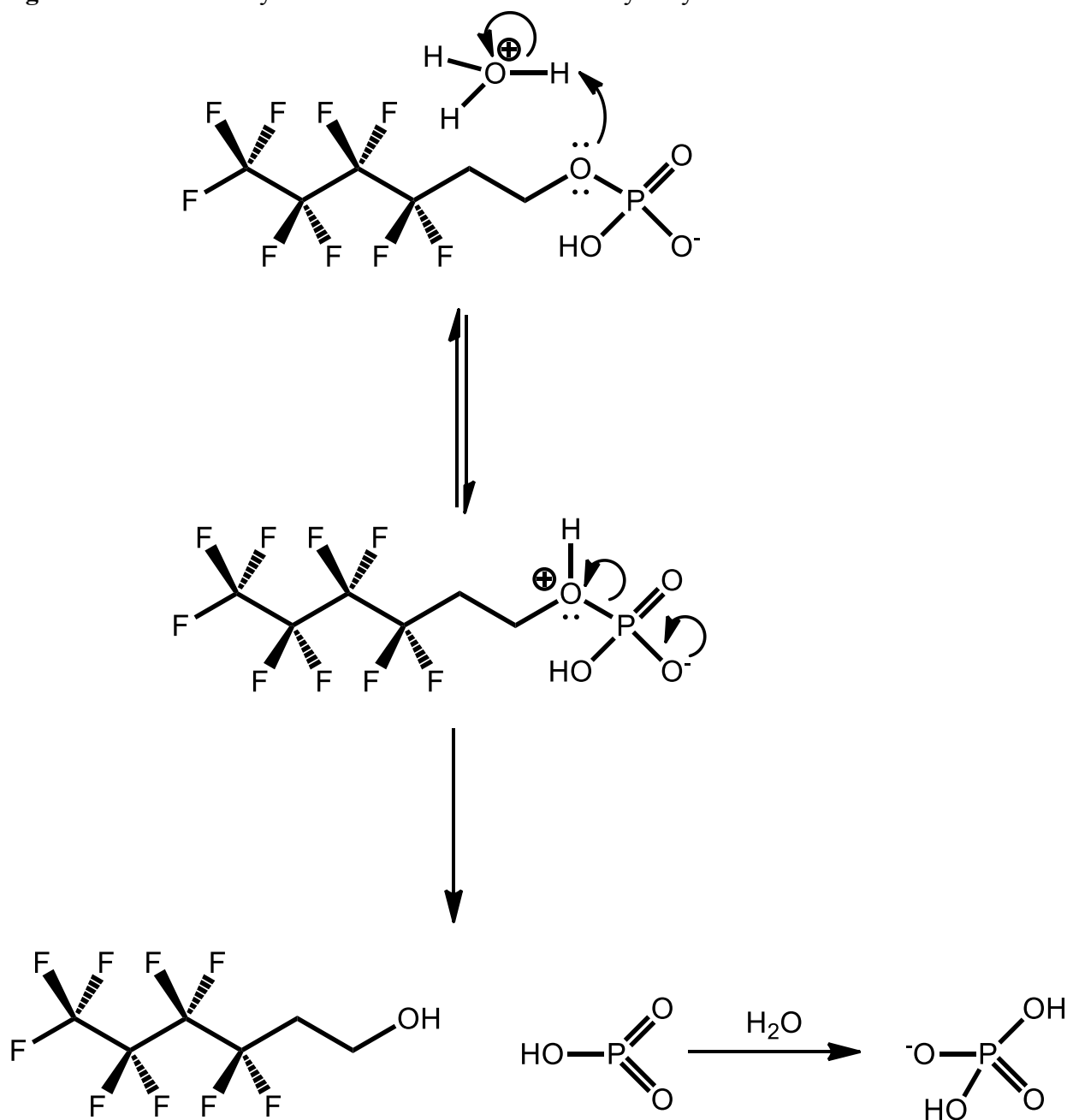
diesters (diPAPs) and triesters (triPAPs). Of these three, the diPAPs are usually the desired end product with monoPAPs and triPAPs being produced as byproducts. The formation of byproducts is likely due to the high electrophilicity of POCl_3 and that the formation of diPAPs would require neither FTOH nor POCl_3 be present in large excess.

The diPAPs are potent surfactants and are used primarily in the paper industry to impart water and oil repellent properties onto surfaces used for food contact. Since PAPs are phosphate esters of fluorotelomer alcohols, hydrolysis reactions of PAPs should give FTOHs, and this has been observed for both monoPAPs and diPAPs in rats.^{115,116} A subsequent study confirmed that monoPAPs are efficiently hydrolyzed by mammalian alkaline phosphatase enzyme at a rate significantly greater than an analogous hydrogenated phosphate ester,¹¹⁷ (Chapter 5 of this dissertation) due to the fluorinated chain withdrawing electron density by induction from the reactive portion of the molecule.¹¹⁸ This effect is diminished somewhat since the CH_2CH_2 group is present bridging the fluorinated chain with the phosphate group but the effect is still easily observed.¹¹⁷

Abiotically, most phosphate esters are stable under environmentally relevant conditions of temperature and pH with the monoester being more stable than the diester.¹¹⁹ The mechanism for abiotic hydrolysis of a phosphate monoester (shown in Figure 1.23) is acid-catalyzed and involves a very slow dissociation step to produce an alcohol and PO_3^- , which is rapidly hydrolyzed to inorganic phosphate.^{120,121} Such conditions are unlikely to be met in the environment. Both monoPAPs and diPAPs are very stable abiotically and have not been observed to degrade under strongly alkaline conditions, as expected from their structure.¹¹⁵ Of

the three possible substituted PAPs, only the triPAPs will likely hydrolyze abiotically in the environment. Since triPAPs are neutral, the electrophilic phosphorous atom is not shielded from nucleophilic attack by a negative charge.¹²²

Figure 1.23: Acid catalyzed mechanism for the abiotic hydrolysis of 4:2 monoPAP.



Both phosphate mono- and di- esters are weak acids since the pK_a of the first OH group is predicted as 1.2 and for monoPAPs the second pK_a is predicted to be 5.0 (calculated using SPARC on-line v 4.6; <http://archemcalc.com/sparc>).¹²³ Under most environmental conditions, both monoPAPs and diPAPs will be charged, increasing their water solubility. It is the additional negative charge on monoPAPs that makes them very challenging to analyze by liquid chromatography as it results in extreme peak tailing. This obstacle can be overcome by adding formic acid to the mobile phase to protonate one of the two OH groups on the monoPAPs.¹²⁴ In combination with an ion pairing agent such as ammonium acetate, this gives much improved peak shapes on a reverse phase HPLC column.

1.4.8 Perfluorinated phosphonates and phosphinates

A family of perfluorinated acids that have only recently received environmental attention are the perfluorinated phosphonates (PFPAs) and the perfluorinated phosphinates (PFPiAs).¹²⁵ These compounds are high production volume chemicals used commercially as leveling and wetting agents in household cleaning products.

The PFPiAs (general structure $C_xF_{2x+1}P(O)(OH)_2$) are synthesized by the reaction of a PFAI with elemental phosphorous.⁸³ The initial product is an iodophosphine containing phosphorous bonded to two fluorinated chains and one iodine atom. This compound is then oxidized using nitrogen dioxide followed by hydrolysis to give the desired PFPiA.⁸³ The PFPAs (general structure $C_xF_{2x+1}P(O)(OH)_2$) can be synthesized by the hydrolysis of the corresponding PFPiA at high temperature.¹²⁶

Unlike monoPAPs and diPAPs, the PFPAs and PFPiAs do not contain an oxygen atom linking the fluorinated chain with the phosphorous atom and therefore are not susceptible to the same mechanism of hydrolysis. Although both compound classes are expected to be abiotically stable at ambient temperature, a recent study showed that fish exposed to PFPiAs metabolized them to the corresponding PFPA¹²⁷ although the mechanism was not elucidated. Although PFPiAs can be hydrolyzed to form PFPAs, this reaction requires very high temperatures.¹²⁶ Previous work on alkyl phosphonates and phosphinates have shown they are capable of biodegradation by *E. coli* and a radical-based mechanism of P-C bond cleavage was proposed.¹²⁸ Using this mechanistic scheme, a perfluorinated radical would be an initial product of the reaction. Since perfluorinated radicals are known intermediates in many environmental reactions, this mechanism is not unreasonable.

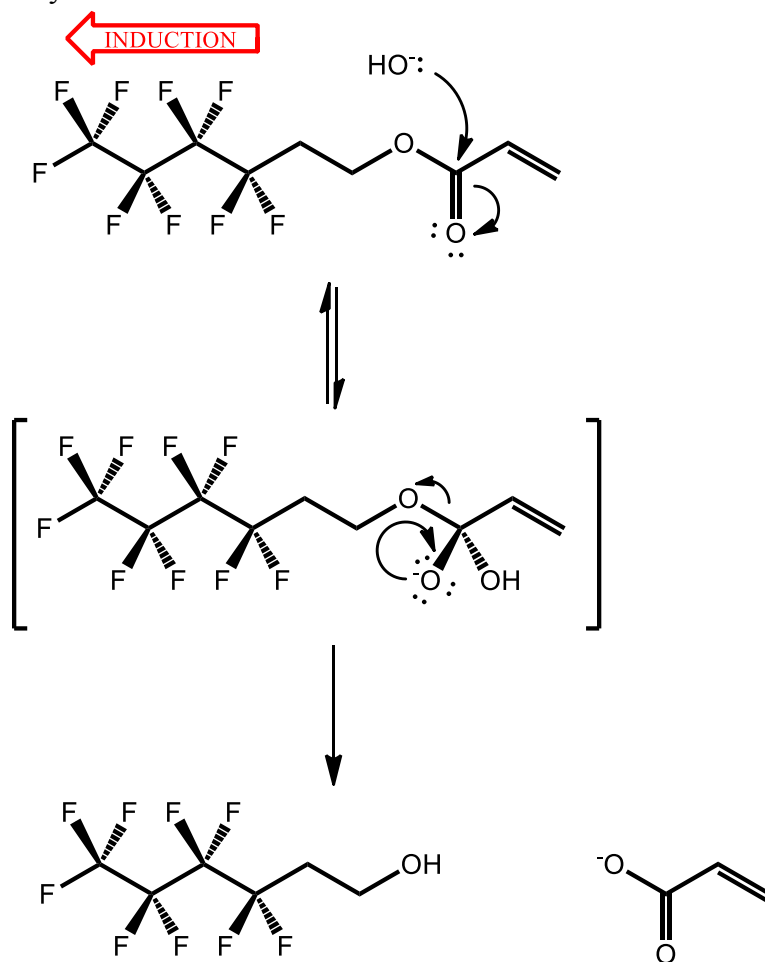
1.4.9 Fluorotelomer acrylates

From the reaction of FTOHs with acrylic acid,¹²⁹ fluorotelomer acrylates (FTAcS) can be prepared that are useful in the manufacture of fluorinated polymers. The x:2 FTAcS all have the general structure $C_xF_{2x+1}CH_2CH_2OC(O)CH=CH_2$, and therefore are unsaturated esters of FTOHs. It is the double bond that serves as the reactive site for polymerization reactions and allows the synthesis of fluorotelomer polymers which are widely used commercially. The FTAcS can be present in residual impurities in fluorotelomer polymers and can volatilize into the atmosphere where they can undergo atmospheric oxidation.¹³⁰

Since FTAcS contain an ester group, they will be susceptible to base catalyzed hydrolysis reactions. However, they must be present in water for this reaction to occur and their Henry's

Law constants are expected to be quite high. It is not known how relevant the hydrolysis of FTAcS are in the environment however the reaction would produce the corresponding FTOH and acrylic acid as products. The hydrolysis reaction is expected to be accelerated due to the fluorinated chain withdrawing electron density from the carbonyl functionality as shown in Figure 1.24. Similar to the hydrolysis of monoPAPs, the CH_2CH_2 bridge between the fluorinated chain and the reactive site will diminish the effect but not eliminate it completely.¹¹⁷

Figure 1.24: Base-catalyzed mechanism for the hydrolysis of 4:2 FTAc, producing the 4:2 FTOH and acrylate.



1.5 Fluorine-19 nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is a powerful technique to elucidate molecular structure. It requires a nucleus that is spin-active such as ^1H , ^{19}F , ^{13}C and ^{31}P . Since fluorine is isotopically pure and has a high gyromagnetic ratio,¹³¹ ^{19}F NMR offers relatively high sensitivity compared to other nuclei and the ability to be used for environmental work. Since fluorine atoms possess p orbitals, ^{19}F NMR spectra cover a large range in chemical shift which allows many signals to be resolved and spectra are usually first order.¹³¹ The basic principles behind ^{19}F spectrum interpretation are very similar to commonly analyzed nuclei such as ^1H but there are some important differences.

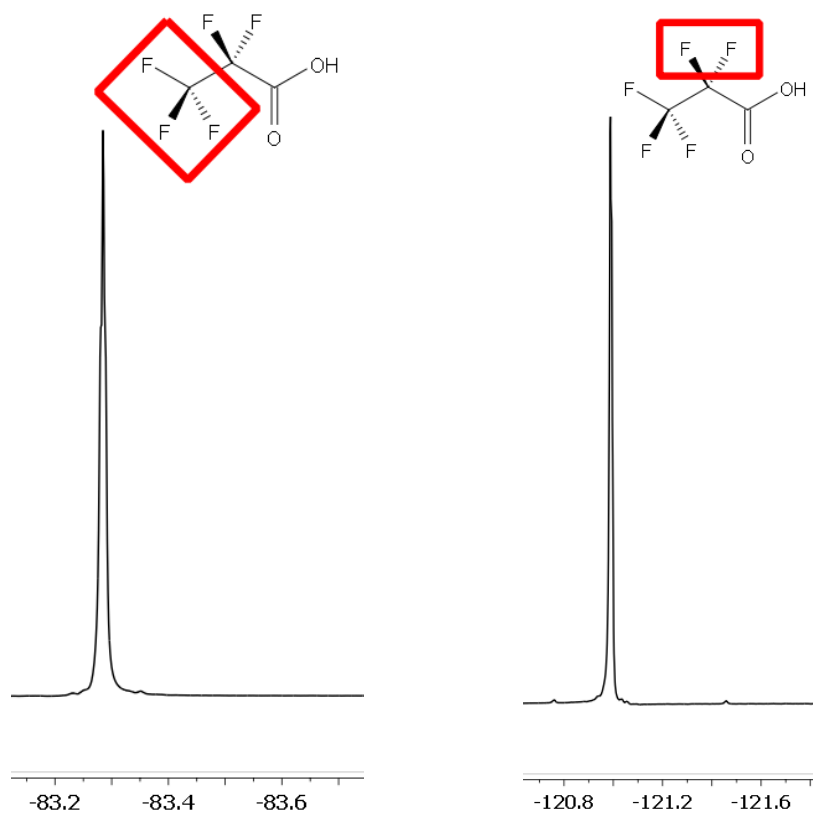
The chemical shift reference standard for ^{19}F NMR is CFCl_3 (CFC-11), arbitrarily set to 0 ppm. Since its boiling point is very close to room temperature, other fluorinated compounds are typically used as internal standards that have well defined chemical shifts of their own. One compound typically used is 4-trifluoromethoxyacetanilide (TFMeAc, $\delta = -58$ ppm).¹³²

Spin-spin (J) homonuclear coupling is seen for ^{19}F spectra however patterns are usually more complex since fluorine nuclei are capable of coupling over a longer range of bonds, up to and including ^6J depending on the compound.¹³³ In linear perfluorinated chains, ^4J coupling is usually the strongest whereas ^3J is usually not seen at all.¹³⁴

As an example, perfluoropropanoic acid (PFPrA) has a ^{19}F NMR spectrum consisting of two singlets, one for each equivalent fluorinated group (Figure 1.25). The ^3J coupling between the two groups is extremely weak and not visible in the spectrum, thus giving two singlets in the

spectrum. This contrasts with the ^1H NMR spectrum of propanoic acid which consists of a triplet and a quartet as expected from ^3J coupling.

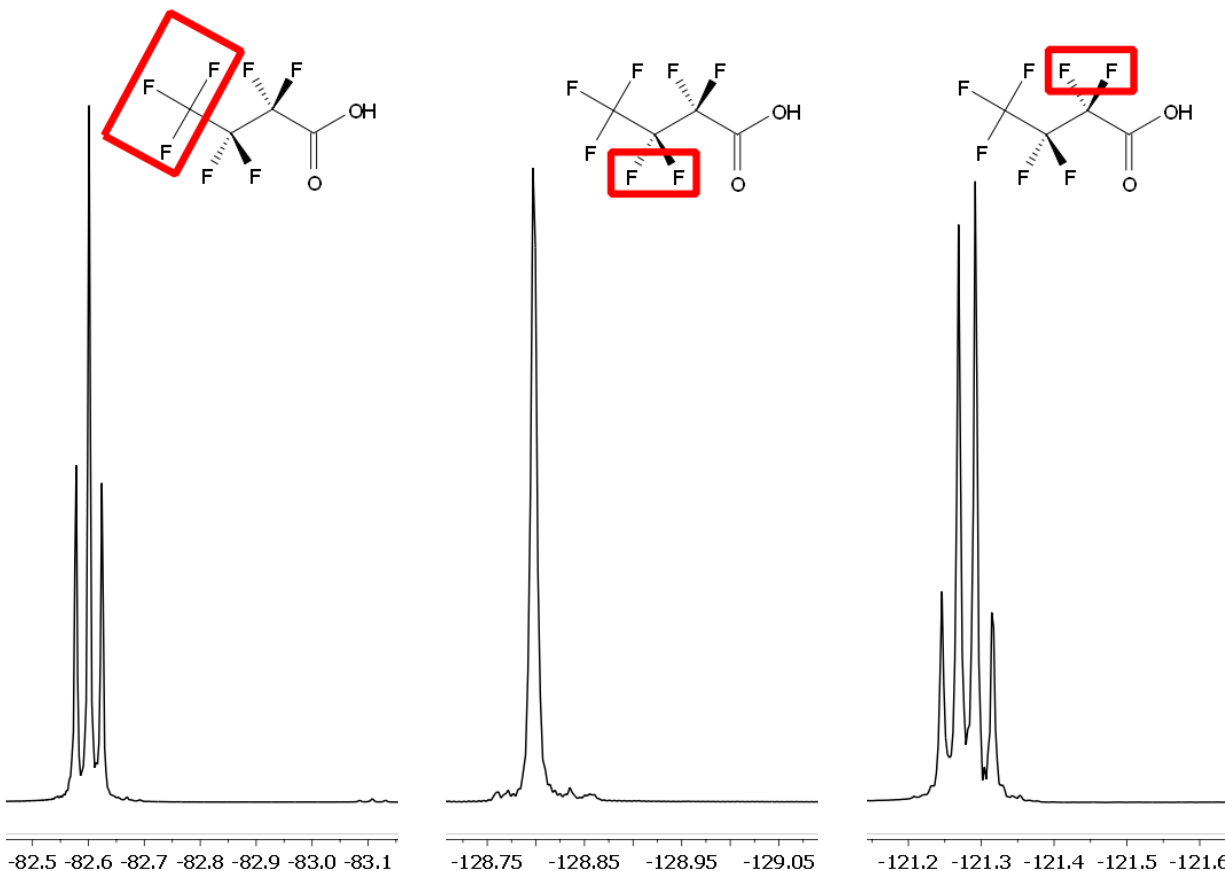
Figure 1.25: ^{19}F NMR spectrum of perfluoropropanoic acid showing two singlets.



Adding one more CF_2 group gives perfluorobutanoic acid (PFBA) which gives a slightly more complicated spectrum consisting of a triplet and a quartet ($^4\text{J} = 8.7 \text{ Hz}$) and a singlet (Figure 1.26). The observed peak splitting is due to ^4J coupling between the terminal CF_3 group and the terminal CF_2 group. The interior CF_2 group does not show any splitting since it is incapable of any ^4J coupling. Again this can be contrasted with the ^1H NMR spectrum of butanoic acid which gives the expected pattern of two triplets and a sextet. Once the fluorinated

chain lengthens further the spectrum becomes much harder to interpret. All the interior CF_2 units have very similar chemical shifts and despite ^{19}F NMR having a wide chemical shift range, many peaks in the fluorinated chain will overlap even on a high field magnet.

Figure 1.26: ^{19}F NMR spectrum of perfluorobutanoic acid showing exclusively ^4J coupling therein.



The perfluorinated ketone perfluoro-2-methyl-3-pentanone (PFMP) is marketed by 3M as Novec 1230, a new firefighting fluid that is more environmentally benign than previously used compounds such as Halons.¹³⁵ Its ^{19}F NMR spectrum provides an excellent example to illustrate many salient features of fluorine chemical shifts and long range J coupling, summarized in Figures 1.27 and 1.28. Overall, the spectrum is first order due to the relatively large chemical

shift spacing between peaks compared to their coupling constants. The terminal CF_3 group has a chemical shift of -82 ppm and is a doublet due to ^5J coupling (6 Hz) with the tertiary fluorine atom. The CF_2 group has a chemical shift of -118.2 ppm and is a doublet of septets. The doublet (27 Hz) is a result of ^4J coupling with the tertiary fluorine atom and the septet (3 Hz) from long range ^5J coupling with the six equivalent perfluoroisopropyl fluorines. No ^3J coupling was observed between the vicinal CF_2 and CF_3 groups that would be expected in a ^1H NMR spectrum. The two equivalent CF_3 groups on the perfluoroisopropyl group have a chemical shift of -74.3 ppm and shows up as a first order multiplet of 5 peaks. Deconvoluting this multiplet using previously determined coupling constants shows it is a doublet of triplets, composed of ^3J coupling with the tertiary fluorine (6 Hz) and long range ^5J coupling to the CF_2 group (3 Hz). Finally, the tertiary fluorine atom has a chemical shift of -184.1 ppm and is a first order multiplet with a large number of peaks. This multiplet may appear to be too complex to analyze but prior determination of coupling constants from simpler multiplets in the spectrum allows this peak to be deconvoluted with relative simplicity. The tertiary fluorine atom gives rise to a triplet of quartets of septets. The ^4J coupling to the CF_2 group is 27 Hz as described earlier. The remaining ^3J and ^5J couplings are both 6 Hz.

Figure 1.27: Coupling constants within perfluoro-2-methyl-3-pentanone (PFMP).

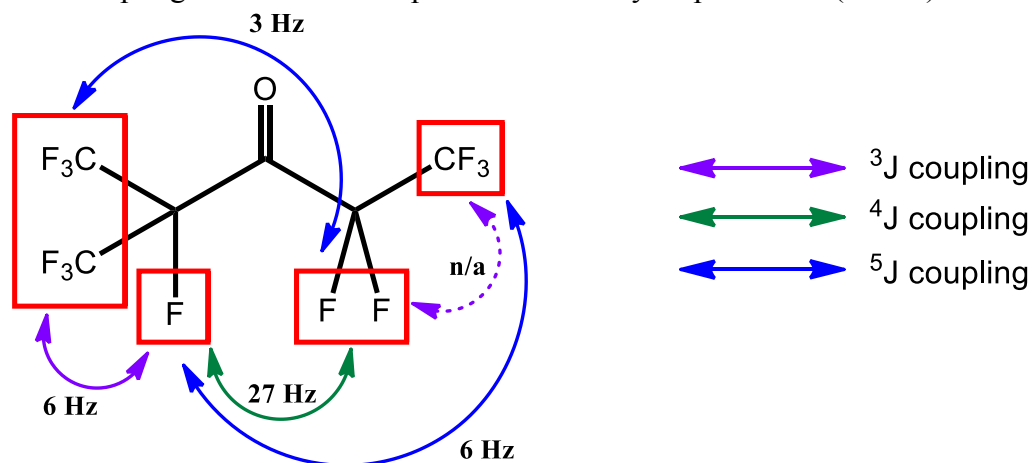
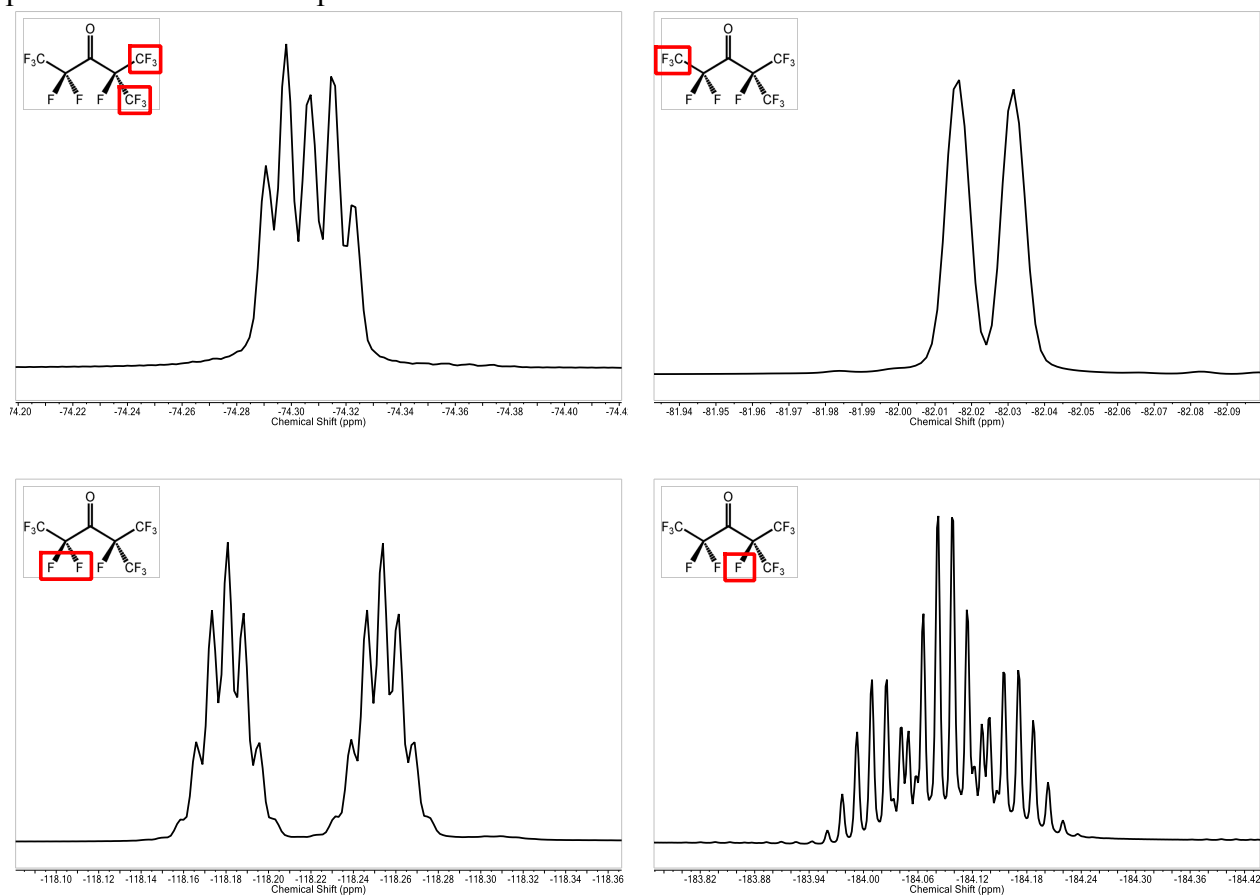
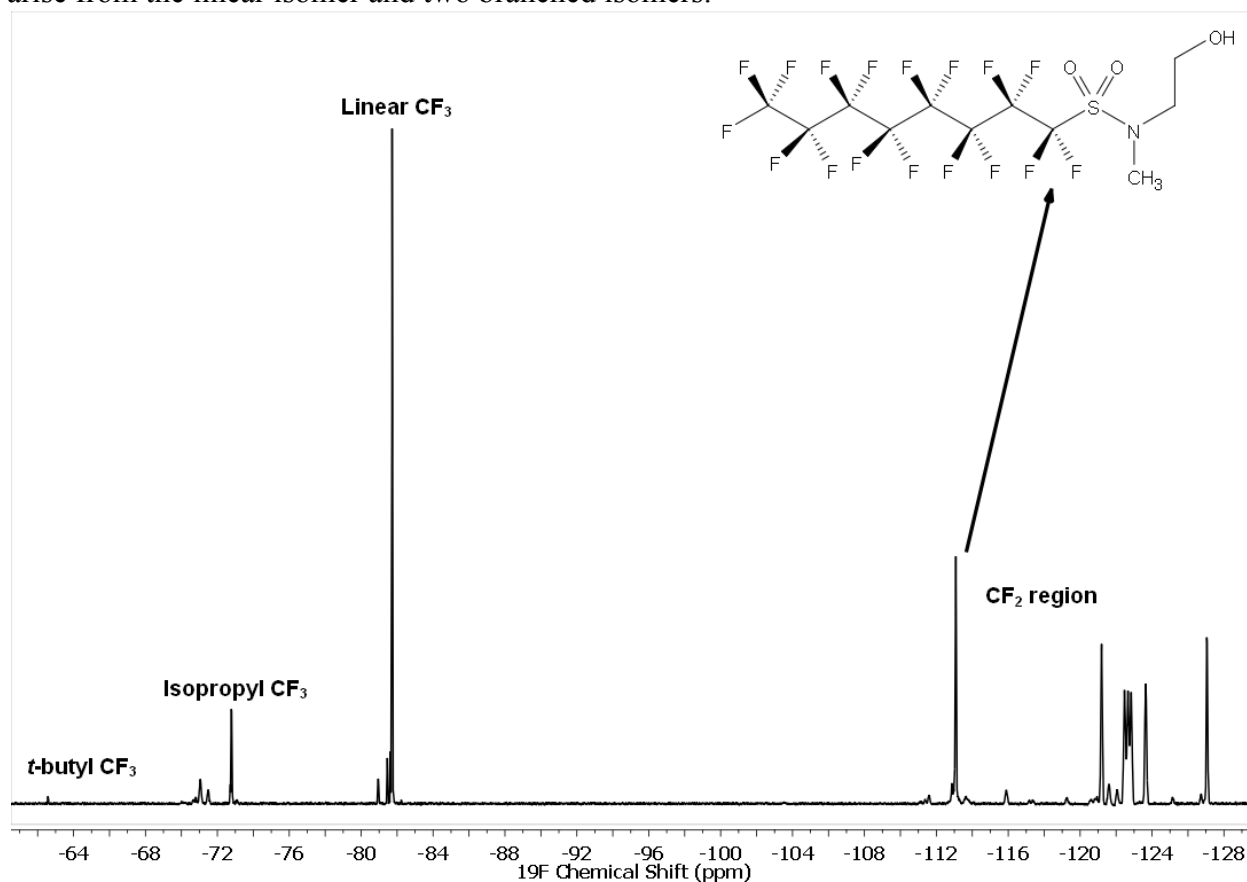


Figure 1.28: ¹⁹F NMR of perfluoro-2-methyl-3-pentanone (PFMP) with expansions on each peak to show each multiplet in detail.



Determining if a fluorinated compound was synthesized by electrochemical fluorination (ECF) can be easily achieved using ^{19}F NMR. The presence of constitutional isomers in measurable proportions gives peaks at predictable chemical shifts depending on the nature of the CF_3 group(s).¹³⁶ Notably, the CF_3 group for the isopropyl isomer gives a moderately strong signal at approximately -73 ppm and provides empirical support for an ECF material (an example of EtFOSE is given in Figure 1.29). The CF_3 peak corresponding to the linear isomer should give a peak area between 70-80% of the total CF_3 signal¹³⁶ although the exact value will vary depending on the exact material and relaxation delay time used in the NMR experiment.

Figure 1.29: ^{19}F NMR spectrum of EtFOSE synthesized by ECF showing the CF_3 signals that arise from the linear isomer and two branched isomers.



1.6 Goals and Hypotheses

Throughout this dissertation, four projects will be described that each investigate the mechanistic pathways by which PFCAs can be formed under environmental conditions. Both the compounds described and the pathways they undergo cover a wide range of chemical architecture.

In chapter 2, a series of experiments and computational work was performed on perfluoro-2-methyl-3-pentanone (PFMP), produced by 3M as a new fire fighting fluid. This compound represented an improvement over Halons which deplete the ozone layer and are long lived greenhouse gases. Although PFMP was already known to degrade by direct photolysis in approximately one week (thereby greatly reducing its potential to contribute to climate change), its degradation pathways had not been fully elucidated. We hypothesized that a perfluoroacyl radical would be produced as an initial product of photolysis that could undergo further atmospheric reactions to produce PFPrA, one of the PFCAs detected in North American precipitation. This was tested using the smog chamber setup at the Ford Motor Company combined with offline sampling. Early work using PFMP combined with offline sampling using aqueous base consistently showed extremely high levels of contamination from PFPrA. Our hypothesis was that PFMP was hydrolyzing by a mechanism analogous to the Haloform reaction, and this was tested using ^{19}F NMR.

Chapters 3 and 4 both obtained their origins from an idea by the principal investigator ten years ago. In studying the electrochemical fluorination reactions that produced perfluorooctane sulfonyl fluoride (POSF), it was known that perfluorooctanoyl fluoride (PFOAF) could be

produced as an unintentional byproduct. We hypothesized that when POSF was reacted with amines to produce sulfonamide compounds, the PFOAF impurity could also react and produce analogous polyfluorinated amide (PFAM) compounds as residuals. The PFAMs could then hydrolyze to PFOA once released to the environment and serve as an unexplored class of PFCA precursor. In chapter 3, model PFAM compounds were synthesized and used as analytical standards. Several historical ECF materials were analyzed by GC-MS to quantify PFAM content and simple calculations were performed to illustrate their potential as historical sources of PFOA to human blood. In chapter 4, we used the smog chamber at the Ford Motor Company to study the atmospheric oxidation pathways of one model PFAM compound. Our objective was to determine if PFAMs could degrade to PFCAs abiotically by reaction with chlorine atoms or hydroxyl radicals. Offline samples were also taken for analysis by GC and LC to find stable intermediates and propose a mechanism for this process.

In chapter 5, the biological hydrolysis of polyfluoroalkyl phosphate monoesters (monoPAPs) using an alkaline phosphatase enzyme were studied. Although this reaction was known to occur by previous studies that dosed these compounds in rats, the exact location in the body of this reaction had not been ascertained. In addition, the rats dosed with monoPAPs never had detectable levels of monoPAP at any sampling timepoint, suggesting they were hydrolyzed very quickly in the body. We hypothesized that the electron withdrawing fluorinated chain enhanced the enzymatic rates of hydrolysis of monoPAPs. We tested this by measuring Michaelis-Menten kinetic parameters for the reaction of three monoPAPs and comparing them to the hydrolysis rate of hexyl phosphate. Simple calculations were also performed to estimate the time needed to hydrolyze a dose of monoPAP in a mammalian small intestine.

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CHAPTER TWO

Atmospheric Degradation of Perfluoro-2-methyl-3-pentanone: Photolysis, Hydrolysis and Hydration

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2.1 Abstract

Perfluorinated carboxylic acids are widely distributed in the environment, including in remote regions but their sources are not well understood. Perfluoropropionic acid (PFPrA, $\text{CF}_3\text{CF}_2\text{C}(\text{O})\text{OH}$) has been observed in rainwater but the observed amounts can not be explained by currently known degradation pathways. Smog chamber studies were performed to assess the potential of photolysis of perfluoro-2-methyl-3-pentanone (PFMP, $\text{CF}_3\text{CF}_2\text{C}(\text{O})\text{CF}(\text{CF}_3)_2$), a commonly used fire fighting fluid, to contribute to the observed PFPrA loadings. The photolysis of PFMP gives $\text{CF}_3\text{CF}_2\text{C}\cdot(\text{O})$ and $\cdot\text{CF}(\text{CF}_3)_2$ radicals. A small (0.6%) but discernable yield of PFPrA was observed in smog chamber experiments by liquid chromatography mass spectrometry offline chamber samples. The Tropospheric Ultraviolet-Visible (TUV) model was used to estimate an atmospheric lifetime of PFMP with respect to photolysis of 4 – 14 days depending on latitude and time of year. PFMP can undergo hydrolysis to produce PFPrA and $\text{CF}_3\text{CFHCF}_3$ (HFC-227ea) in a manner analogous to the haloform reaction. The rate of hydrolysis was measured using ^{19}F NMR at two different pHs and was too slow to be of importance in the atmosphere. Hydration of PFMP to give a geminal diol was investigated computationally using density functional theory. It was determined that hydration is not an important environmental fate of PFMP. The atmospheric fate of PFMP seems to be dominated by direct photolysis which, under low NO_x conditions, gives PFPrA in a small yield. PFMP degradation contributes to, but does not appear to be the major source of, PFPrA observed in rain water.

2.2 Introduction

Perfluorinated carboxylic acids (PFCAs) are ubiquitous in biotic¹ and abiotic environments.^{2,3} Longer-chain ($>C_7$) PFCAs are bioaccumulative⁴ and have attracted substantial research interest. Precipitation measurements by Scott et al.³ have demonstrated that short-chain PFCAs, notably trifluoroacetic acid (TFA) and perfluoropropionic acid (PFPrA), dominate the PFCA profile. While these smaller compounds are not expected to bioaccumulate and are not believed to represent a threat to ecosystems, their source is unclear and requires study. Thermolysis of fluoropolymers has been suggested as a potential source of TFA observed in rainwater.⁵ Other, likely smaller, sources of TFA include the atmospheric oxidation of hydrofluorocarbons^{6,7} and polyfluorinated compounds.^{8,9} Small yields of PFPrA have been proposed from thermolysis of fluoropolymers and atmospheric oxidation of fluorotelomer alcohols^{5,8,9} but do not explain the levels of PFPrA observed in precipitation.

Perfluoro-2-methyl-3-pentanone (PFMP) is a fire protection fluid, marketed as Novec 1230™ by 3M. It is a replacement for Halons, which deplete stratospheric ozone. The atmospheric lifetime of PFMP from previous work seems to be determined by photolysis and is approximately 1 week.^{10,11} PFMP does not contribute to stratospheric ozone depletion and has a negligible global warming potential.^{10,11} The major photolysis products are $CF_3C(O)F$ and COF_2 .¹⁰ The atmospheric fate of $CF_3C(O)F$ is hydrolysis to yield TFA. It is possible that chemistry in remote environments following the photolysis of PFMP would give small yields of PFPrA or isoperfluorobutanoic acid (*i*-PFBA) via reactions of the corresponding perfluoroacyl radicals with HO_2 radicals.^{12,13}

In addition to photolysis, hydration or abiotic hydrolysis may be a significant sink of PFMP in the environment. In the hydration reaction, PFMP would react either reversibly or irreversibly with water to form a geminal diol which would shut down the photolysis pathway. Ketones are typically unreactive towards hydrolysis because the leaving group after nucleophilic attack is an aliphatic carbanion. Carbanions are highly basic and are not good leaving groups. However, hydrolysis of PFMP gives a perfluorinated carbanion which, because the fluorine atoms stabilize the departing carbanion through hyperconjugation, is a much better leaving group. This effect is the basis of the well known haloform reaction, one of the oldest organic reactions known.¹⁴

Applying the haloform reaction mechanism to hydrolysis of PFMP should give PFPrA and $\text{CF}_3\text{CFHCF}_3$ (HFC-227ea). HFC-227ea is a long-lived greenhouse gas and its formation would be problematic. A detailed understanding of the rate and products of PFMP hydrolysis under environmentally relevant conditions is clearly desirable.

The present work had three goals: (i) to confirm the rate of atmospheric photolysis of PFMP and to investigate the possible formation of PFPrA, (ii) to determine whether hydrolysis of PFMP is of significance in the environment, and (iii) to investigate whether hydration is an environmental fate of PFMP.

2.3 Experimental Details

2.3.1 Measurements of UV spectra and calculations of photolysis rates

UV spectra of PFMP in the region 200 – 400 nm were recorded in a 6 cm cell using a Perkin Elmer UV/Vis spectrometer with a resolution of 1 nm, a slit width of 0.25 nm and a scan speed of 15 nm min⁻¹. Photolysis rates were estimated using the Tropospheric Ultraviolet-Visible (TUV 4.2) package.¹⁵ All rates were calculated for 0.5 km above the surface. The quantum yield was assumed to be 0.043, as measured by D'Anna et al.¹¹

2.3.2 Smog chamber methods

Experiments were performed in a 140 L Pyrex reactor interfaced to a Mattson Sirius 100 FTIR spectrometer. The reactor was surrounded by 10 fluorescent blacklamps (GE F15T8-BL, maximum emission 360 nm) and 12 sunlamps (GE-FS40, maximum emission 310 nm), which were used to photolyze PFMP. The spectral overlap of the emission of blacklamps and sunlamps and the absorption by PFMP has been discussed by Taniguichi et al.¹⁰

All reagents were obtained from commercial sources. Concentrations of reactants and products were monitored by FTIR spectroscopy. IR spectra were derived from 32 coadded interferograms with a spectral resolution of 0.25 cm⁻¹ and an analytical path length of 27 m. Photolysis experiments were performed using mixtures containing 0.49-0.62 Torr of PFMP in 50 Torr of oxygen. We chose a diluent pressure of 50 Torr for the photolysis experiments as Taniguichi et al.¹⁰ have established that the photolysis proceeds more rapidly at lower total pressures. After photolysis the reaction mixtures were pressurized to 750 Torr with air and sampled as described below.

The experimental conditions employed in the smog chamber experiments (296 K, 50 Torr total pressure of O₂ diluent, in the absence of water vapor, NO_x, and other important atmospheric constituents) are not the same as the range of conditions in the real atmosphere. However, the chemical processes studied in the chamber are very similar to those which will occur in the real atmosphere. Photolysis of PFMP in the chamber will occur via the same mechanism, the fate of the radicals formed (decomposition and addition of O₂) will be similar, and subsequent reactions of the peroxy radicals are similar to those in the real atmosphere. Hence, the results from such smog chamber experiments shed important light on the behavior of PFMP in the real atmosphere.

2.3.3 Offline sample collection and analysis

Offline samples were collected by bubbling approximately 5 L of chamber air through 10 mL sodium carbonate solution (pH = 11) after dilution of the chamber contents with air (P_T = 750 Torr). Triplicate samples were collected following 45 minutes of irradiation. Sodium carbonate solutions were acidified to pH 4 using HCl and analyzed using a Waters 616 LC pump and 600 controller with detection by a Micromass Quattro Micro MS/MS detector. Analytes were separated on a Genesis C8 column (2.1 mm × 50 mm × 4 μm) using a 5 min isocratic run of 40% methanol and 60% water, both containing 10 mM ammonium acetate. Triplicate 10 μL injections were made using a Waters 717 autosampler. PFCAs were analyzed with an electrospray source using a cone voltage of 17 V and collision energy of 9 eV and the following transitions were monitored: PFBA 213 > 169, PFPrA 163 > 119 and TFA 113 > 69. Analytes were quantified using external calibration.

2.3.4 Hydrolysis Kinetic Experiments

To quantify the rate of PFMP hydrolysis and identify the final products of hydrolysis, ^{19}F NMR was used. The rates of hydrolysis were measured at pH values of 5.6 and 8.5 to simulate the upper and lower boundaries of realistic environmental pH conditions. To achieve this, either 50 mM potassium hydrogen phthalate (pH 5.6) or 50 mM sodium borate (pH 8.5) buffer was used. A Varian 400 spectrometer equipped with an ATB8123-400 autoswitchable probe tuned to ^{19}F (376.14 MHz) was used. Reaction solutions were composed of 600 μL buffer solution and 200 μL D_2O in a 5 mm NMR tube. Immediately prior to sample insertion, 20 μL PFMP was added to the NMR tube followed by inversion. Reaction kinetics were followed by acquiring NMR spectra using a pre-acquisition delay program such that one complete spectrum was obtained every 20-30 minutes. Each spectrum consisted of 12 scans with an acquisition time of 1 second. To ensure quantitative results, a standard of PFPrA under the same reaction conditions as PFMP hydrolysis was subject to a pulse inversion-recovery T_1 relaxation experiment to determine a suitable relaxation delay time for PFMP. In this case, a delay time of 20 s for PFMP was chosen. After acquisition, data analysis was performed using the VnmrJ software (Agilent Technologies) as it possesses a built-in kinetic analysis module. Each arrayed spectrum was Fourier transformed with a line broadening apodization of 6 Hz to improve its signal to noise ratio. Kinetic data were obtained by fitting an exponential growth or decay function to the fluorinated signals in the NMR spectra (see Appendix A, Figure S5). All hydrolysis experiments were performed at 25°C.

2.3.5 Computational Methods

Calculations to determine the significance of PFMP hydration were performed using the *Gaussian 03* program¹⁶ with the WebMO interface. All computations were performed using Density Functional Theory (DFT) with B3LYP functionals using the 6-311++G(d,p) basis set. Computations were carried out for both the gas phase and the aqueous phase using a polarizable continuum solvent model (PCM).¹⁷ Equilibrium constants for hydration were computed using the relative method of Gomez-Bombarelli et al.¹⁸ and using a training set calibration of fluoroacetone, trifluoroacetone and hexafluoroacetone (see Appendix A for details).

2.3.6 Reagents

All chemicals were used as received. PFMP was purchased from Synquest Laboratories (Alachua, FL). Disodium tetraborate and potassium hydrogen phthalate were purchased from BDH (Toronto, ON). Trifluoroacetic acid and heptafluoropropionic acid (PFPrA) were purchased from Sigma-Aldrich (Oakville, ON).

2.4 Results and Discussion

2.4.1 Photolysis kinetics

Photolysis lifetimes of PFMP have been determined experimentally in two previous studies, yielding lifetimes of approximately 1-2 weeks¹⁰ and 1 week.¹¹ Using the flux conditions and quantum yield (0.043) previously described,¹¹ and the UV spectrum measured in this study (see SI), photolysis rates for PFMP were estimated. The photolysis rates, presented in Table 2.1, agree to within a factor of two with those reported in previous studies as well as previous measurements of the UV spectrum.^{10,11} The 24-hour averaged rate constants for photolysis of

PFMP for different latitudes are given in the SI. Annual averaged photolytic rate constants (J) ranged from 3.1×10^{-6} to $8.2 \times 10^{-7} \text{ s}^{-1}$ corresponding to lifetimes of 4 – 14 days depending on latitude and time of year.

Table 2.1 Kinetic data for PFMP degradation via photolysis and hydrolysis (N=2) at two different pH values. For complete photolysis data, refer to Appendix A.

* Averaged 24 hour rate constant, † Pseudo-first-order rate constant

Mechanism	Conditions	Rate constant $k \text{ (s}^{-1}\text{)}$	Lifetime τ (hours)
Photolysis	45°N	$3.5 \times 10^{-6} *$	79.4
June 21			
Photolysis	45°N	$5.9 \times 10^{-7} *$	471
December 21			
Photolysis	45°N	$2.1 \times 10^{-6} *$	132
March 21/Sept 21			
Hydrolysis	pH 5.6	$1.9 \times 10^{-4} \pm 1 \times 10^{-5} \dagger$	1.5 ± 0.1
Hydrolysis	pH 8.5	$3.1 \times 10^{-4} \pm 3 \times 10^{-5} \dagger$	0.9 ± 0.1

2.4.2 Photolytic production of PFCAs under low NO_x conditions

Offline samples were taken to determine if photolytic degradation of PFMP could yield PFCAs. The formation of PFCAs in the chamber is only expected under low-NO_x conditions in the presence of HO₂ radicals. Material was not added specifically for the purpose of forming HO₂ radicals, but it is likely that HO₂ radicals are present in small quantities in all chamber experiments because of hydrocarbon residue on the walls of the chamber (the chamber has been used at Ford for many years to study hydrocarbon oxidation mechanisms). Large initial concentrations of PFMP (520 mTorr) were used in the smog chamber to facilitate detection of small yields of PFCAs.

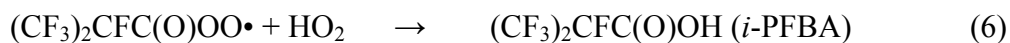
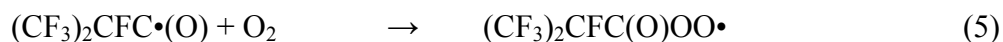
Photolysis of PFMP can generate two different perfluoroacyl radicals:



Perfluoroacyl radicals either decompose via elimination of CO or add O₂ to give perfluoroacyl peroxy radicals. In low-NO_x environments, perfluoroacyl peroxy radicals can react with HO₂ to give PFCAs:¹²



The perfluoroacyl radicals derived from the photolysis of PFMP can react to give *i*-PFBA or PFPrA as follows:



PFPrA was observed in offline samples taken after 45 minutes of irradiation, at a concentration of 0.061 mTorr. *i*-PFBA was not detected in any of the samples.

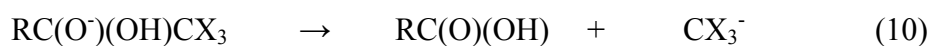
The high concentrations of PFMP used in the experiments saturated the FTIR signal and a direct determination of the amount of PFMP photolyzed was not possible. The amount of PFMP lost via photolysis was estimated from the photolysis half-life (determined to be 26 hours by the observed formation of $\text{CF}_3\text{C}(\text{O})\text{F}$ as discussed previously)¹⁰ in the chamber conditions. We estimate that 10.4 mTorr of PFMP was photolyzed after 45 minutes and hence the yield of PFPrA is 0.6%. The low PFPrA yield observed in this experiment probably reflects the low level of HO_2 radicals available in the system. Sulbaek Andersen et al.¹⁹ reported that the yield of PFPrA from $\text{CF}_3\text{CF}_2\text{C}\cdot(\text{O})$ via reactions (7) and (8) was $24 \pm 4 \%$. Similarly, the yield of *n*-PFBA in reactions analogous to (5) and (6) was shown to be $10 \pm 2\%$.¹² We expect the yield of *i*-PFBA following formation of $(\text{CF}_3)_2\text{CFC}\cdot(\text{O})$ radicals in an excess of HO_2 radicals to be similar to that reported for *n*-PFBA. The low yield of PFPrA observed in the present experiments suggests either that the yield of $\text{CF}_3\text{CF}_2\text{C}\cdot(\text{O})$ radicals in the photolysis of PFMP is low, or that the concentration of HO_2 radicals in the channel is low and conversion of $\text{CF}_3\text{CF}_2\text{C}\cdot(\text{O})$ radicals into PFPrA is inefficient. The absence of any discernable formation of *i*-PFBA suggests the latter explanation is more probable. Figure 2.1 illustrates some pathways leading to PFCAs following photolysis of PFMP in the absence of NO_x . Note, as indicated in Figure 2.1, decomposition via elimination of CO is a significant fate of $\text{CF}_3\text{CF}_2\text{C}\cdot(\text{O})$ radicals.¹³

donate electron density from their lone pair orbitals into the singly occupied p orbital on the radical centre, resulting in stabilization. Since the experimental results suggest this is happening, it is proposed that the stabilities of the corresponding perfluoroacyl radicals must allow this observed regioselectivity to occur.

2.4.3 Hydrolysis Kinetics

The hydrolysis reaction of PFMP can proceed by the well known haloform reaction mechanism in which a ketone with a suitable alkyl leaving group reacts with water to form a carboxylate and an alkane.

In a typical haloform reaction, a methyl ketone is tri-iodinated followed by treatment with base to produce a carboxylic acid and iodoform which precipitates as a yellow solid. This reaction is the classic qualitative test for a methyl ketone. The following steps mechanistically describe the haloform reaction:

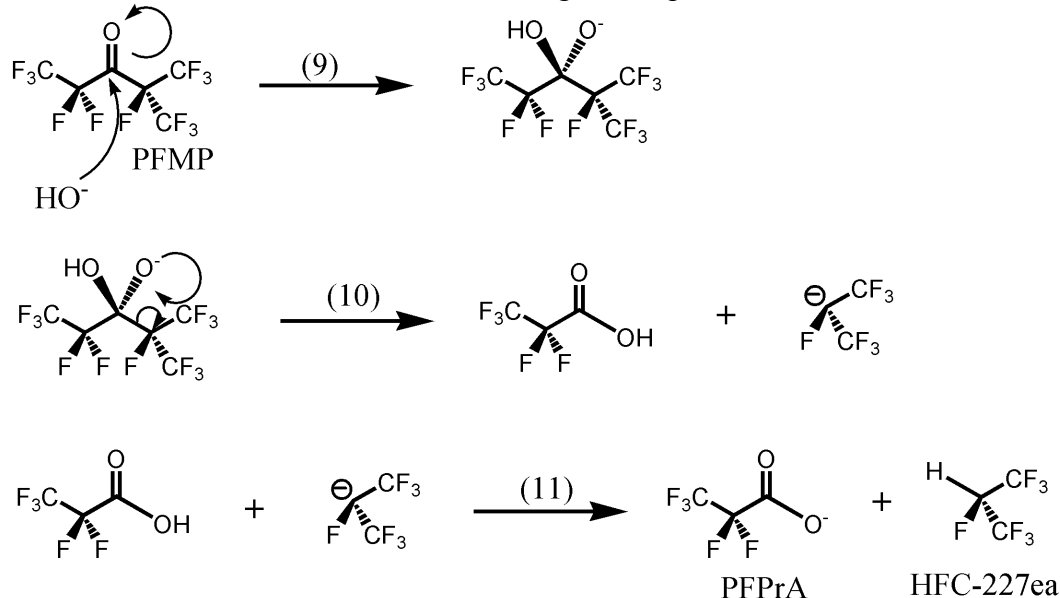


Where X = Cl/Br/I

The final step in the haloform reaction is a rapid and exothermic proton transfer from the carboxylic acid to the carbanion which makes the whole process irreversible. The overall mechanism of the reaction is B_{AC}2 which consists of separate addition and elimination steps via a tetrahedral intermediate. The rate determining step is reaction (9). The final two products

expected from PFMP hydrolysis are PFPrA and HFC-227ea. The mechanism for hydrolysis of PFMP is shown in Figure 2.2.

Figure 2.2. Hydrolysis mechanism of PFMP to produce PFPrA and HFC-227ea under mildly basic conditions. Reaction numbers in the text are given in parentheses.



The hydrolysis of PFMP and the detection of both products has been reported by Saloutina et al.²⁰ however this study was performed at pH values much higher than those relevant for the environment. The objective of the present study was to investigate whether PFMP could undergo hydrolysis at pH values more typical of those found in the environment. The two pH values chosen were 5.6 and 8.5 because pH 5.6 is typical of atmospheric water.²¹ A pH of 8.5 was also chosen to represent the upper environmental limit where hydrolysis would likely be the fastest since the haloform reaction is base catalyzed.

To measure the kinetics of PFMP degradation, an analytical method to quantify PFMP is required. Liquid chromatography is not suitable to analyze PFMP because authentic standards would rapidly degrade in any protic solvent. It was confirmed in a separate study (data not shown) that PFMP reacts rapidly with methanol to produce HFC-227ea and the methyl ester of

PFPrA. PFMP is certainly volatile enough to be analyzed by gas chromatography-mass spectrometry. However aqueous samples would need to be extracted into a suitable GC solvent prior to injection. PFMP was found to have very low solubilities in almost every solvent tested. In addition, such a procedure would require a separate extraction for every time point, greatly increasing the amount of material needed. We decided that ^{19}F NMR would offer the best capability for measuring the kinetics of PFMP *in situ*. The hydrolysis reaction was performed in an NMR tube and scans of the reaction mixture were taken at various time intervals for subsequent analysis. ^{19}F NMR offers acceptable signal to noise ratios and since neither water nor the buffers used contain fluorine atoms, a purely deuterated solvent does not need to be used. For NMR data to be considered quantitative to 99+% accuracy, it is necessary that the relaxation delay between scans be five times that of the longest spin-lattice relaxation time (T_1) in the compound of interest. Since T_1 values can depend on the solvent used, a standard of PFPrA in the aqueous buffer of interest was used as a surrogate for the T_1 of PFMP. It was found that the longest observed T_1 (PFPrA) = 4.0 s, thus making a suitable relaxation delay for PFMP to be 20 s.

The current Varian NMR processing software, VnmrJ, is capable of analyzing kinetic data using a non-linear fitting algorithm, provided the fit is exponential. Since the concentration of both OH^- and water are constant in each experiment, pseudo-first-order conditions with respect to PFMP were achieved and an exponential decrease in [PFMP] is expected due to hydrolysis. After fitting the data points, the software provides the $1/e$ lifetime of the compound (τ), which is simply the reciprocal of the pseudo first order rate constant, k_{obs} .

The ^{19}F NMR spectrum of PFMP consists of four peaks, each a multiplet due to the long range J coupling observed for fluorine atoms. The spectra of PFPrA and HFC-227ea combined resemble that of PFMP but the chemical shifts are distinct and the coupling patterns are very different. Thus, it is straightforward to distinguish PFMP from its degradation products. For examples of ^{19}F NMR spectra of both PFMP and its photolysis products, please see the SI.

In summary, we observed the $1/e$ lifetime of PFMP hydrolysis to vary depending on the pH of the buffer used. Although the rate was slightly faster at higher pH as shown in Table 2.1, the hydrolysis reaction can not be concluded as base catalyzed from these results since the rate constants are within the same order of magnitude despite being 3 pH units apart. Both PFPrA and HFC-227ea were positively identified as the sole products of the hydrolysis reaction. PFPrA was confirmed by comparison to an authentic standard. HFC-227ea was confirmed by comparison to a literature spectrum.²²

Saloutina et al.²⁰ did not report any kinetics in their study on the hydrolysis of PFMP however it is not surprising they observed high yields in PFPrA and HFC-227ea given the strongly basic conditions of their reaction solutions. A further study by the same group²³ elaborated on the specificity of the C-C bond cleavage step to exclusively produce the more stable carbanion leaving group. In the case of perfluorinated compounds, the more substituted anion is more stable because of increased hyperconjugation from the anion lone pair to the vicinal antibonding C-F orbitals. Sykes et al.²⁴ confirmed the regioselectivity of the haloform reaction for a number of polyfluorinated ketones. Hence, there is precedent for the haloform

reaction to occur regioselectively in fluorinated ketones to produce the less substituted carboxylate and the more substituted hydrofluoroalkane.

2.4.4 Hydration of PFMP

Aldehydes and ketones can react with water to produce a geminal diol by the following reaction scheme.



The reaction is catalyzed by both acids and bases and is usually a reversible equilibrium reaction. For most aldehydes and ketones, the equilibrium constant, K_{hyd} , usually strongly favours the carbonyl compound due to the high strength of the C=O bond. Exceptionally, formaldehyde (HC(O)H) exists in aqueous solution purely as the gem-diol (HC(OH)(OH)H) due to its high K_{hyd} value ($\log K_{\text{hyd}} = 3.36$).²⁵ The vast majority of ketones are quite unreactive to hydration (acetone has $\log K_{\text{hyd}} = -2.85$ ²⁵) and the geminal diol form is usually neglected in reaction schemes. Other exceptions can be halogenated ketones; trichloroacetaldehyde has a $\log K_{\text{hyd}} = 4.45$ and hexafluoroacetone (HFA) has $\log K_{\text{hyd}} = 6.08$.²⁵ Effectively, there is quantitative conversion of the carbonyl to the hydrate in aqueous solution and the reverse reaction back to the carbonyl does not occur appreciably at room temperature. For example, HFA is provided commercially as the geminal diol derivative.

It might be reasonable to assume that the electron withdrawing groups of HFA impart a strong partial positive charge at the fluorinated carbonyl carbon, resulting in enhanced electrophilicity and hence, a greater degree of hydration. However, Linderman et al.²⁶ used

Hartree-Fock computational methods and found most of the positive electric potential in HFA is found on the CF_3 carbons and not the carbonyl carbon. Instead, they propose the lower energy level of the LUMO of fluorinated ketones compared to their hydrogenated analogs is the major cause of the enhanced reactivity towards water. Since PFMP is perfluorinated like HFA, it would be a reasonable assumption that PFMP could rapidly and irreversibly form a geminal diol in the environment. The PFMP hydrate would not absorb actinic radiation due to the absence of the $\text{C}=\text{O}$ chromophore. In addition, formation of the diol would increase water solubility and decrease vapour pressure, resulting in a greater rate of wet deposition and enhancing the potential role of hydrolysis. Thus, it is important to determine whether PFMP could form a stable hydrate in the same manner as HFA.

The hydration reaction of PFMP was investigated in our laboratory and no evidence of such a hydrated species was observed (data not shown). This was puzzling as other fluorinated ketones are known to hydrate readily²⁵. To provide further insight, computational methods were used to estimate K_{hyd} for PFMP and compare it to other fluorinated carbonyls using the methods of Gomez-Bombarelli et al.¹⁸ The effects of including an aqueous PCM solvent model were also studied although Guthrie et al.²⁷ previously noted difficulties of applying the PCM model to halogenated compounds. For full details on the computational work, please see Appendix A.

Depending on the method used to calculate K_{hyd} (see Appendix A), different values for PFMP were obtained ($-2.09 < \log K_{\text{hyd}} < -0.43$) but the range suggests hydrate formation is not significant for PFMP. Given the perfluorinated nature of PFMP and that even partially fluorinated ketones such as trifluoroacetone ($\log K_{\text{hyd}} = 1.54$)²⁵ have large K_{hyd} values we were

surprised by the low values of K_{hyd} calculated for PFMP. The computational methods used in the present study (B3LYP/6-311++G(d,p)) were able to compute K_{hyd} values for several fluorinated ketones (fluoroacetone, trifluoroacetone and hexafluoroacetone) with fairly good accuracy, providing confidence in the method used. A single point molecular orbital calculation on geometry-optimized PFMP in the gas phase (B3LYP/6-311++G(d,p)) gave the energy level of the LUMO (-84.1 kcal/mol) as almost identical to the LUMO of HFA (-81.4 kcal/mol), especially when compared to the computed LUMO of acetone (-19.3 kcal/mol). This supports the results of Linderman et al.²⁶ who proposed these energy differences as the reason for the enhanced reactivity of HFA to hydration. In the case of PFMP, steric hindrance could be the reason for its decreased hydration equilibrium constant compared to HFA. We conclude that geminal diol formation is not a significant environmental fate for PFMP.

2.5 Environmental Implications

We have investigated the potential for photolysis, hydrolysis and hydration to contribute to the environmental fate of PFMP. As discussed in the previous section, hydration is not a significant fate for PFMP. While the rate constant for hydrolysis is much greater than that for photolysis, the levels of liquid water in the atmosphere are usually very low. A typical cloud only contains approximately $3 \times 10^{-7} \text{ cm}^3$ liquid water per millilitre of total volume²⁸ and we conclude that even at night, the amount of PFPrA and HFC-227ea produced would not be significant and that photolysis dominates hydrolysis as the atmospheric fate of PFMP. Cahill and Mackay²⁹ came to the same conclusion in their modelling study. Interestingly, Cahill and Mackay predicted a hydrolysis rate constant at pH 5.6 of 2.2 s^{-1} which is approximately 10^4 times larger than the hydrolysis rate constant we measured. Hence, our work suggests hydrolysis is an even less

important fate for PFMP compared to photolysis than the ratio Cahill and Mackay²⁹ predicted; the ratio of rates of photolysis to hydrolysis is approximately 980,000,000:1. For full details on this calculation, please see Appendix A. Photolysis will always dominate over hydrolysis. It is clear the very low fraction of liquid water in the atmosphere contributes heavily to this ratio and more than offsets the higher hydrolysis rate constant. This ratio is so great that even at night time during a heavy rain event it is unlikely hydrolysis will occur to any significant extent.

Photolysis is the dominant mechanism by which PFMP is removed from the atmosphere. It has been established previously^{10,11} that photolysis of PFMP in the presence and absence of NO_x will lead to the formation of CF₃C(O)F in a molar yield of approximately 100%. The atmospheric fate of CF₃C(O)F is hydrolysis to give trifluoroacetic acid (TFA). TFA is a ubiquitous naturally occurring component of the hydrosphere and the additional burden associated with PFMP photolysis is not significant. In the present work, we also show that small amounts of PFPrA are also formed as a result of PFMP photolysis. To provide a crude upper limit estimate for the amount of PFPrA that might be expected in precipitation as a result of atmospheric degradation of PFMP we applied the following logic (see Appendix A for details). The production of PFMP by 3M is 100 – 1000 t year⁻¹ and began in approximately 2003.³⁰ Given PFMP is used entirely in fire-protection systems that are released by an alarm, it can be considered stored emission potential with releases averaging 1 – 3 % year⁻¹.³⁰ Combining the upper limit of production (1000 t year⁻¹) with a 3% emission factor provides an upper limit of 30 t PFMP released into the atmosphere each year. Reactions subsequent to the formation of CF₃CF₂C(O) radicals in air in the presence of excess HO₂ give PFPrA in a molar yield of 24%.¹² Using a simple model (see SI), and assuming the photolysis of PFMP proceeds exclusively via

reaction (2), we derive an upper limit of 0.6 ng L^{-1} for the average concentration of PFPrA in precipitation resulting from PFMP oxidation. Perfluoropropionic acid has been detected in rainwater at several sites in North America at concentrations on the order of $1\text{-}10 \text{ ng L}^{-1}$ and these levels have yet to be explained.³ The photolysis of PFMP contributes to, but does not appear to be the major source of, PFPrA observed in precipitation.

2.6 Acknowledgements

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CHAPTER THREE

Polyfluorinated Amides as a Historical PFCA Source by Electrochemical Fluorination of Alkyl Sulfonyl Fluorides

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Derek Jackson performed all experimental work related to this project.

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3.1 Abstract

Polyfluorinated amides (PFAMs) are a class of compounds produced as byproducts of polyfluorinated sulfonamide synthesis by electrochemical fluorination (ECF). We measured four PFAM derivatives of perfluorooctanoic acid (PFOA) in a wide range of compounds, experimental materials, and commercial products synthesized by ECF. Initial screening was performed using headspace SPME-GC-MS and quantification using in-house synthesized standards was accomplished with GC-MS using positive chemical ionization. Two monosubstituted PFAMs, *N*-methylperfluorooctanamide (MeFOA) and *N*-ethylperfluorooctanamide (EtFOA), were detected in the majority of materials that were analyzed. Two disubstituted PFAMs, *N*-methyl-*N*-(2-hydroxyethyl)perfluorooctanamide (MeFOAE) and *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanamide (EtFOAE), were not detected in any sample, likely because they were never synthesized. The concentrations of PFAMs in the sulfonamide compounds under study ranged from 12 µg/g – 6736 µg/g, suggesting their historical importance as perfluorinated carboxylic acid (PFCA) precursors. In each case, branched isomers for PFAMs were detected, providing further support for their link to an ECF source. A hydrolysis study performed at pH 8.5 showed no degradation of EtFOA to PFOA after 8 days due to the stability of the amide bond. The environmental fate of PFAMs is suggested to be volatilization to the atmosphere followed by oxidation by hydroxyl radical with a predicted lifetime of 3 – 20 days. PFAM exposure to biota will likely lead to enzymatic hydrolysis of the amide linkage to give a PFCA. Human exposure to PFAMs may have contributed to the presence of branched PFOA isomers in blood by serving as an indirect source. The decline in PFOA concentrations in human blood is consistent with a significant drop in PFAM production concurrent with the perfluorooctylsulfonyl fluoride (POSF) phase-out in 2000-2001.

3.2 Introduction

The two major synthetic routes for polyfluorinated alkyl compounds widely used in commercial products are telomerization and electrochemical fluorination (ECF).¹ The telomerization process is currently used to manufacture surfactants and polymers that contain a fluorotelomer functionality such as polyfluorinated phosphate esters and fluorotelomer alcohols¹. In contrast, ECF is a fluorination process to synthesize commercial products based on polyfluorinated sulfonamides. In the historical ECF process used predominantly by 3M,¹ octanesulfonyl fluoride was reacted with hydrogen fluoride in an electrolytic cell to produce perfluorooctylsulfonyl fluoride (POSF), the synthon of polyfluorinated sulfonamide materials. Once synthesized, POSF was derivatized to produce either *N*-methylperfluorooctanesulfonamide (MeFOSA) or *N*-ethylperfluorooctanesulfonamide (EtFOSA). These two intermediates can undergo further reaction with ethylene carbonate to give *N*-methyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide (MeFOSE) or *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide (EtFOSE).² Both of these compounds were the precursors to a wide variety of commercial products and were produced in large quantities. Side-chain fluorinated polymer products such as Scotchgard (3M) were based on MeFOSE whereas lower molecular weight paper protection products such as Scotchban (3M) were based on EtFOSE.² Biotransformation of EtFOSE has been shown to give perfluorooctanesulfonate (PFOS) as the major product.^{3,4} Production of perfluorooctyl compounds by 3M was voluntarily ceased in 2000-2001.⁵ Compounds currently produced by 3M are based on perfluorobutylsulfonyl fluoride (PBSF), the four carbon analogs of the historical eight carbon materials.⁶ The 3M Company also produced perfluorooctanoic acid (PFOA) by ECF for use as a fluoropolymer processing aid from 1947-2002.⁷ Recent monitoring studies indicate

PFOA concentrations in human blood declining after 2001, although not as rapidly as the decline in PFOS concentrations.⁸ This observation has been puzzling to our research group as they suggest a major source of PFOA was ended along with POSF manufacture. This led to our motivation of elucidating analogous compounds to PFOS precursors that could have served as historical PFOA precursors.

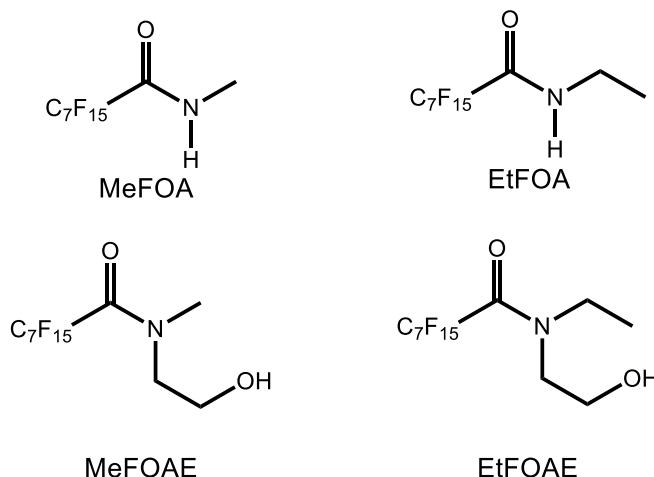
The ECF process occurs under harsh conditions and produces a mixture of fluorinated products.⁹ Most notably, rearrangement of the carbon skeleton can take place to produce constitutional isomers of POSF where perfluorinated chain branching has occurred. A typical PFOS isomer profile consists of ~70% linear and ~30% branched compounds.² Isomer distributions of ECF fluorochemicals in the environment has recently become a valuable tool for source elucidation.¹⁰

The chemical transformations that occur during ECF might suggest another mechanism by which PFOA precursors are formed during POSF synthesis. It is possible to inadvertently produce an acyl fluoride in small yields during ECF by a mechanism not understood. Gramstad and Haszeldine isolated a 1% yield of perfluorooctanoyl fluoride (PFOAF) from their electrochemical fluorination of octanesulfonyl fluoride.¹¹ Acyl fluorides are strong electrophiles and will hydrolyze in the presence of water to produce carboxylic acids.¹² This could account for PFOA being an observed contaminant in POSF-based products at an average concentration of 0.09% by mass,¹³ albeit an order of magnitude lower than the PFOAF yield obtained by Gramstad and Haszeldine.¹¹ This suggests an alternative fate of PFOAF rather than just

hydrolysis. Acyl fluorides can react with amines to produce amides and HF by nucleophilic acyl substitution.

We hypothesize polyfluorinated amides (PFAMs) are previously unobserved byproducts of polyfluorinated sulfonamide synthesis from POSF₃, assuming PFOAF is not completely hydrolyzed to PFOA after the ECF reaction. The monosubstituted amides *N*-methylperfluorooctanamide (MeFOA) and *N*-ethylperfluorooctanamide (EtFOA) are analogous to MeFOSA and EtFOSA respectively. Using the synthetic method developed by 3M², further derivatization with ethylene carbonate could give *N*-methyl-*N*-(2-hydroxyethyl)perfluorooctanamide (MeFOAE) and *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanamide (EtFOAE), the amide analogs of MeFOSE and EtFOSE respectively. The amide structures of interest are shown in Figure 3.1. All four amides are PFOA precursors via hydrolysis of their amide linkages. Although the amide bond is normally very stable towards abiotic environmental degradation, it is possible the electron withdrawing fluorinated chain could enhance reactivity and allow hydrolysis to proceed under mild conditions.¹⁴

Figure 3.1. Polyfluorinated amides (PFAMs) synthesized in the present study with their respective acronyms.



There has been little published literature on PFAMs. Several monosubstituted amides including MeFOA and EtFOA were synthesized and analyzed with regards to their surfactant properties.¹⁵ Lewis synthesized the trifluoromethyl analog of MeFOAE for use in a synthetic reaction to produce cyclic amide acetals but no further characterizations nor links to sulfonamide chemistry were given.¹⁶ The most relevant find was an internal 3M report by Seacat in which MeFOA (referred to as MePFOAA) was orally dosed in rats and found to hydrolyze to PFOA *in vivo*.¹⁷ Although this study was performed in 2004, the MeFOA material was synthesized in 2000. This represents the only literature, albeit not peer-reviewed and difficult to find, in which the presence of fluorinated amides within sulfonamide products was reported.

The objectives of the present study were to synthesize four PFAMs as analytical standards and to quantitate historical polyfluorinated sulfonamide compounds and commercial products for PFAMs. The compounds were chosen to encompass a diversity in production date and manufacturer. The stability of the amide linkage toward abiotic hydrolysis at environmental pH for a model PFAM was studied to investigate potential PFCA formation. Finally, the overall environmental fate and historical significance of PFAMs as PFCA precursors were elucidated.

3.3 Experimental Details

3.3.1 Chemicals and commercial materials

All compounds were used as received. Perfluorooctanoyl chloride was purchased from PCR (Gainesville, FL). Perfluorononanoyl chloride was purchased from Synquest Labs (Alachua, FL). Ethylamine (2.0 M solution in tetrahydrofuran), methylamine (13 M solution in water), 2-methylaminoethanol and 2-ethylaminoethanol were purchased from Sigma-Aldrich.

Two lots of *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide (EtFOSE, lot A and lot B) and one lot of *N*-methyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide (MeFOSE) were donated by 3M. All 3M experimental material dated from prior to 2001 were continuously stored at -20°C prior to the present study. Additional EtFOSE was purchased from 3B Pharmachem (Wuhan, China, 98% pure). *N*-ethylperfluorooctanesulfonamide (EtFOSA) was purchased from Lancaster Scientific (Windham, NH, 99.8% pure). Two Scotchgard carpet protector spray cans (3M) manufactured before and after 2001 were purchased from a local hardware store. Unless otherwise stated, all references to “Scotchgard” herein refer to the pre-2001 formulation. Scotchban FC-807A (3M) was donated by the United States Environmental Protection Agency as an aqueous formulation. Technical grade EtFOSE-based phosphate diester (di-SAmPAP, CAS 2965-52-8) was purchased from Defu (China). Methyl *t*-butyl ether (MTBE) and ethyl acetate (Omnisolv grade) were purchased from EMD. Purified standards of perfluorooctanoate (PFOA) and mass-labeled PFOA were obtained from Wellington Laboratories.

3.3.2 Synthesis of *N*-ethylperfluorooctanamide (EtFOA)

Ethylamine (2.0 M solution, tetrahydrofuran, 8 mmol) was added to a round bottom flask and cooled in an ice bath. Perfluorooctanoyl chloride (4 mmol) was added drop wise with continuous stirring and a white precipitate formed immediately. The reaction mixture was allowed to warm to room temperature before workup. Cold water was added to dissolve the ethylammonium chloride byproduct before an extraction was performed using MTBE. The MTBE layer was removed and dried using anhydrous magnesium sulfate. Evaporation under a gentle stream of nitrogen gas gave EtFOA as a yellow oil which solidified on standing. The purity was determined to be 86% from ^{19}F NMR with the only measurable impurity being

perfluorooctanoic acid (PFOA). ^1H NMR (400 MHz, methanol- d_4): δ 3.0 (q, 2H, N- CH_2), 1.3 (t, 3H, CH_2 - CH_3). ^{19}F NMR (400 MHz, methanol- d_4): δ -83 (t, 3F, CF_3), -122 (t, 2F, CF_2 -C(O)), -123 (m, 2F, CF_2), -124 (m, 2F, CF_2), -125 (m, 4F, CF_2), -128 (m, 2F, CF_2).

3.3.3 Synthesis of N-methylperfluorooctanamide (MeFOA)

Methylamine (12.9 M, aqueous, 1.6 mmol) was added to a round bottom flask and cooled in an ice bath. Perfluorooctanoyl chloride (0.8 mmol) was added dropwise along with continuous stirring. After warming to room temperature, the reaction mixture was extracted with MTBE. The MTBE layer was dried with anhydrous magnesium sulfate and was evaporated under a gentle stream of nitrogen to give MeFOA as a white solid. The purity was determined to be 81% from ^{19}F NMR with the only measurable impurity being PFOA. ^1H NMR (400 MHz, methanol- d_4): δ 2.85 (s, 3H, N- CH_3). ^{19}F NMR (400 MHz, methanol- d_4): δ -83 (t, 3F, CF_3), -122 (t, 2F, CF_2 -C(O)), -123 (m, 2F, CF_2), -124 (m, 2F, CF_2), -125 (m, 4F, CF_2), -128 (m, 2F, CF_2).

3.3.4 Synthesis of N-methylperfluorononanamide (MeFNA)

Methylamine (12.9 M, aqueous, 2.6 mmol) was added to a round bottom flask and was cooled in an ice bath. Perfluorononanoyl chloride (1.1 mmol) was added dropwise along with continuous stirring. After warming to room temperature, the reaction mixture was extracted with 1:1 MTBE:H₂O. The MTBE layer was dried with anhydrous magnesium sulfate and evaporated under a gentle stream of nitrogen to give a white solid. The product was found to be significantly contaminated with perfluorononanoic acid (PFNA) from ^{19}F NMR (approximately 25% pure). ^1H NMR (400 MHz, methanol- d_4): δ 2.85 (s, 3H, N- CH_3).

3.3.5 Synthesis of methyl perfluorooctanoate

The syntheses of MeFOAE and EtFOAE by using an ester precursor were roughly adapted from Lewis.¹⁶ Methanol (4.0 mmol) and triethylamine (4.0 mmol) were added to a round bottomed flask and were cooled in an ice bath. Perfluorooctanoyl chloride (4.0 mmol) was added dropwise with continuous stirring. The reaction mixture turned pale yellow immediately. After warming to room temperature, cold water was added followed by extraction with an equal volume of MTBE. The MTBE layer was dried with anhydrous magnesium sulfate and evaporated under a gentle stream of nitrogen to give methylperfluorooctanoate as a pale yellow oil in 20% yield by mass.

3.3.6 Synthesis of N-ethyl-N-(2-hydroxyethyl)perfluorooctanamide (EtFOAE)

Methylperfluorooctanoate (0.8 mmol) was added to a microcentrifuge tube followed by the addition of 2-ethylaminoethanol (0.8 mmol). The reaction was left uncapped overnight and gave a viscous pale yellow oil as the product in a quantitative yield as determined by ¹H and ¹⁹F NMR. ¹H NMR (400 MHz, acetone-d₆): δ 3.8 (m, 2H), 3.2 (m, 4H), 1.4 (t, 3H). ¹⁹F NMR (400 MHz, acetone-d₆): δ -82 (t, 3F, CF₃), -117 (t, 2F, CF₂-C(O)), -120 to -124 (m, 8F, CF₂), -127 (m, 2F, CF₂).

3.3.7 Synthesis of N-methyl-N-(2-hydroxyethyl)perfluorooctanamide (MeFOAE)

Methylperfluorooctanoate (0.3 mmol) was added to a microcentrifuge tube followed by the addition of 2-methylaminoethanol (0.3 mmol). The reaction was left uncapped overnight and gave a viscous pale yellow oil as the product in a quantitative yield as determined by ¹H and ¹⁹F NMR. ¹H NMR (400 MHz, acetone-d₆): δ 3.8 (m, 2H), 3.2 (m, 2H), 2.8 (s, 3H). ¹⁹F NMR (400

MHz, acetone- d_6): δ -82 (tt, 3F, CF_3), -117 (tt, 2F, CF_2 -C(O)), -122 (m, 2F, CF_2), -123 (m, 4F, CF_2), -124 (m, 2F, CF_2), -127 (m, 2F, CF_2).

3.3.8 Screening commercial materials for amides by headspace SPME-GC-MS

Initial screening of all commercial materials for amides was accomplished using headspace solid phase microextraction followed by GC-MS analysis. A small amount of solid or aqueous sample was placed into a glass vial with a Mininert valve cap. The SPME fibre was 100 μ m 100% polydimethylsiloxane and the headspace sampling time was 1 minute. A vial blank was run after every sample to ensure sample carryover was not a concern. As SPME was only used for qualitative screening, attempts to quantify extraction efficiency were not performed.

3.3.9 Quantitative analysis of commercial materials

Specific masses of each electrochemical sulfonamide-based commercial material were weighed in triplicate and dissolved in ethyl acetate to make a concentrated standard solution with concentrations ranging from 20 ng/mL to 1000 μ g/mL. The concentrations depended on the approximate amide concentration within the material as determined by range finding experiments. Concentrations of amides relative to their corresponding sulfonamides on a mass per mass basis were determined by GC-MS. The amide concentrations in both Scotchgard and Scotchban FC-807A are expressed relative to the dry mass of the commercial material as determined following evaporation of the water phase.

3.3.10 Hydrolysis of polyfluorinated amides

Hydrolysis studies were carried out on EtFOA using 50 mM borate buffer (pH 8.5), 50 mM tris buffer (pH 8.5) and 1 M sodium hydroxide (pH 14). The starting concentration of EtFOA was 500 ng/mL. Experiments were performed in triplicate within a polypropylene autosampler vial. Solutions were 50:50 methanol:water to improve amide solubility with a total volume of 600 μ L. The experiments at pH 14 were neutralized using acetic acid after 24 hr; samples were analyzed by LC-MS/MS. All experiments at pH 8.5 were well shaken and then directly analyzed by LC-MS/MS at various time intervals over the course of 24 hr and once again after 8 days.

3.3.11 GC-MS analysis

Monosubstituted amides (MeFOA and EtFOA) were quantified using an Agilent 7890A gas chromatograph interfaced with an Agilent 5975-inert mass spectrometer operating in positive chemical ionization (PCI) mode with methane as the reagent gas. All injections were performed in the splitless mode with an inlet temperature of 280°C. Separation was achieved using an Agilent DB-1701 column (30 m x 0.25 mm x 0.25 μ m) at a constant helium flow rate of 0.9 mL/min. The oven program consisted of an initial hold at 50°C for 2 min, then a 20°C/min ramp to 160°C and a 35°C/min ramp to 280°C and hold for 2 min. The transfer line temperature was held at 280°C. Analytes were monitored mainly as their [M+1] ions in single ion monitoring mode. A complete listing of analytes and their monitored ions is given in Appendix B (Table S1). The PCI mass spectra of MeFOA and EtFOA are also given in Appendix B (Figures S1 and S2). For analysis of cleaner samples, a double tapered inlet liner without glass wool was used. For samples that contained nonvolatile constituents such as polymers or phosphates, an inlet liner

with glass wool was used to protect the head of the column at the cost of broader peak shapes. Separate external calibration curves showed loss of PFAMs on the glass wool was negligible. Both MeFOA and EtFOA were quantified in commercial materials using external calibration. The lack of a matrix makes the usage of internal standards not mandatory. The calculated purity of the synthesized standards was taken into account when constructing the calibration curves. Multiple solvent blanks were injected to ensure carryover was negligible. Spike and recovery experiments were not performed since sample preparation simply consisted of dissolving the sulfomanide compounds of interest in ethyl acetate.

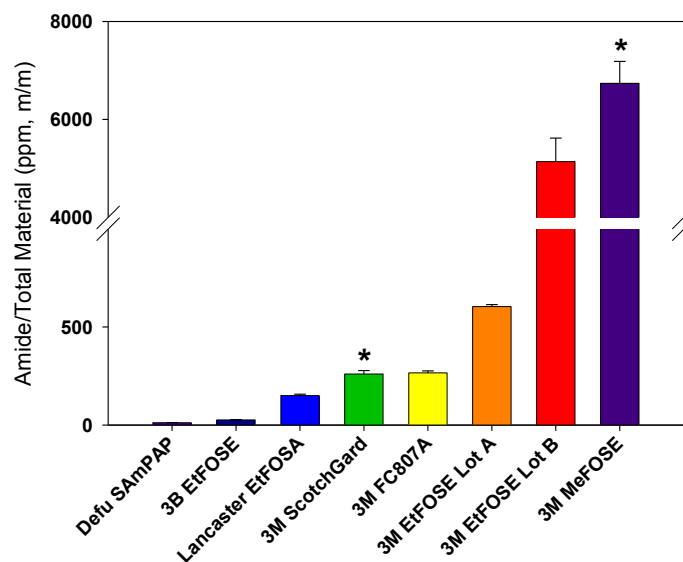
3.3.12 LC-MS/MS analysis

For quantification of EtFOA and PFOA during hydrolysis experiments, an Agilent 1100 LC interfaced with a Micromass Quattro-Micro electrospray mass spectrometer was used. Separation was achieved using an ACE 3 μm C₁₈ column (50 x 2.1 mm). The LC program consisted of a gradient starting at 50:50 methanol:water ramping to 86% methanol over 1 min followed by a reduction to 63% methanol over 5.5 min before returning to initial conditions at 8 min followed by a 4.5 min hold. Both mobile phase solvents contained 1 mM ammonium acetate as an ion-pairing agent. All injection volumes were 10 μL and standards were made up using 50:50 methanol:water solvent. The analytes were detected in multiple reaction monitoring mode with the transitions 440>369 (EtFOA) and 413>369 (PFOA) with argon as the collision gas. Internal calibration using a mass labeled internal standard was performed for PFOA analyses (415>370). Only qualitative analyses were done for EtFOA as no suitable internal standard was available.

3.4 Results

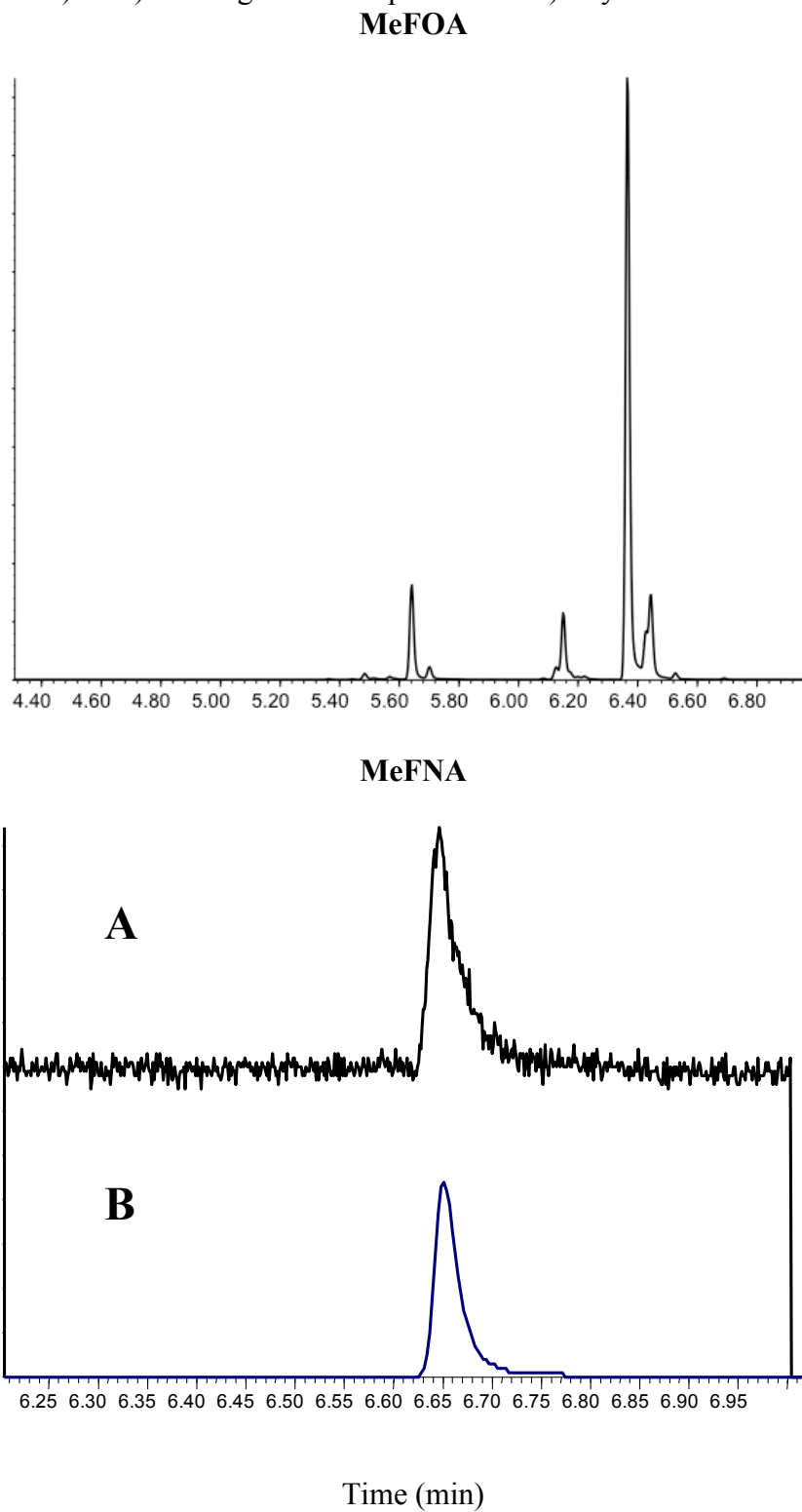
Polyfluorinated amides (PFAMs) were detected in the majority (80%) of sulfonamide materials tested. Samples that gave a non-detect by SPME screening were not subjected to quantitative analysis by GC-MS. The concentrations of MeFOA or EtFOA in each sample are shown in Figure 3.2; results are completely tabulated in Appendix B (Table S2). Neither MeFOAE nor EtFOAE were detected in any sample. The highest concentration of MeFOA was found in 3M MeFOSE experimental material at 6736 $\mu\text{g/g}$. This concentration approaches the yield of PFOAF (1% by mass) reported by Gramstad and Haszeldine.¹¹ Similarly, the highest EtFOA concentrations were detected in 3M EtFOSE experimental material (lot B) at 5139 $\mu\text{g/g}$. The other lot of 3M EtFOSE (lot A) contained far lower amounts of EtFOA and illustrates the importance of variation within a production line. It is possible lot A was subjected to additional cleanup after synthesis which removed large quantities of EtFOA although both lots contained significant quantities of EtFOSA as the major impurity. In addition, two commercial products (Scotchgard and Scotchban FC-807A) contained PFAMs at concentrations approximating 200 $\mu\text{g/g}$. The purified standard of EtFOSE from Wellington Laboratories (Guelph, ON) contained no PFAM content and provided a suitable negative control. Likewise, the new formulation of Scotchgard (post-2001) was found to not contain PFAMs above the instrumental detection limit of approximately 100 pg/mL.

Figure 3.2. Polyfluorinated amide (PFAM) concentrations within sulfonamide products as quantified by GC-MS. Concentrations are derived from the summed integration of the two most predominant isomers in the chromatogram. All concentrations are of EtFOA except * = MeFOA. Concentrations for Scotchgard and FC-807A normalized to dry mass.



Both MeFOA and EtFOA were amenable to GC-MS analysis and displayed extremely low limits of detection (~ 100 fg/mL) in the positive chemical ionization (PCI) mode. The DB-1701 column was efficient at separating amides from sulfonamides. For these reasons, we recommend GC-MS as the preferred analytical technique for further studies on PFAMs. A sample chromatogram showing the presence of MeFOA in Scotchgard is shown in Figure 3.3. The amidoethanols MeFOAE and EtFOAE gave poor peak shape during GC-MS analysis which led to significantly higher limits of detection. The perfluorooctanoyl chloride used for all PFAM syntheses was manufactured by liquid phase direct fluorination (LPDF), resulting in a small but measurable percentage of the one branched isomer, seen by GC-MS and ^{19}F NMR. At the standard concentrations used in the present study, this isomer could not be detected by GC-MS and was not taken into account when quantifying PFAMs.

Figure 3.3. Extracted ion chromatograms showing the presence of *N*-methylperfluorooctanamide (MeFOA, $m/z = 428$) in Scotchgard and the detection of *N*-methylperfluorononanamide (MeFNA, $m/z = 478$) in A) Scotchgard as compared with B) a synthesized standard of MeFNA.



All polyfluorinated sulfonamide compounds synthesized by ECF consist of a mixture of constitutional isomers, all of which are capable of being separated by GC-MS using long polar columns. Although no deliberate attempt was made in the present study to separate isomers, multiple peaks for both MeFOA and EtFOA were found in every sample; we suggest these represent branched isomers. Further support for this hypothesis comes from the fact that approximately 70% of the total peak area is composed of the linear isomer in the majority of samples tested.² In the present study amide concentrations are reported by summing the areas of the two largest peaks, one being the linear isomer and the other presumably the isopropyl isomer. Some samples, most notably 3B EtFOSE (China), have unusual isomer patterns wherein only 50% of the total peak area comes from linear EtFOA.

One puzzling result from the present study is the lack of MeFOAE and EtFOAE in the sulfonamidoethanol-based samples tested. One hypothesis is the monosubstituted amides, MeFOA and EtFOA, cannot react with ethylene carbonate to produce the corresponding amidoethanols. Therefore, as MeFOSE and EtFOSE are synthesized, the amides remain in their monosubstituted forms. A literature search failed to find any instances of a monosubstituted amide reaction with ethylene carbonate to give an amidoethanol and attempts to duplicate this reaction in our lab were unsuccessful. Since amides are less acidic than sulfonamides, the initial deprotonation step in the reaction mechanism may not be possible for the amides.

Boulanger et al. detected PFOA in pre-2001 Scotchgard at a concentration of 13 $\mu\text{g/g}$, accounting for the majority of involatile fluorinated residuals quantified using LC-MS.¹⁸ The current detection of MeFOA in legacy Scotchgard at 260 $\mu\text{g/g}$ (dry mass basis) is not surprising

given that it was a polymeric product based on MeFOSE. It is not clear whether the PFOA detected in Scotchgard is a product of MeFOA hydrolysis or not. The amide MeFOAE was not detected in pre-2001 Scotchgard, therefore it is unlikely PFAMs are becoming incorporated into polymers themselves but are present as residuals from polymer synthesis.

3.4.1 Hydrolysis kinetics of EtFOA

The monosubstituted amine EtFOA was subjected to two hydrolysis experiments. The first experiment, carried out in 5 mM Tris buffer pH 8.5, investigated whether the amide linkage could be abiotically hydrolyzed under environmentally relevant conditions. The second experiment was an overnight reaction in 1 M sodium hydroxide (pH 14) to quantitatively hydrolyze EtFOA to PFOA and provide quality assurance for the mass balance study. No hydrolysis of EtFOA to PFOA was observed at pH 8.5 after 8 days. The inherent stability of the amide linkage is therefore not overcome by the enhanced electrophilicity of the carbonyl group caused by the fluorinated chain. Surprisingly, trifluoroacetamide has a measured half-life of 24 hours at pH 8.5¹⁴ implying that EtFOA might have similar hydrolysis kinetics based on the presence of a fluorinated group. If 50 mM borate buffer was used instead, degradation of EtFOA occurred fairly rapidly, but PFOA was not observed as a product. This reaction is only observed at high borate concentrations and not environmentally relevant. At pH 14, quantitative (98%) conversion of EtFOA to PFOA was observed after 24 hours at room temperature.

The hydrolysis experiments with EtFOA in the present study were carried out in 50:50 methanol:water due to solubility limitations. The results from the present study indicate abiotic hydrolysis of the amide bond at environmental pH will be negligible. It might be reasonable to

assume the hydrolysis rate in pure water would be faster compared to 50:50 methanol:water since the negatively charged transition state leading to the first intermediate will be more greatly stabilized. However, the energy of the reagents in pure water will also be decreased due to enhanced solvation of hydroxide ions. Overall, the hydrolysis rate might be faster or slower in pure water depending on the relative contributions of these two stabilization effects.

The hydrolysis kinetics of MeFOA were not measured in the present study however it is possible to estimate its hydrolytic rate based on previous findings on analogous amides. Yamada et al. measured bimolecular rate constants and found *N*-methylacetamide hydrolyzed approximately twice as fast as *N*-ethylacetamide with the difference being attributed to steric effects.¹⁹ Based on this finding, we can postulate MeFOA will have a hydrolysis rate approximately double that of EtFOA.

3.4.2 Mass balance study

The sample with the highest amide concentration, 3M MeFOSE experimental material, was hydrolyzed at pH 14 overnight to convert all PFOA precursors to PFOA. Since MeFOA was the only amide detected, this experiment was performed to determine how much total PFOA precursor in MeFOSE can be accounted for by MeFOA alone. The results suggest that 96% of the total PFOA precursor content of 3M MeFOSE can be accounted for by MeFOA alone, achieving an almost quantitative mass balance. This result provides further support for the hypothesis that MeFOAE was never produced by a reaction of MeFOA with ethylene carbonate.

3.5 Environmental implications

In the present study we detected polyfluorinated amides (PFAMs) in a variety of sulfonamide compounds and commercial materials. This result can offer plausible hypotheses for several monitoring observations; most notably the widespread detection of branched PFOA in environmental matrices.

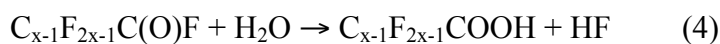
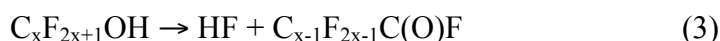
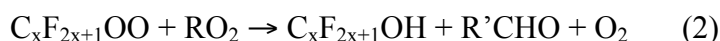
3.5.1 Environmental fate of polyfluorinated amides

Both MeFOA and EtFOA are expected to volatilize to the atmosphere or partition onto the surface of aerosol particles. The environmental fate of the monosubstituted amides is probably atmospheric oxidation by hydroxyl radical (OH). Both MeFOA and EtFOA contain abstractable hydrogen atoms on alkyl groups that are capable of being oxidized to carbonyl groups.

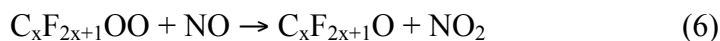
Using AOPWin,²⁰ the lifetime of MeFOA and EtFOA by OH oxidation is estimated at 19 and 2.7 days respectively. Using this program, we also predicted the bimolecular OH rate constant for three fluorinated compounds that have literature values: 1H,1H,2H,2H-perfluoro-1-hexanol (4:2 FTOH),²¹ *N*-ethylperfluorobutanesulfonamide (EtFBSA)²² and *N*-methyl-*N*-(2-hydroxyethyl)perfluorobutanesulfonamide (MeFBSE).²³ In each case the experimental rate constants were overpredicted by factors of 4, 24 and 3, respectively. This is likely due to the fact that AOPWin does not take the electron withdrawing fluorinated chain into account during its calculations. The actual atmospheric lifetimes of MeFOA and EtFOA are likely longer than those predicted by AOPWin.

It is unclear what the ultimate products of atmospheric oxidation would be. A recent study showed that for OH oxidation of *N*-methylacetamide, *N*-formylacetamide was the first stable product,²⁴ implying that *N*-formylperfluorooctanamide will be the corresponding product for MeFOA. However, a minor product from *N*-methylacetamide was methyl isocyanate with concurrent ejection of a CH₃ radical.²⁴ If MeFOA were to undergo a similar reaction, the perfluorinated C₇F₁₅ radical would be produced.

Perfluorinated radicals, under low NO_x conditions, will react by a series of well characterized atmospheric steps²⁵ to form PFCAs. These series of reactions are summarized below in reactions 1-4.



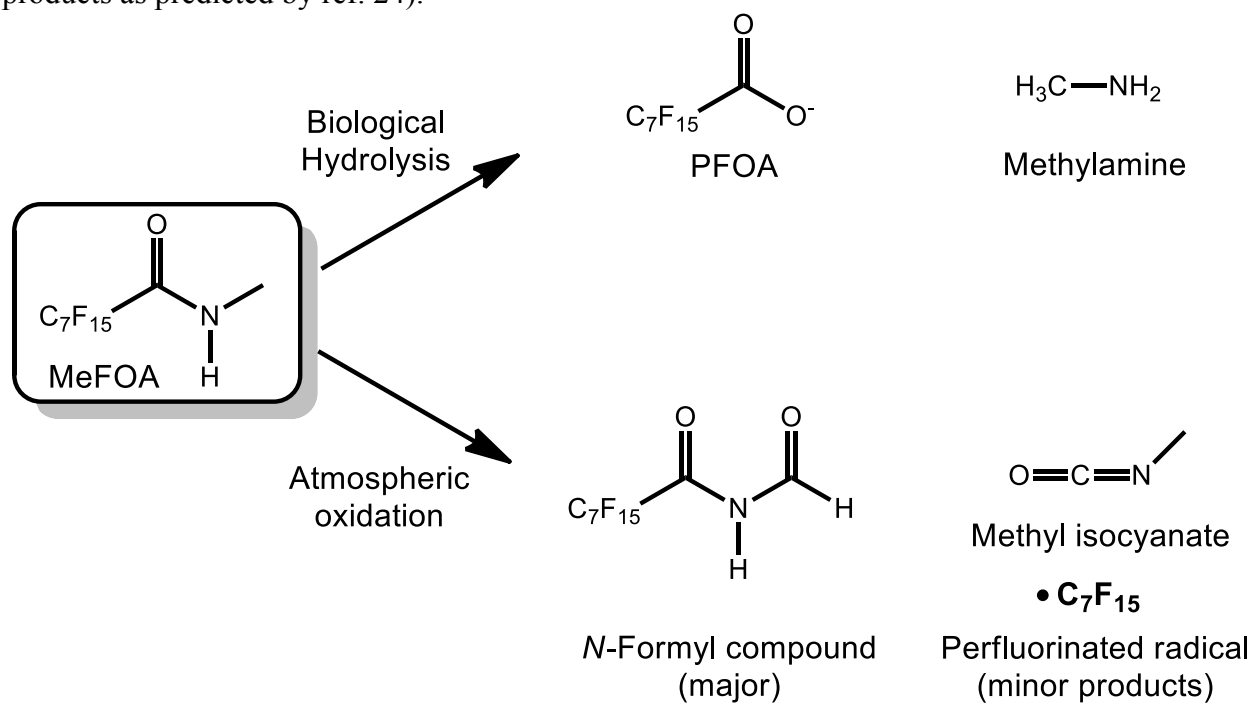
Under higher NO_x conditions, “unzipping” of the perfluorinated radical will occur²⁵ to give COF₂ as the major fluorinated product as shown in reactions 5-7.



Depending on the atmospheric HO_x/NO_x ratio, the unzipping cycle can be halted by RO_2 . This leads to the production of a homologous series of PFCAs of varying fluorinated chain lengths.²⁵

A schematic diagram showing the proposed environmental fates of PFAMs using MeFOA as an example is given in Figure 3.4.

Figure 3.4. Simplified environmental fate diagram for *N*-methylperfluorooctanamide (MeFOA) showing enzyme-catalyzed hydrolysis to PFOA as well as atmospheric oxidation (atmospheric products as predicted by ref. 24).

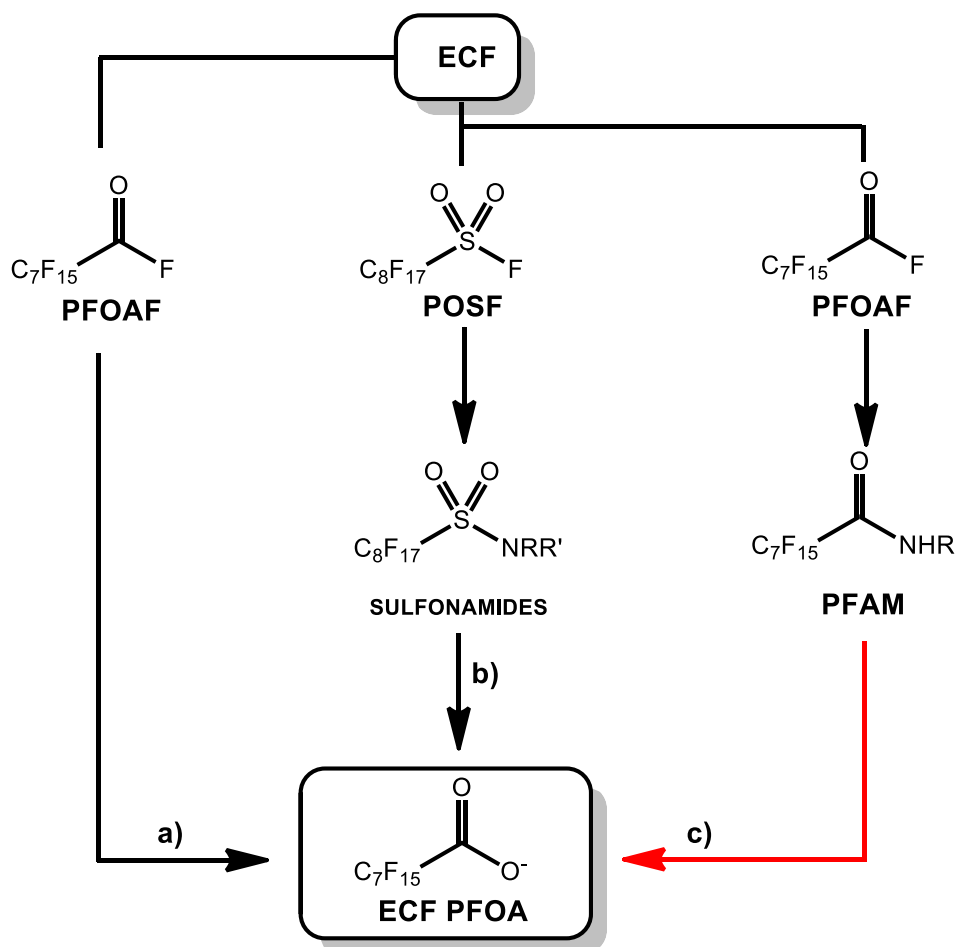


3.5.2 Human exposure to PFAMs

There are three major pathways by which humans could be exposed to branched isomers of PFOA as shown in Figure 3.5. The first is direct exposure from PFOA that was produced by ECF from 1947-2002⁷ as suggested by De Silva and Mabury.²⁶ Prevedouros calculated 400-700 t of ECF PFOA was emitted to the environment over this time period.⁷ A second possibility is

atmospheric oxidation of polyfluorinated sulfonamides^{22,23} such as MeFOSE and EtFOSE, which are present as residuals in polymer and surfactant materials produced by ECF chemistry.²⁷ This oxidation pathway is thought to only be important in rural environments since the presence of NO_x favours “unzipping” the perfluorinated chain rather than forming a PFCA.²⁵ Such a pathway could explain the detection of ECF PFOA in the Arctic environment.²⁸ Human exposure through this route would still be considered a direct exposure since the transformation pathways to make PFOA have already occurred in the atmosphere.

Figure 3.5. Simplified human exposure pathways to ECF (branched) PFOA showing a) direct exposure to PFOA deliberately produced by ECF, b) atmospheric oxidation of polyfluorinated sulfonamides in low NO_x atmospheres and c) biotransformation of polyfluorinated amides (PFAMs). A new exposure pathway to ECF PFOA is shown in red.



The third possibility for human exposure is via the PFAMs, which might act as an indirect source of PFCAs, provided enzyme-catalyzed hydrolysis takes place. The polyfluorinated amides such as MeFOA and EtFOA are produced as byproducts from POSF-based syntheses as shown in the present study. This supports the statements of previous researchers^{8,29} who hypothesized that an unknown PFOA precursor was somehow linked with ECF production of polyfluorinated sulfonamides. Paul et al. reported that up to 45,000 t of POSF-derived compounds were released to the environment since 1970.³⁰ Assuming an upper yield 1% yield of PFAMs from the synthesis of sulfonamide compounds¹¹ gives a maximum 450 t of potential ECF PFOA precursor in the environment, on the same scale as PFOA deliberately produced by ECF.

The PFAMs are unambiguous PFCA precursors by enzyme-catalyzed hydrolysis and would give branched as well as linear isomers. Seacat reported MeFOA was metabolized to PFOA after a dosing study using Sprague-Dawley rats.¹⁷ Although the mechanism of hydrolysis was not elucidated, any number of hydrolase enzymes³¹ could hydrolyze the amide linkage giving the perfluorocarboxylate as a product. We hypothesize biotransformation of polyfluorinated amides as a contributing source of branched PFOA in human blood. This exposure pathway would be potentially significant for indoor exposure since PFAM residuals are present in commercial products such as Scotchgard. Previous studies have measured relatively high MeFOSE and EtFOSE concentrations in indoor air.^{32,33} This suggests MeFOA and EtFOA might have also been present and subsequently inhaled. Archived indoor air samples might provide valuable insight if PFAMs could be detected and quantified.

Analyses performed on human blood from North America show a consistent drop in both PFOS and PFOA concentrations after the 3M phase-out of POSF based materials in 2000-2001.^{34,35,36} The drop in PFOS can readily be explained by the phase-out of precursor compounds,³⁵ although the decline in PFOA concentrations is not as clear because biotransformation of PFOS precursors have not been shown to give PFOA. Direct sources to PFOA are mainly due to consumption of food and to a smaller extent, water.²⁹ Since levels of PFOA in these sources have not significantly changed over time,⁸ the decline in PFOA in human blood can not fully be explained by the halt in ECF PFOA synthesis.

If PFAMs acted as volatile PFOA precursors prior to 2001 then a similar trend in human blood concentration to PFOS would be expected. While PFOA concentrations do decrease after 2001, this decline is slower compared to PFOS. This difference is likely due to increased production of fluorotelomers,⁸ many of which are capable of metabolism to PFOA. One example is the metabolism of fluorotelomer phosphate esters (PAPs) to PFCAs in rats.³⁷ We therefore suggest a significant decline in PFAM production, as byproducts in POSF synthesis, is consistent with the evidence of PFOA declining in human blood after 2001.

The source of branched perfluorononanoate (PFNA) in human blood has not yet been conclusively determined. Branched PFNA has also been detected in Arctic samples,²⁸ with historical atmospheric oxidation of nine carbon sulfonamides being a potential source. In the present study, *N*-methylperfluorononamide (MeFNA) was detected in pre-2001 Scotchgard at very low concentrations by reference to an in-house synthesized standard of MeFNA as shown in Figure 3.3. Since the standard was impure by NMR and the concentrations in Scotchgard just

above detection limits, a quantitative measurement of MeFNA in Scotchgard was not possible. From the present study, we can not conclude whether Scotchgard was a significant source of branched PFNA in human blood. Another contributing factor is direct exposure to ECF PFNA, produced as a byproduct of ECF PFOA synthesis.²⁸

Monosubstituted amides were present in historical electrochemical products consisting mainly of eight fluorinated carbons. The amide EtFOA has been detected in more recent ECF materials produced in China, albeit at far lower concentrations compared to the legacy samples. A likely hypothesis is cleaner synthetic techniques and additional purification steps being used today. The current form of Scotchgard (post-2001 formulation) is completely free of any fluorinated residuals, which may have been removed by thoroughly purging the fluorinated polymers after synthesis. The polyfluorinated amides are predicted to be more reactive in the environment compared to fluorinated sulfonamides due to the resistance of sulfonamides to hydrolysis. For all these reasons, polyfluorinated amides are far less likely to contribute to human PFCA burden today compared to when fluorinated alkyl compounds were overwhelmingly produced by ECF. In current environmental media such as air, precipitation and human blood, it is unlikely polyfluorinated amides will be detected. It would be of value to analyze any historical air samples for MeFOA and EtFOA and their detection would provide further support for their significance as PFCA precursors.

3.6 Acknowledgements

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CHAPTER FOUR

Atmospheric Oxidation of Polyfluorinated Amides: Historical Source of Perfluorinated Carboxylic Acids to the Environment

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4.1 Abstract

Polyfluorinated amides (PFAMs) are a class of fluorinated compounds which were produced as unintentional byproducts in the electrochemical fluorination process used for polyfluorinated sulfonamide synthesis in 1947-2002. To investigate the historical potential of PFAMs as an atmospheric perfluorinated acid (PFCA) source we studied *N*-ethylperfluorobutyramide (EtFBA) as a surrogate for longer chained PFAMs. Smog chamber relative rate techniques were used to measure bimolecular rate coefficients for reactions of EtFBA with chlorine atoms and hydroxyl radicals. It was found $k_{\text{Cl}} = (2.08 \pm 0.15) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ and $k_{\text{OH}} = (2.65 \pm 0.50) \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ and the atmospheric lifetime of EtFBA with respect to reaction with OH was estimated to be approximately 4.4 days. Offline sampling with both GC-MS and LC-MS/MS techniques was used to determine the products and hence a plausible pathway of atmospheric oxidation of EtFBA. Three primary oxidation products were observed by GC-MS, the *N*-dealkylation product $\text{C}_3\text{F}_7\text{C}(\text{O})\text{NH}_2$ and two carbonyl products, probably $\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}(\text{H})\text{C}(\text{O})\text{CH}_3$ and $\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}(\text{H})\text{CH}_2\text{CHO}$. These primary products react further to give perfluorocarboxylic acids (PFCAs) as detected by LC-MS/MS, suggesting that eight carbon PFAMs were a historical source of PFCAs to remote regions, including the Canadian Arctic.

4.2 Introduction

From 1947-2002, the major production method for perfluorooctanoic acid (PFOA) was by the electrochemical fluorination (ECF) process with 3M being the dominant manufacturer.¹ The ECF process used to make PFOA produces multiple byproducts, the most studied of which are branched constitutional isomers of PFOA. A multitude of monitoring studies have

established isomeric PFOA as a worldwide human blood contaminant^{2,3,4,5} that does not degrade under environmentally relevant conditions. Therefore, understanding the sources of branched PFOA isomers to the environment, including human blood, has been a significant area of study.

Recently, the polyfluorinated amides (PFAMs) have been discovered as historical environmental contaminants.⁶ These compounds were historically produced as unintentional byproducts of polyfluorinated sulfonamide synthesis by ECF⁷ and can serve as precursors of perfluorocarboxylic acids (PFCAs) including PFOA. The PFAMs have the general structure $C_xF_{2x+1}C(O)N(H)(R)$ where x is an integer, typically 7 for historical materials and R is an alkyl group, either methyl (MeFOA when $x=7$) or ethyl (EtFOA when $x=7$). Such compounds could have served as historical PFOA precursors, both linear and branched, by biological hydrolysis of the amide bond.⁶ Since PFAMs are predicted to be more volatile than their sulfonamide analogs, partitioning to the atmosphere is expected to be significant. Once in the atmosphere, they would be capable of undergoing oxidation reactions initiated by hydroxyl radicals (OH).

The amide compounds MeFOA and EtFOA are analogs of the sulfonamides MeFOSA and EtFOSA respectively. Previous studies to determine the atmospheric reactions of polyfluorinated sulfonamides have used the photochemical smog chamber at the Ford Motor Company.^{8,9} In the previous studies, a more volatile four carbon analog of the eight carbon material was studied to facilitate introduction into the smog chamber. It was found that EtFBSA ($C_4F_9SO_2N(H)CH_2CH_3$) produces a homologous series of PFCAs as final degradation products by reaction with chlorine atoms.⁸

In the present study, a four carbon version of a historical PFAM compound (EtFBA, $\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}(\text{H})\text{CH}_2\text{CH}_3$) was synthesized and the kinetics and pathway of atmospheric oxidation initiated by reaction with with Cl atoms and OH radicals were studied. Specifically, our focus was to understand whether eight carbon PFAMs could have served as historical atmospheric precursors of branched eight carbon PFOA isomers and/or shorter chained PFCA homologs.

4.3 Experimental Details

4.3.1 Chemicals and commercial materials

All compounds were used as received. Methyl perfluorobutyrate was purchased from Synquest Labs (Alachua, FL). Ethylamine (2.0 M solution in tetrahydrofuran) and pentafluoropropanoic acid (PFPrA) was purchased from Sigma-Aldrich (Oakville, ON). Methyl *t*-butyl ether (MTBE) was purchased from EMD (Mississauga, ON). Ammonia (8 M aqueous) was purchased from ACP (Montreal, PQ). Trifluoroacetic acid (TFA) was obtained from Caledon (Georgetown, ON). Heptafluorobutanoic acid (PFBA) and $^{13}\text{C}_4$ -heptafluorobutanoic acid ($^{13}\text{C}_4$ -PFBA) were obtained from Wellington Labs (Guelph, ON).

4.3.2 Synthesis of N-ethylperfluorobutyramide ($\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}(\text{H})\text{CH}_2\text{CH}_3$, EtFBA)

Ethylamine (2.0 M solution in tetrahydrofuran, 40 mmol) was added to a round bottom flask and methyl perfluorobutyrate (32 mmol) was added drop wise at room temperature with continuous stirring. After addition was complete, the solution was left to stir for 12 h. The tetrahydrofuran was removed using a flux of nitrogen gas and the remaining material was extracted using a 1:1 mixture of ddH₂O/MTBE. The MTBE layer was removed and dried using anhydrous magnesium sulfate. Evaporation under a gentle stream of nitrogen gas gave crude

EtFBA as a yellow oil (70% yield). The crude product was purified by distillation to give pure EtFBA as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 6.48 (s, 1H, N-*H*), 3.44 (quin, 2H, N- CH_2), 1.24 (t, 3H, $\text{CH}_2\text{-CH}_3$). ^{19}F NMR (376 MHz, CDCl_3): δ -81 (t, 3F, CF_3), -121 (q, 2F, $\text{CF}_2\text{-CON}$), -127 (s, 2F, $\text{CF}_2\text{-CF}_3$).

4.3.3 Synthesis of perfluorobutyramide ($\text{C}_3\text{F}_7\text{C(O)NH}_2$)

Aqueous ammonia (8 M, 4.3 mmol) was added to a round bottom flask along with 1 mL tetrahydrofuran and cooled on an ice bath. Perfluorobutyryl chloride (2 mmol) was added dropwise with vigorous stirring and the reaction mixture was allowed to warm to room temperature. The resultant solution was then extracted with a 1:1 mixture of ddH₂O/MTBE. The MTBE layer was removed and dried with anhydrous magnesium sulfate. Evaporation under a gentle stream of nitrogen gave perfluorobutyramide as a colorless semisolid. Analysis by ^{19}F NMR indicated approximately 50% contamination with PFBA. ^{19}F NMR (376 MHz, methanol- d_4): δ -82 (t, 3F, CF_3), -119 (s, 2F, $\text{CF}_2\text{-CON}$), -129 (s, 2F, $\text{CF}_2\text{-CF}_3$).

4.3.4 Relative rate kinetic experiments

Atmospheric oxidation experiments to determine the rates of reaction of EtFBA with Cl and OH were carried out at 296 K at the Ford Motor Company (Dearborn, MI) using a 140 L Pyrex photochemical smog chamber.¹⁰ Before use EtFBA was subjected by freeze-pump-thaw cycling to remove volatile impurities. Initial concentrations of EtFBA in the chamber experiments were 4.7-7.2 mTorr. The reference compounds ethylene (C_2H_4), acetylene (C_2H_2) or ethyl chloride ($\text{C}_2\text{H}_5\text{Cl}$) were present at an initial concentration of 4-10 mTorr. For oxidations using Cl atoms, chlorine gas (Cl_2) was added to an approximate concentration of 120 mTorr. For

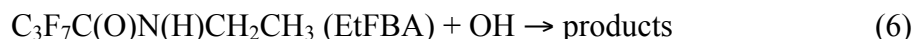
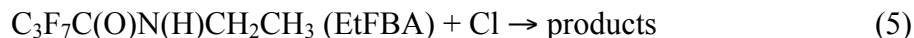
oxidations initiated by OH radical, methyl nitrite (CH_3ONO) was added to an approximate concentration of 100 mTorr. For reactions performed in the presence of NO_x , nitric oxide (NO) was added to a concentration of 8 mTorr. Diluent air (ultra pure) was added to achieve a pressure inside the smog chamber of 700 Torr. Photochemical oxidations were initiated using 22 fluorescent blacklamps (GE F15T80BL, 365 nm) surrounding the chamber. Chlorine atoms were generated by the photolysis of molecular chlorine:



Hydroxyl radicals were generated by the photolysis of methyl nitrite (CH_3ONO):



Reaction progress was monitored using a Mattson Sirius 100 Fourier transform infrared (FTIR) spectrometer with a 27 m pathlength and a resolution of 0.25 cm^{-1} . The concentrations of EtFBA and the reference compounds were monitored using their characteristic IR bands at 1525 cm^{-1} (EtFBA), 1300 cm^{-1} (C_2H_2), 1288 cm^{-1} ($\text{C}_2\text{H}_5\text{Cl}$) and 950 cm^{-1} (C_2H_4). Data points were collected after successive 5-10 s UV exposures and total reaction time generally did not exceed 60 s for reactions with Cl and 180 s for reactions with OH. Using the relative rate technique, bimolecular rate constants were obtained for the following reactions:



In the presence of a reference compound that also reacts with Cl or OH, the following reactions take place concurrently with reactions 5 and 6:



It can be shown (e.g. for experiments employing chlorine atoms) that the loss of EtFBA and the reference are related by the expression:

$$\ln \left(\frac{[\text{EtFBA}]_0}{[\text{EtFBA}]_t} \right) = \frac{k_5}{k_7} \ln \left(\frac{[\text{reference}]_0}{[\text{reference}]_t} \right) \quad (9)$$

where k_5 is the desired rate coefficient for the reaction of Cl with EtFBA and k_7 is the rate coefficient for the reference reaction. The slope of a plot of the decay of EtFBA versus the reference compound gives the rate coefficient ratio from which the rate of reaction with EtFBA can be determined. Typical UV irradiation times ranged from 5-10 seconds and were followed by acquisition of an infrared spectrum from which the loss of EtFBA and the reference compound were determined. The uncertainties reported for k_5 and k_6 include both two standard deviations in the slopes of the regression analyses and our estimate of potential systematic uncertainties in the spectral subtraction process which contributed approximately 5% uncertainty to the measure rate coefficient ratio.

Control experiments were performed that showed there was no discernable (<1%) loss of EtFBA via photolysis or partitioning to the walls of the smog chamber over the course of a typical oxidation experiment.

4.3.5 Offline sample collection

To characterize the products produced during the oxidation of EtFBA with Cl atoms, offline sampling was performed onto sampling media for subsequent analysis. The procedure using chlorine atom initiated oxidation was as described above, except that no reference compound was introduced and the smog chamber was pressurized with air to the atmospheric pressure (approximately 750 Torr). At specified timepoints, smog chamber air was withdrawn using a calibrated personal air sampler (1 L/min) into either an ORBO 605 Amberlite XAD-2 cartridge (Supelco, 400/200 mg) or bubbled through an aqueous 0.1 M sodium carbonate solution (pH 11) to convert any perfluorinated acyl fluorides formed in the chamber to the corresponding PFCAs. The five collection timepoints corresponded to EtFBA concentrations as determined by FTIR which were 78%, 48%, 12%, 3% and <1% of the initial levels. The sampling times were 5 min and two replicates for each sampling medium were taken. The chamber was evacuated and a new oxidation experiment started after each sample was collected with the exception of the last two sampling times. Air blanks and control samples were taken to ensure sample carryover in the chamber was not an issue. Offline samples were kept at 4°C until extraction.

4.3.6 GC-MS analysis

The XAD-2 cartridges were extracted using two 5 mL aliquots of ethyl acetate with the main and breakthrough beds being extracted separately. The two aliquots were later combined for GC-MS analysis. Samples were analyzed using an Agilent 7890A gas chromatograph interfaced with an Agilent 5975-inert mass spectrometer operating in positive chemical ionization (PCI) mode with methane as the reagent gas. All injections were 1 μ L and performed in the splitless mode with an inlet temperature of 250°C. Separation was achieved using an Agilent DB-1701 column (30 m x 0.25 mm x 0.25 μ m) at a constant helium flow rate of 0.9 mL/min. The oven program consisted of an initial hold at 50°C for 2 min, then a 10°C/min ramp to 120°C. The transfer line temperature was held at 280°C. Analytes were monitored in full scan mode to look for any possible volatile products of atmospheric oxidation.

4.3.7 LC-MS/MS analysis

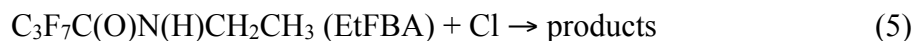
For quantification of TFA and PFPrA the aqueous extracts were neutralized using 3 M HCl and diluted 100 times using doubly distilled H₂O. For quantification of PFBA, 1 mL of each XAD extract was evaporated to dryness, reconstituted in 1 mL methanol and diluted 100 times using ddH₂O. Each sample was spiked with ¹³C₄-PFBA prior to analysis and was run on a Waters Xevo TQ-S mass spectrometer with an electrospray source interfaced with a Waters Acquity UPLC pump. Separation was achieved using a Waters Acquity BEH C₁₈ column (50 mm x 2.1 mm x 1.7 μ m). The LC program consisted of a gradient starting at 1% methanol for 0.5 min then ramping to 95% methanol over 1.5 min and hold for 1 min followed by a reduction back 1% methanol over 0.1 min and hold for 1.4 min. The flow rate was 0.5 mL/min and both mobile phase solvents contained 10 mM ammonium acetate as an ion-pairing agent. All injection

volumes were 5 μ L. The analytes were detected using multiple reaction monitoring with the transitions 112.9>68.94 (TFA), 162.97>68.94 (PFPrA) and 212.9>168.9 (PFBA) with argon as the collision gas. Internal calibration with $^{13}\text{C}_4$ -PFBA was used for TFA, PFPrA and PFBA quantification (216.9>171.9).

4.4 Results

4.4.1 Relative rate study of the reaction of Cl atoms with EtFBA

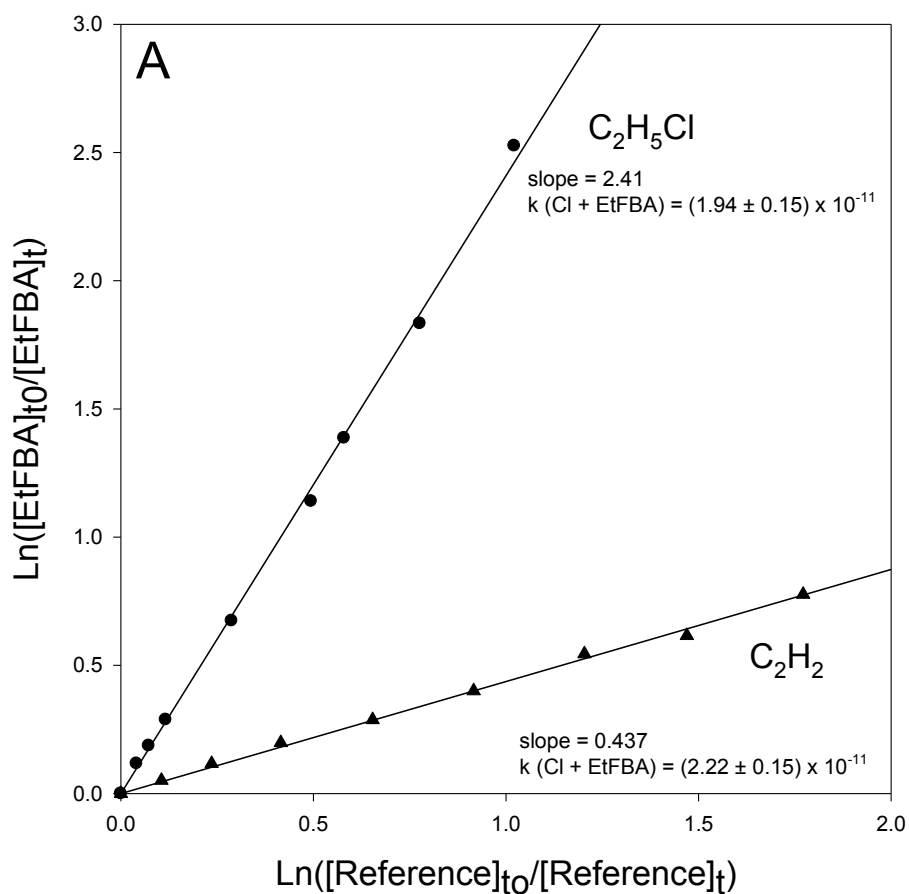
The rate coefficient for reaction 5 was measured in 700 Torr air using the relative rate technique with two competitors: ethyl chloride ($\text{C}_2\text{H}_5\text{Cl}$, reaction 10) and acetylene (C_2H_2 , reaction 11).

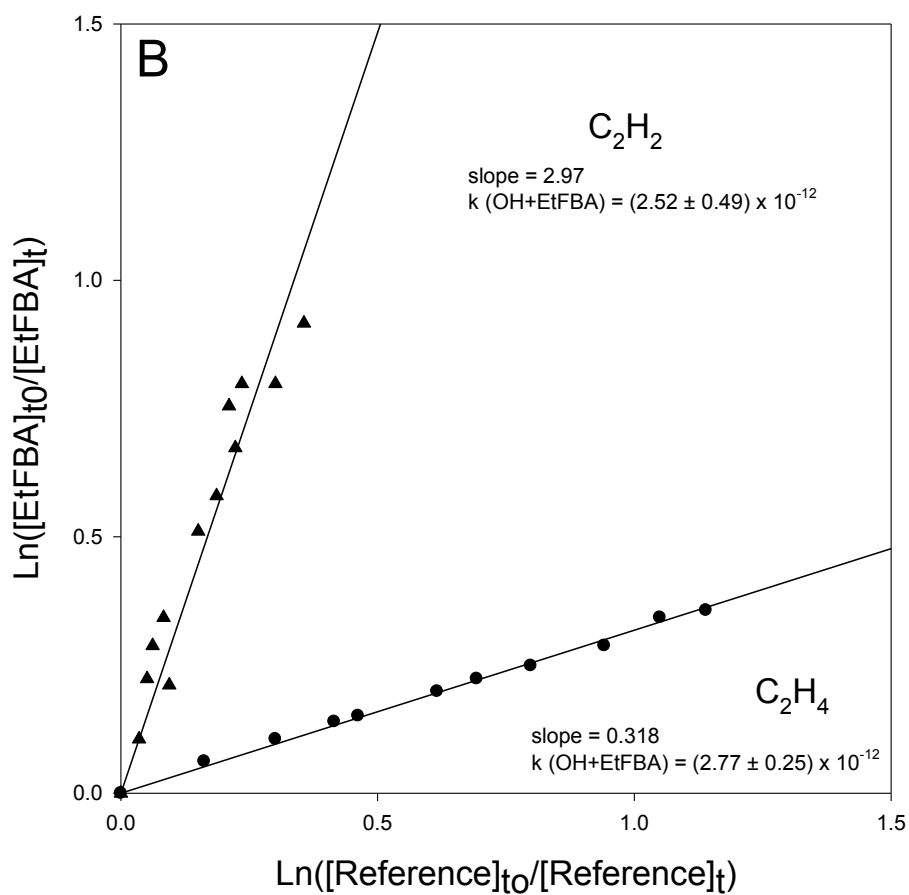


The kinetic plots are given in Figure 4.1A. The lines through the data sets are the linear fits which give values of $k_5/k_{10} = 2.41$ and $k_5/k_{11} = 0.437$. Using literature values^{11,12} for $k_{10} = 8.04 \times 10^{-12} \text{ cm}^3$ and $k_{11} = 5.07 \times 10^{-11}$ we derive $k_5 = (1.94 \pm 0.15) \times 10^{-11}$ and $(2.22 \pm 0.15) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ respectively. Within experimental error, the results obtained from the two reference compounds were indistinguishable. We cite a final value for k_5 that is the average of the two measurements with error limits encompassing the extremes of the individual determinations, $k_5 = (2.08 \pm 0.15) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. By contrast, the rate constant for the reaction of Cl with EtFBSA is $8.37 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ ⁸, making EtFBA 2.5 times more

reactive to chlorine atoms. This increase in reactivity can be explained by the amide functional group being a less powerful electron withdrawing group compared to the sulfonamide group in EtFBSA.

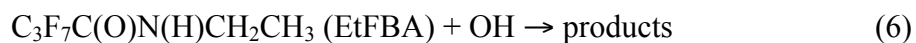
Figure 4.1: Relative rate kinetic plots for the reaction of EtFBA with A) chlorine atoms and B) hydroxyl radical. Molecular formulae given identify the competitor used in the relative rate experiment. Second order rate constants derived from each competitor are given along with one standard error.





4.4.2 Relative rate study of the reaction of OH radicals with EtFBA

The rate coefficient for reaction 6 was measured in 700 Torr using the relative rate technique with two competitors: acetylene (C_2H_2 , reaction 12) and ethylene (C_2H_4 , reaction 13).



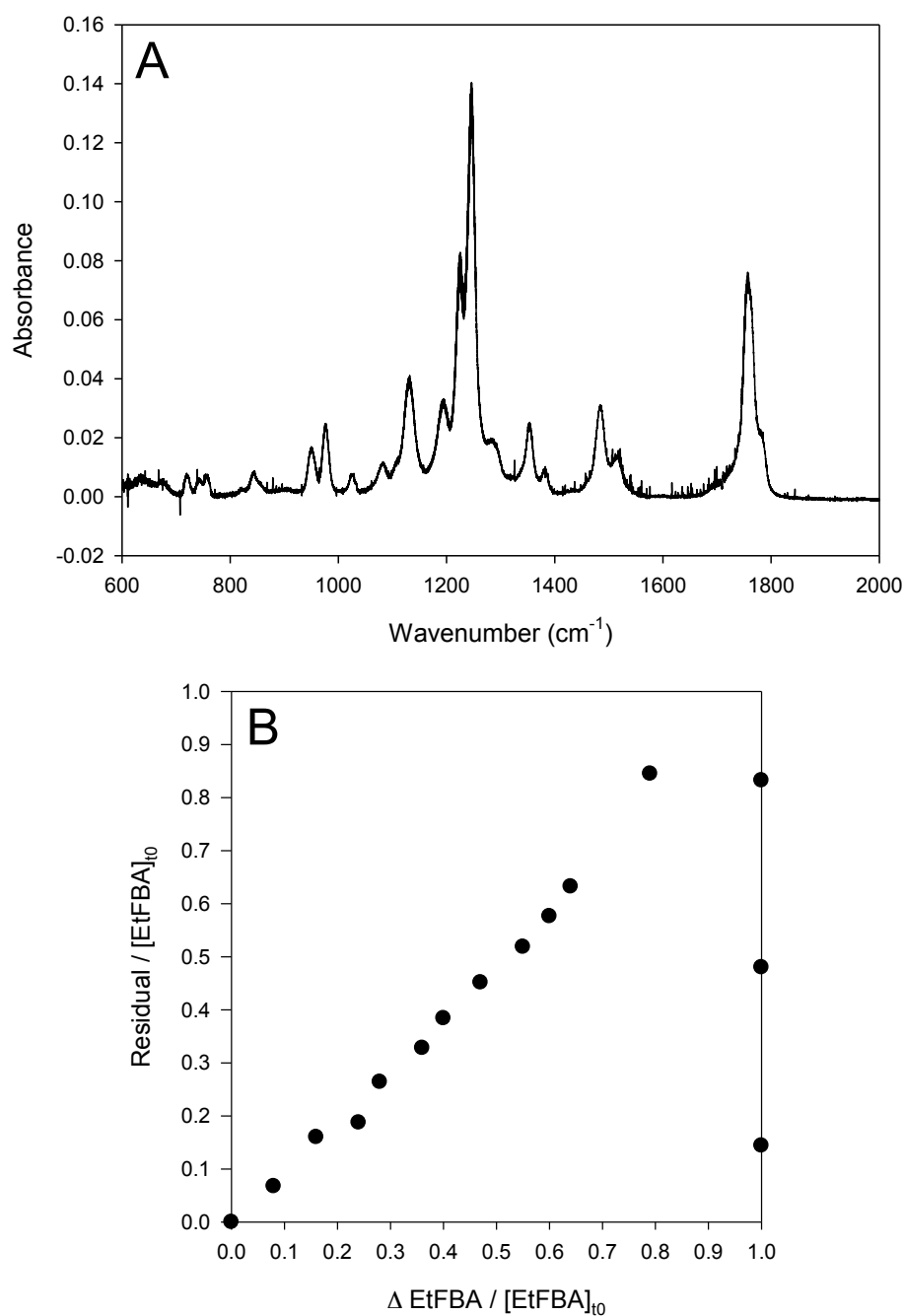
The kinetic data are given in Figure 4.1B. The lines through the data sets are the linear fits which give values of $k_6/k_{12} = 2.97$ and $k_6/k_{13} = 0.318$. Using literature values^{13,14} of $k_{12} = 8.5 \times 10^{-13}$ and $k_{13} = 8.7 \times 10^{-12}$ we derive $k_6 = (2.52 \pm 0.49) \times 10^{-12}$ and $(2.77 \pm 0.25) \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ respectively. Within experimental error, the results obtained from the two reference compounds were indistinguishable and there was no discernable difference in the reaction rates when NO was added to the smog chamber. We cite a final value for k_6 that is the average of the two measurements with error limits encompassing the extremes of the individual determinations, $k_6 = (2.65 \pm 0.50) \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. We can compare this result with $k(\text{OH} + \text{EtFBSA}) = (3.74 \pm 0.77) \times 10^{-13} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$.⁸ With respect to OH radicals, EtFBA is 7 times more reactive than EtFBSA. As with chlorine atoms, the increase in reactivity towards OH radicals can be explained by the amide functional group in EtFBA being a less powerful electron withdrawing group than the sulfonamide group in EtFBSA. Assuming a global average $[\text{OH}]$ of $1.0 \times 10^6 \text{ molecules cm}^{-3}$,¹⁵ gives an estimate of the atmospheric lifetime of EtFBA of approximately 4.4 days. By comparison, EtFBSA has an atmospheric lifetime of 31 days.⁸ Under most atmospherically relevant conditions, oxidation reactions with chlorine are not significant due to the generally low concentrations of Cl in the troposphere.¹⁶ EtFBA is not expected to react significantly with ozone and is not expected to undergo photolysis in the troposphere. Hence the atmospheric lifetime of EtFBA will be determined by reaction with OH radicals and is approximately 4.4 days.

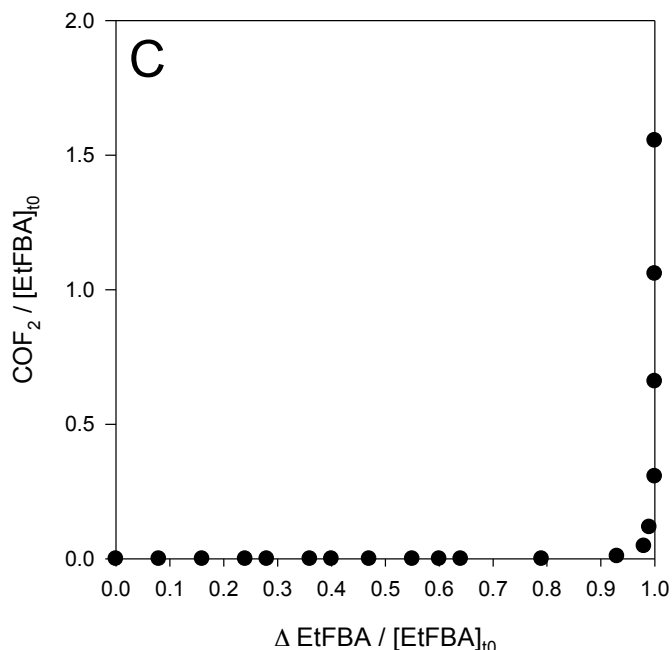
4.4.3 Product Analysis by FTIR

The reaction between EtFBA and either Cl or OH is expected to lead to one or more primary oxidation products which will oxidize further to give secondary and tertiary oxidation

products. The online FTIR spectrometer allows oxidation products to be measured and characterized within the smog chamber. In particular, COF_2 gives a very characteristic series of peaks, most notably the sharp band at 774 cm^{-1} .¹⁷ Product analysis by FTIR was performed using the chlorine atom initiated oxidation of EtFBA since the pathway of oxidation following reaction with chlorine atoms is expected to be similar to that for the more atmospherically relevant OH radicals. The IR product spectra for experiments using chlorine atoms are generally easier to interpret because of the absence of overlapping IR features associated with the methyl nitrite OH precursor and its oxidation products. A residual spectrum was obtained by subtracting out the spectral features of EtFBA in a chlorine initiated oxidation experiment after 16% of EtFBA had been consumed and is shown in Figure 4.2A. This spectrum is due to one or more primary oxidation products formed in the early stages of the reaction between EtFBA and Cl. As EtFBA is consumed, this residual signal increases steadily and was monitored at 1482 cm^{-1} throughout the reaction and plotted against the loss of EtFBA as shown in Figure 4.2B. The steady increase of the product feature at 1482 cm^{-1} followed by a steep loss concurrent with EtFBA being completely consumed suggests that with respect to chlorine atoms this primary oxidation product(s) is much less reactive to Cl. This would be expected for a product such as $\text{C}_3\text{F}_7\text{C(O)N(H)C(O)CH}_3$ where the reactive CH_2 group in EtFBA is replaced by a carbonyl group which is relatively unreactive to atmospheric oxidants.¹⁸

Figure 4.2: A) Residual FTIR spectrum showing the primary oxidation product(s) formed by the reaction of EtFBA with chlorine atoms, B) Residuals plot showing the formation of primary oxidation product(s) relative to the amount of EtFBA consumed and C) Plot showing the formation of COF_2 relative to the amount of EtFBA consumed.

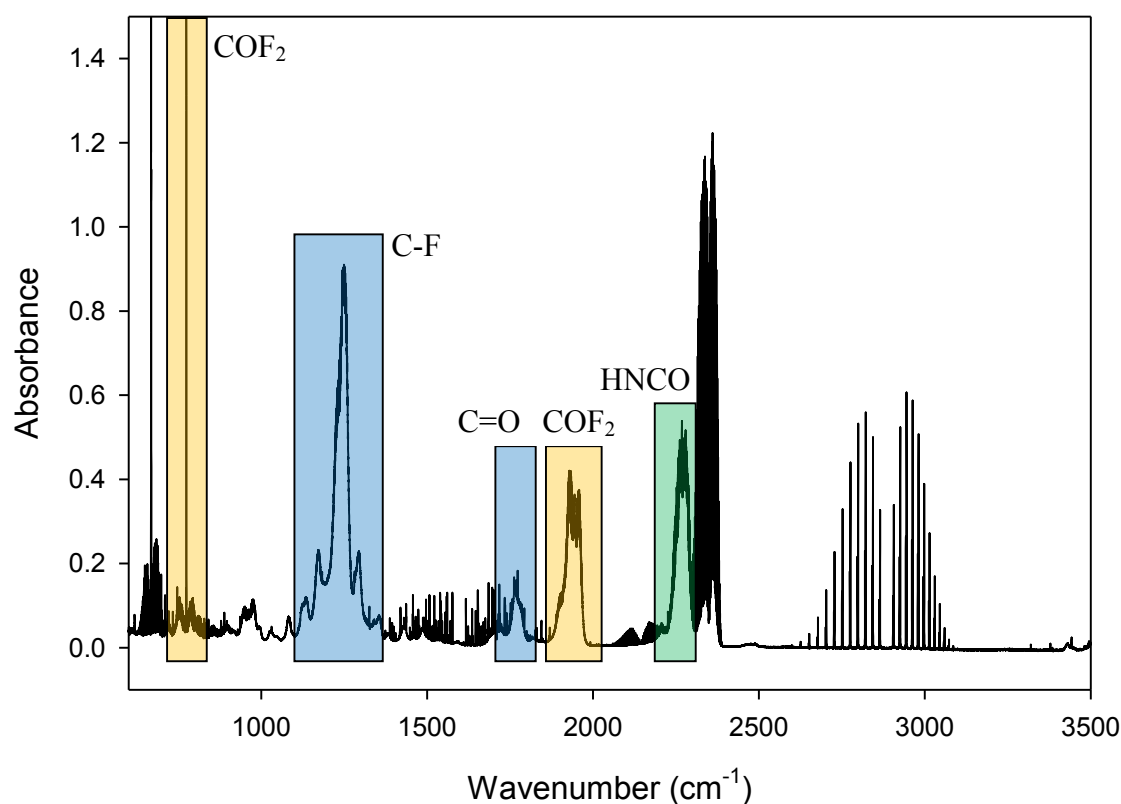




The production of COF_2 as a final oxidation product can also be tracked throughout the reaction of EtFBA with Cl as shown in Figure 4.2C. No COF_2 is seen until over 90% of EtFBA has been consumed, after which production rapidly increases. The production of COF_2 tracks the decline of the primary oxidation product(s), suggesting that degradation of one or more of the initial products of EtFBA oxidation leads to COF_2 . Using a calibrated gas standard of COF_2 , the molar yield of COF_2 after the final UV exposure was determined to be 160% (see Figure 4.2C).

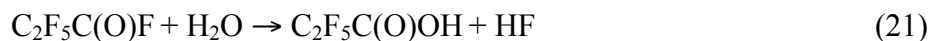
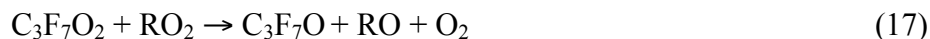
In addition to the primary oxidation product(s) and COF_2 , other signals in the FTIR can be seen as the reaction progresses. The formation of HCl and CO_2 are both expected from oxidation reactions by chlorine atoms. One further signal in the IR at 9 min UV irradiation (shown in Figure 4.3) appears at 2270 cm^{-1} which by comparison to literature spectra we identify as isocyanic acid (HNCO).

Figure 4.3: FTIR spectrum of the reaction of EtFBA with chlorine atoms after 9 min UV exposure showing the formation of multiple products as identified.



This compound has previously been observed in the atmospheric oxidation of other amides such as formamide and acetamide¹⁹ during which a nitrogenous radical intermediate RC(O)NH unimolecularly decomposes releasing HNCO and an alkyl radical. In contrast, no signals corresponding to ethyl isocyanate were observed. In the case of EtFBA, the formation of HNCO indicates the amide functional group has been cleaved, releasing the perfluorinated radical C_3F_7 as shown in reaction 14. The $\text{C}_3\text{F}_7\text{C(O)NH}$ radical could be formed following the oxidation of primary oxidation products such as $\text{C}_3\text{F}_7\text{C(O)NH}_2$, $\text{C}_3\text{F}_7\text{C(O)N(H)CH}_2\text{CHO}$, or $\text{C}_3\text{F}_7\text{C(O)N(H)C(O)CH}_3$. Perfluorinated radicals have been shown to undergo a series of

reactions producing COF_2 (reactions 14-18) as the major product and PFCAs (reactions 14,15,19-21) as minor products.²⁰



The presence of COF_2 in the FTIR spectra indicates the formation of perfluorinated radicals and suggests that PFCAs may also be present. This possibility was investigated using offline sampling.

4.4.4 Product analysis by offline sampling

Offline samples were collected using two complementary sampling media: XAD-2 cartridges for volatile analysis and aqueous base sampling for PFCA analysis.

Analysis of the XAD-2 extracts by GC-MS reveal the presence of three products of EtFBA being formed in the smog chamber after reacting with chlorine atoms. A sample GC

chromatogram is given in Figure 4.4 and shows three products (A, B and C) along with residual EtFBA after 60 s UV irradiation (3% EtFBA remaining).

Figure 4.4: GC-MS extracted ion chromatograms ($m/z=214$ and $m/z=242$) of the XAD-2 extract corresponding to chamber air sampled after 1 min UV exposure showing the formation of three products (A, B and C) as well as residual EtFBA. Product C has been identified as $C_3F_7C(O)NH_2$.

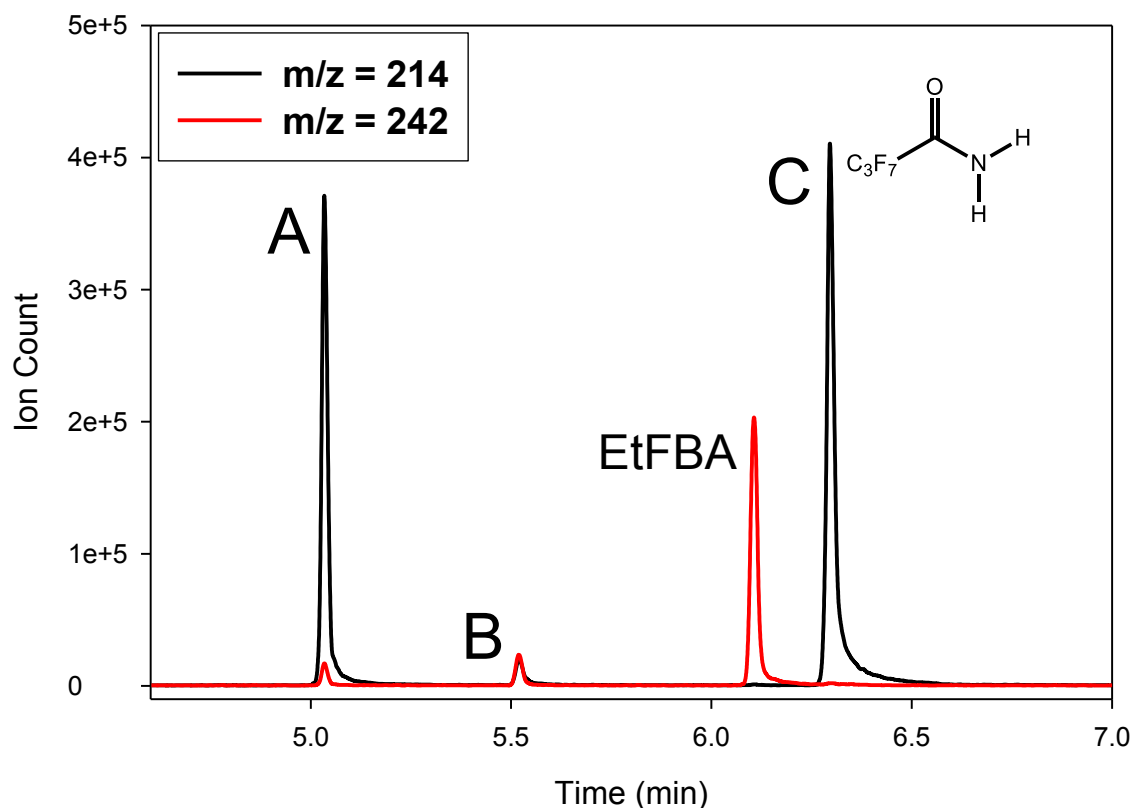
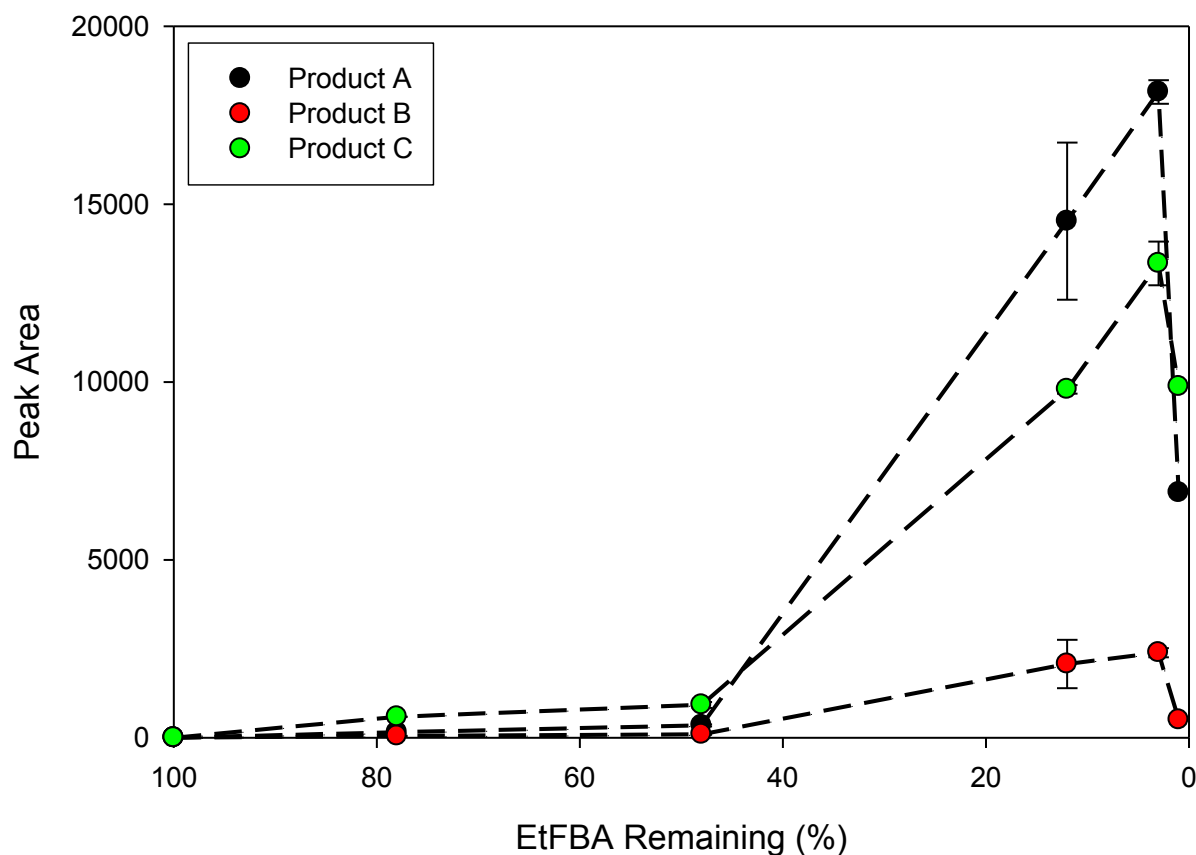


Figure 4.5 shows a plot of the peak areas of three products versus the relative quantity of EtFBA remaining in the chamber. The shape of each product curve suggests each is a primary oxidation product that steadily grows in concentration until the penultimate timepoint, at which time they are consumed to give further or final products of oxidation that are not seen by GC-MS. Therefore, we propose the residual IR spectrum shown in Figure 4.2A is a combination of the spectra of the three compounds detected by GC-MS.

Figure 4.5: GC-MS peak areas of products A, B and C from Figure 4.4 at each collection timepoint. Product C has been identified as $\text{C}_3\text{F}_7\text{C}(\text{O})\text{NH}_2$.



Product C elutes after EtFBA and has been identified as perfluorobutyramide by comparison of peak shape, retention time and mass spectrum to a synthesized standard. Perfluorobutyramide is the *N*-dealkylation product of EtFBA and the strength of its GC signal suggests this reaction pathway is a major fate of EtFBA upon atmospheric oxidation. While such dealkylation reactions are well known in the aqueous phase, until recently²¹ it has been unclear how this process might proceed in gas-phase reactions. It is now established that gas-phase oxidation of amines leads to formation of imines in significant yields and that imines undergo hydrolysis to give the dealkylation products.²¹ In the case of EtFBA the dominant imine intermediate would be $\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}=\text{CHCH}_3$ which would hydrolyze to give $\text{C}_3\text{F}_7\text{C}(\text{O})\text{NH}_2$ and

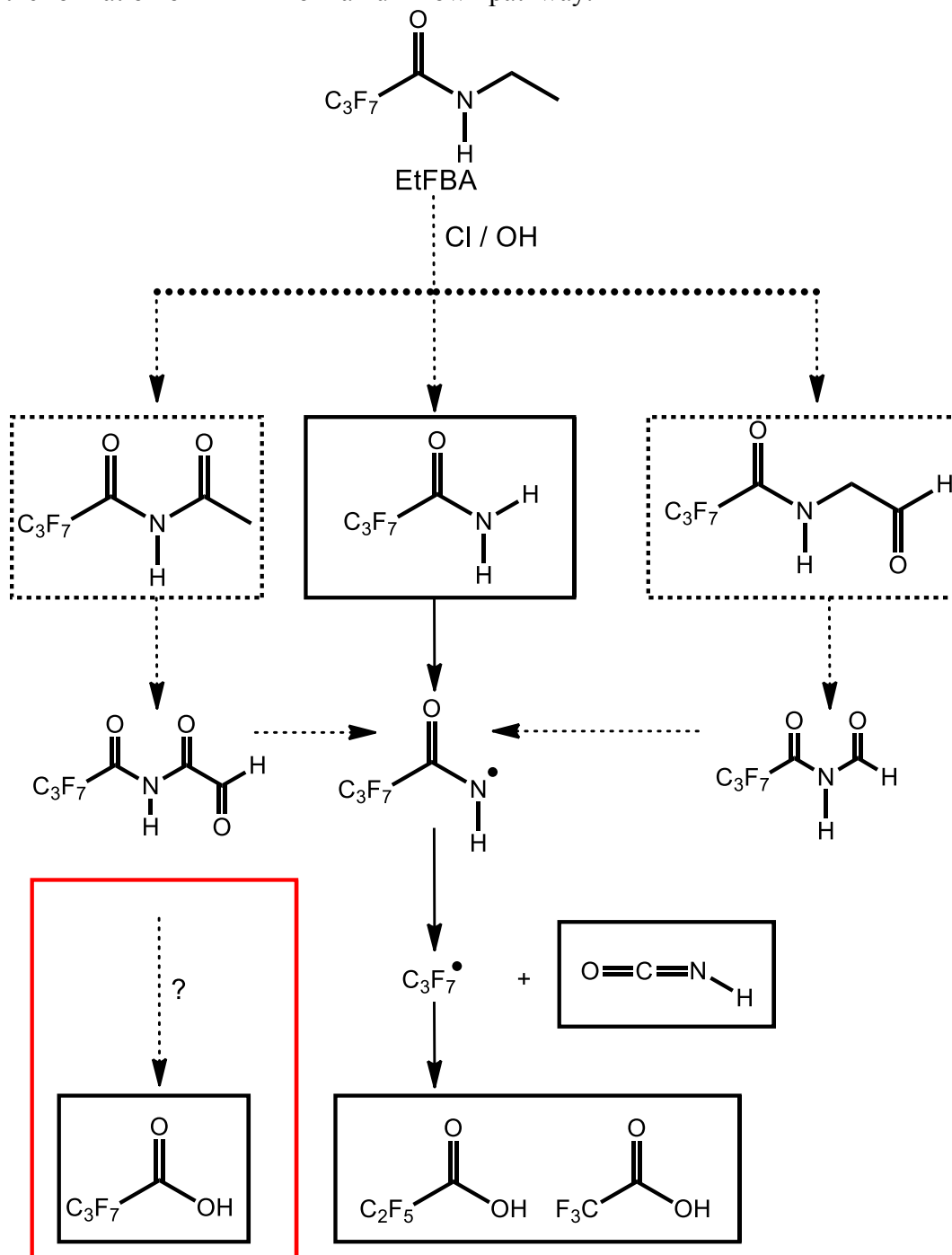
CH₃CHO. At present, we are unable to discern whether this reaction is taking place within the chamber itself, or a result of the high temperatures in the GC inlet. Two polyfluorinated sulfonamide compounds have previously been shown to undergo *N*-dealkylation under atmospheric conditions^{8,9} thus providing precedence for their amide analogs to undergo the same degradation pathway. In the present case the *N*-dealkylation product is perfluorobutyramide (C₃F₇C(O)NH₂). In the smog chamber, perfluorobutyramide can react with chlorine atoms to give the nitrogen-centered radical C₃F₇C(O)NH. This species can then eliminate isocyanic acid¹⁹ (HNCO) as shown in reaction 14, which was detected by FTIR at the last timepoint. The other product is the perfluorinated radical C₃F₇, which can form COF₂, TFA and PFPrA as described earlier.

The other two primary oxidation products detected by GC-MS elute prior to EtFBA, with product A being much more prominent than product B. From the structure of EtFBA (C₃F₇C(O)N(H)CH₂CH₃) it is possible to predict two products from atmospheric oxidation; an imide (C₃F₇C(O)N(H)C(O)CH₃) and an aldehyde (C₃F₇C(O)N(H)CH₂C(O)H). The imide is expected to be formed to a much greater extent than the aldehyde due to abstraction taking place at a secondary carbon and adjacent to a nitrogen atom¹⁸. Product A gives M+1 peaks at 256 and 214 in its PCI mass spectrum which would suggest it being the imide product. However, the imide would not be expected to elute prior to EtFBA after oxidation of a CH₂ group to a more polar C=O functionality. Likewise, we can not prove product B is the aldehyde compound based on its mass spectrum alone without a standard and we do not expect it to elute prior to EtFBA. Unfortunately, efforts to synthesize standards of C₃F₇C(O)N(H)C(O)CH₃ and C₃F₇-C(O)N(H)CH₂C(O)H for retention time comparison were unsuccessful.

Both of the compounds proposed for products A and B will lead to the same nitrogen centered radical, $\text{C}_3\text{F}_7\text{C}(\text{O})\text{NH}$, upon further atmospheric oxidation as shown in 4.6. In both cases, an aldehyde intermediate would be formed although no evidence of any secondary oxidation products were found in the smog chamber. Assuming all three primary oxidation products can be produced under realistic atmospheric conditions, the expected yield for the perfluorinated radical C_3F_7 should be high.

Analysis of the aqueous base extracts show both TFA and PFPrA are formed at the final timepoint of the EtFBA oxidation reaction with Cl (180 s UV irradiation, EtFBA at <1% of initial concentration). Prior to the final timepoint, TFA and PFPrA were not detected. The yields of TFA and PFPrA were 0.3% and 0.3% by mass respectively. As the yield of COF_2 after 180 s UV exposure was 18% by mass, this “unzipping” pathway is highly preferred over PFCA production in the chamber. Perfluorobutanoic acid (PFBA) was also detected at much higher concentrations in the aqueous samples at all timepoints, however this was due to base-catalyzed hydrolysis of EtFBA and its primary oxidation products at pH 11 during sampling. Using the data from the aqueous samples alone, it is not possible to determine if PFBA had been formed within the chamber.

Figure 4.6: Simplified atmospheric oxidation pathway of EtFBA leading to perfluorinated acid formation. Solid arrows represent pathways confirmed in the present study and dashed arrows show plausible but unconfirmed pathways. Compounds in solid black boxes represent confirmed products whereas dashed boxes show unconfirmed products from the present study. The red box shows the formation of PFBA from an unknown pathway.



The XAD-2 extracts were analyzed by LC-MS/MS to determine if PFBA or its corresponding acyl fluoride had been unambiguously formed in the smog chamber. PFBA was detected at significantly higher concentrations compared to TFA and PFPrA and reached a maximum yield of 16% by mass as EtFBA decreased to 3% of its initial concentration. The PFBA concentration in the chamber then decreased to 4% at the final timepoint when EtFBA decreased below the limits of detection. It is somewhat puzzling that PFBA decreases in concentration within the chamber because we are not aware of any atmospheric degradation pathway. One possibility is adsorption of PFBA to the smog chamber walls.

The detection of PFBA in the XAD extracts suggests the historical eight carbon amides, MeFOA and EtFOA, might form branched PFOA upon atmospheric oxidation in addition to shorter chained homologs. During the oxidation of EtFBA, PFBA can not be formed from the perfluorinated radical C_3F_7 . One radical intermediate that could lead to PFBA formation is the perfluorinated acyl radical $C_3F_7C(O)$ which can add O_2 and then react with HO_2 to give PFBA.^{22,23} However, we can exclude the $C_3F_7C(O)O_2 + HO_2$ reaction as a significant source of PFBA on the basis of the relative yields of COF_2 and PFBA. For every $C_3F_7C(O)$ radical that adds O_2 to give $C_3F_7C(O)O_2$, there are approximately 4 $C_3F_7C(O)$ radicals that decompose to give C_3F_7 radicals which then react to give COF_2 .²³ Also, not all $C_3F_7C(O)O_2$ radicals will react with HO_2 and of those that do, the yield of PFBA is only 53%. Hence, if the $C_3F_7C(O)O_2 + HO_2$ reaction was the source of the observed PFBA we should observe the formation of COF_2 in a yield at least 8 times that of PFBA. However, when 97% of EtFBA was consumed the yield of COF_2 was only 5% (see Figure 2C), substantially *lower* than the 16% yield of PFBA. The source of the PFBA observed in the smog chamber experiments is unclear at the present time. We can

not conclusively rule out the possibility that observed PFBA was an artifact of sampling or extraction (although control experiments conducted with the same reaction mixture but without UV irradiation) did not reveal any PFBA formation.

4.4.5 Mass balance

Using the data from the present study it is possible to derive a mass balance of the products formed from the oxidation of EtFBA using chlorine atoms as a suitable proxy for hydroxyl radicals. The maximal mass yields of products detected, in descending order, were: COF₂ (18%), PFBA (16%), TFA (0.3%) and PFPrA (0.3%) giving a sum of 35% with the remainder consisting of unreacted EtFBA and primary oxidation products. The PFAMs can be compared to fluorinated sulfonamides which have previously been shown to be atmospheric sources of branched perfluorinated acids.^{8,9} The atmospheric oxidation of EtFBA is best compared to its sulfonamide analog EtFBSA (C₄F₉SO₂N(H)CH₂CH₃).⁸ Qualitatively, the two compounds share similar reaction profiles in the smog chamber. The starting material degrades to form primary oxidation products with carbonyl groups that are in turn oxidized more slowly. The release and unzipping of the fluorinated chain occurs late in the reaction and rapidly rises, at which time PFCAs are produced. Martin et al. reported yields of PFBA (0.33%), PFPrA (0.11%), TFA (0.09%) and COF₂ (0.65%) when EtFBSA has been depleted to 8% of its starting concentration.⁸

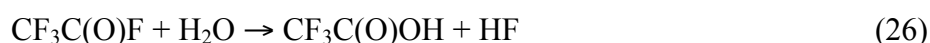
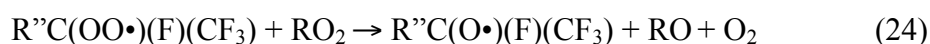
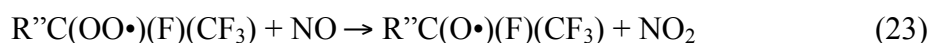
4.5 Environmental Implications

In the present study, the polyfluorinated amide *N*-ethylperfluorobutyramide (EtFBA) was chosen for investigation as a more volatile surrogate for the historically relevant compound

N-ethylperfluorooctanamide (EtFOA). A previous study suggested EtFOA was an environmental contaminant prior to the 3M phaseout of POSF-based materials in 2001 and was detected in a wide variety of sulfonamide compounds including its methyl analog, MeFOA.⁶ Both MeFOA and EtFOA are predicted to be ECF PFOA precursors by enzyme-catalyzed hydrolysis *in vivo*. It was also proposed that due to their volatility, PFAMs might have been present as atmospheric contaminants and therefore susceptible to atmospheric oxidation. In the present study it is shown that EtFBA degrades to produce small amounts of perfluoropropanoic acid (PFPrA) and trifluoroacetic acid (TFA). The observation of HNCO, a significant product in the present work and in previous studies of the atmospheric oxidation of amides suggests the gas-phase atmospheric oxidation of PFAMs of the general formula $C_xF_{2x+1}C(O)N(H)(R)$, including MeFOA, leads to the release of C_xF_{2x-1} radicals. It has been shown that C_xF_{2x+1} radicals can participate in a series of reactions in the atmosphere resulting in the formation of a suite of perfluorocarboxylic acids of the general formula $C_{x-1}F_{2x-1}C(O)OH$ and all shorter chained homologs.

The formation of PFBA in significant yields from EtFBA in the chamber experiments is intriguing and may have important environmental consequences. If the reactions leading to PFBA in the chamber are representative of those occurring in the environment then our observations would imply that historical eight carbon PFAMs would produce PFOA atmospherically. We predict similar reaction kinetics for EtFOA as EtFBA since the length of a perfluorinated chain does not affect the reaction rate with OH.²⁴ As with sulfonamides, historical eight carbon PFAMs such as MeFOA and EtFOA contain branched constitutional isomers at an approximate concentration of 30%.⁶ Therefore, we predict atmospheric oxidation of these

PFAMs will give a mixture of linear and branched PFCAs. A branched PFCA will result when reactions 19-21 occur for primary perfluorinated radicals (i.e. $\text{RCF}_2\cdot$, where R is a branched perfluoroalkyl group). Unzipping occurs via successive elimination of CF_2O units until a secondary perfluorinated radical is formed. The corresponding alkoxy radical ($\text{R}'\text{CF}(\text{O})\text{R}''$) will decompose to give an acyl fluoride and alkyl radical products ($\text{R}'\text{C}(\text{O})\text{F} + \text{R}''\cdot$ and/or $\text{R}''\text{C}(\text{O})\text{F} + \text{R}'\cdot$) as illustrated below in an example where $\text{R}' = \text{CF}_3$.



The available data suggest that branched PFCAs will result from the atmospheric oxidation of historical eight carbon PFAMs and that the ratio of linear to branched PFCAs will increase as the chain length of the PFCA decreases.

Branched isomers of PFOA have been detected in the Canadian Arctic in locations not accessible to oceanic transport such as Amituk Lake surface water and Char Lake sediment.² The source of this contamination could be due to a combination of polyfluorinated sulfonamide and PFAM oxidation in the Arctic atmosphere where $[\text{NO}_x]$ is very low.²⁵ The relative importance of each is hard to predict without historical measurements of PFAM atmospheric concentrations however the maximum PFAM concentration should be no higher than 1% of the sulfonamide

concentration.^{6,7} In 2001, the sulfonamide concentrations in North American urban atmospheres was approximately 80 pg m^{-3} although the variability was very high and depended on sampling locations and local conditions.^{26,27} Therefore, PFAM concentrations should not have exceeded 0.8 pg m^{-3} , however the present study suggests PFCA yields may be significantly higher for PFAMs compared to sulfonamides. The ultimate PFCA yield depends on a tradeoff between these two values and will vary depending on local atmospheric conditions.

The atmospheric lifetime of EtFOA is estimated to be 4.4 days and is not sufficient to reach the Arctic assuming an average wind speed of 13.8 km h^{-1} ²⁴ and a distance from the center of the contiguous United States to Resolute, Nunavut of 3900 km. However, the primary oxidation products of EtFOA are all expected to have much longer lifetimes with respect to reaction with OH and could be capable of contaminating Arctic air. In particular, perfluorobutyramide ($\text{C}_3\text{F}_7\text{C}(\text{O})\text{NH}_2$) should have a lifetime at least 7 times that of EtFBA as derived from a study on aqueous OH oxidations on simple amides.²⁸ This is sufficient to travel the required distance to the Canadian Arctic. Hence, the PFAMs could have served as an atmospheric source of branched PFCA isomers to the environment via their primary oxidation products.

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CHAPTER FIVE

Enzymatic Kinetic Parameters for Polyfluorinated Alkyl Phosphate Hydrolysis by Alkaline Phosphatase

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5.1 Abstract

The hydrolysis kinetics of three polyfluorinated alkyl phosphate monoesters (monoPAPs), differing in fluorinated chain length, were determined using bovine intestinal alkaline phosphatase to catalyze the reaction. Kinetic values were also determined for analogous hydrogenated phosphate monoesters to elucidate the effects of the fluorinated chain on the rate of enzymatic hydrolysis. Michaelis constants (K_M) were obtained by a competition kinetics technique in the presence of p-nitrophenyl phosphate (PNPP) using UV-Vis spectroscopy. Relative to K_M (PNPP), Michaelis constants for monoPAPs ranged from 0.9 to 2.1 compared with hydrogenated phosphates which ranged from 4.0 to 13.0. Specificity constants (k_{cat}/K_M) were determined by monitoring rates of product alcohol formation at low substrate concentrations using GC-MS. The experimental values for k_{cat}/K_M averaged as $1.1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for monoPAPs compared with $3.8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ for hexyl phosphate. This suggests the electron withdrawing nature of the fluorinated chain enhanced the alcohol leaving group ability. The results were used in a simple model to suggest that monoPAPs in a typical mammalian digestive tract would hydrolyze in approximately 100 s, supporting a previous study that shows its absence after a dosing study in rats.

5.2 Introduction

The perfluorinated carboxylic acids (PFCAs) are a class of organic pollutants that have received much attention in recent years due to their extreme environmental persistence. Numerous studies have measured their concentrations in human blood samples worldwide^{1,2,3} and understanding sources of human exposure to these compounds is of high importance. Humans can either be exposed to PFCA compounds directly from the environment or exposure

can take place by biological transformation of the many PFCA precursor fluorochemicals that are in commercial usage. A recent critical review concluded the indirect exposure pathway represents a significant portion of human PFCA contamination.⁴

One class of polyfluorinated surfactants that could represent a sizable quantity of indirect human exposure is the polyfluorinated alkyl phosphates (PAPs). The general structure of PAPs consists of a hydrophilic phosphate head group bonded to either one (monoPAPs) or two (diPAPs) polyfluorinated tails, which impart both water and oil repellency. Both monoPAPs and diPAPs are used extensively in the food contact paper industry, as their fluorinated chains make them both hydrophobic and lipophobic. The polyfluorinated groups in PAPs are synthesized by telomerization, which results in an even number of carbon atoms in the fluorinated tail (usually four, six, eight or 10) and a hydrogenated ethylene moiety that links the fluorinated chain with the phosphate head group. The PAP monoesters are named “x:2 monoPAP” where x represents the number of fluorinated carbons in the aliphatic chain. Likewise, the symmetrical PAP diesters are named “x:2 diPAP”.

Their presence has been detected in several food packaging materials,⁵ and studies have shown their ability to migrate from food packaging into various food simulants,⁶ illustrating their potential for human exposure. More importantly, diPAPs were recently detected in human blood,⁷ with the 6:2 diPAP being the most prevalent congener. The monoPAPs were not analyzed in that study, so their concentrations in human blood are unknown. Since the first degradation product in diPAP digestion is likely the corresponding monoPAP, human exposure to monoPAP congeners from both internal and external sources is a likely scenario.

Recently, monoPAPs and diPAPs were shown to undergo biodegradation in both microbes⁸ and rats⁹ to produce PFCAs as the end products of metabolism. In particular, D'eon and Mabury⁹ did not detect monoPAPs of any chain length in blood after oral gavage dosing. This suggests monoPAPs are rapidly degraded within the organism, although their site of metabolism was unknown.

The first step in the degradation of monoPAPs is hydrolysis of the phosphate head group to produce the corresponding fluorotelomer alcohol (FTOH) and inorganic phosphate. Alkyl phosphate monoesters are among the most stable of functional groups and are extremely slow to hydrolyze under abiotic environmental conditions. The estimated lifetime of an alkyl phosphate monoester in its dianionic form at ambient temperature is 1.1×10^{12} years.¹⁰ Although a recent computational study suggested PAPs could hydrolyze much more rapidly,¹¹ the results are likely in error as the anionic nature of PAPs at environmental pH was not taken into account in the model (for 4:2 monoPAP $pK_{a1} = 1.2$, $pK_{a2} = 5.0$, calculated using SPARC on-line v 4.6; <http://archemcalc.com/sparc>).¹² The rate determining step of the hydrolysis reaction, dissociation of the alkoxide leaving group,¹³ is facilitated by electron withdrawing groups and resonance stabilization. The phosphatase enzyme superfamily catalyzes these monoester hydrolysis reactions in vivo and possesses some of the highest rate enhancements known for enzymatic catalysis; a review detailing the mechanisms of hydrolysis was recently published.¹⁴ Alkaline phosphatase (AP) enzymes comprise a subset of this superfamily and exhibit optimum in vitro activity at elevated pH. The enzyme from *E. coli* is the best studied AP, although mammalian APs have also been investigated and found to have similar active sites and catalytic mechanism to the *E. coli* enzyme despite their 25 to 30% primary sequence homology.¹⁵

Alkaline phosphatases possess a negative feedback mechanism, whereby the inorganic phosphate product binds non-covalently to the active site as a competitive inhibitor; this is well known for both *E. coli* AP¹⁶ and bovine AP.¹⁷ This requires any compound under study to be completely free from inorganic phosphate contamination.

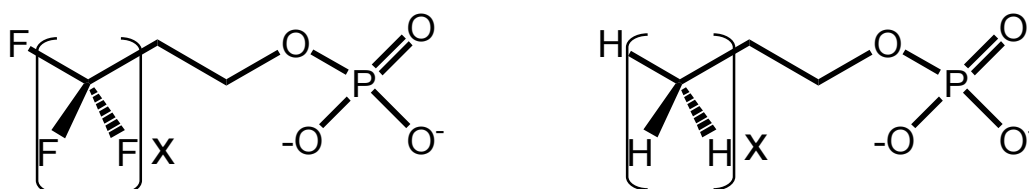
Specificity constants for *E. coli* AP were previously determined for a variety of alkyl phosphates using a radioactivity assay; a strong leaving group dependence was found.¹⁶ If the leaving group alkoxide is stabilized by an electron withdrawing group, the hydrolysis rate should increase. This supports the theory that the rate-determining step of AP catalyzed hydrolysis is phosphorylation of the serine nucleophile in the active site, concurrent with the departure of the alkoxide leaving group from the monoester.

Since mammalian alkaline phosphatases are found predominately in the surface membranes of intestinal microvilli,¹⁸ it is a reasonable hypothesis that hydrolysis within the gut represents the initial step in monoPAP biodegradation. The monoPAPs contain an electron withdrawing group in the form of the fluorinated tail, although this group is separated from the phosphate head group by a hydrogenated group which would attenuate its inductive effects. Hence it is not easy to predict what the relative rate of monoPAP hydrolysis in the body would be compared to a fully hydrogenated phosphate ester (HPME).

The objective of the present study was to measure the enzymatic parameters k_{cat} and K_M for a variety of fluorinated phosphate monoesters (monoPAPs) reacting with AP and compare them to their HPME analogs. General structures of monoPAPs and HPMEs in the present study

are shown in Figure 5.1. Using these data, we attempt to rationalize, using a simple intestinal model, the lack of monoPAPs found in rat tissues by D'eon and Mabury.⁹

Figure 5.1: General structures of both fluorotelomer and hydrogenated phosphate monoesters in the present study ($x = 4, 6, 8, 10$) in their ionized forms at pH 8.5.



5.3 Materials and Methods

5.3.1 Chemicals

The reagents 1-hexanol, 1-octanol, 1-decanol, pyrophosphoric acid, Trizma hydrochloride (Tris), p-nitrophenyl phosphate (disodium hexahydrate salt) and triethylamine were purchased from Sigma-Aldrich. The fluorinated alcohols 1H,1H,2H,2H-perfluorohexanol (4:2 FTOH), 1H,1H,2H,2H-perfluorooctanol (6:2 FTOH), 1H,1H,2H,2H-perfluorodecanol (8:2 FTOH) and 1H,1H,2H,2H-perfluorododecanol (10:2 FTOH) were purchased from SynQuest Laboratories. Ethyl acetate (Omnisolv grade) and methyl t-butyl ether (Omnisolv grade) were purchased from EMD. Dodecylphosphoric acid was purchased from Alfa-Aesar.

5.3.2 Synthesis of hydrogenated and polyfluorinated phosphate monoesters

Both hydrogenated phosphate monoesters (HPMEs) and polyfluorinated phosphate monoesters (monoPAPs) were synthesized based on the methods of Nelson et al.¹⁹ In a round bottom flask, the reagent fluorotelomer (~1 g) or hydrogenated alcohol (~2 g) was added to an excess of liquified pyrophosphoric acid (~5 mL) which resulted in the mixture turning cloudy.

After the reaction mixtures clarified, they were left to stir vigorously for three additional days before workup. To isolate the monoester product, the reaction mixture was shaken vigorously with 50:50 methyl t-butyl ether (MTBE):doubly distilled (dd)H₂O to remove the orthophosphoric acid reaction byproduct. The organic layer was removed and extracted with an equal volume of 1 N aqueous sodium hydroxide, leaving unreacted alcohol in the ether phase. Finally, the aqueous layer was acidified to pH 0 using concentrated aqueous hydrochloric acid. This resulted in precipitation of the phosphate monoester product. This mixture was extracted with an equal volume of MTBE and the organic layer dried using sodium sulfate before being evaporated under reduced pressure to give the desired phosphoric acid product. Hexyl phosphate, octyl phosphate, 4:2 monoPAP and 6:2 monoPAP were isolated as viscous oils, whereas decyl phosphate and 8:2 monoPAP were white solids. Identities and purities were confirmed by ¹H (400 MHz) and ³¹P NMR (161.8 MHz) as well as GC-MS in positive chemical ionization mode (maximum 1% FTOH impurity in 6:2 monoPAP). Most importantly, ³¹P NMR (161.8 MHz) with no decoupling channels activated showed only a triplet for every compound which confirmed no inorganic phosphate was present in the reaction product. Reaction yields were significantly higher for the HPMEs (average 38%) compared to the monoPAPs (average 14%). For monoPAPs the yields decreased as perfluorinated chain length increased. The 10:2 monoPAP syntheses did not result in appreciable amounts of pure product, leading to its omission in the present study.

5.3.3 Alkaline phosphatase enzyme

Bovine intestinal alkaline phosphatase (AP) was purchased from Sigma-Aldrich (P6774-2KU). Its monomeric molecular weight was determined to be 69695 Da using an Applied

Biosystems QStar quadrupole time of flight mass spectrometer equipped with an electrospray ionization source in positive mode. The mobile phase was 80% water, 20% methanol at a flow rate of 0.1 mL/min. The enzyme was dissolved in 0.1% aqueous formic acid. This mass is in good agreement with a previously reported value of approximately 69000 Da per monomer²⁰ and is more accurate. The stock solution provided was at a concentration of 214 μM and was diluted to working concentrations using 50 mM Tris buffer (pH 8.5) and kept at 4°C until used for experiments. Over time, the K_M of the enzyme was found to increase inconsistently (roughly 10 μM /week), necessitating positive controls be performed for each set of kinetic experiments.

5.3.4 Competition kinetics experiments to determine K_M for phosphate monoesters

All experiments were carried out in disposable polystyrene cuvettes (path length 1 cm, VWR Scientific). The solvent used in every case was 50 mM Tris buffer (pH 8.5) with a total volume of 1.5 mL. The temperature for every experiment was 22°C. The compound p-nitrophenyl phosphate (PNPP) was used as a colormetric probe to determine the enzymatic kinetic parameters using a Perkin-Elmer Lambda 12 UV-Vis spectrophotometer operating at 405 nm. Absorbance data were taken every 2 s for a total run time of 90 s. Control Michaelis-Menten kinetic studies were conducted using PNPP alone at six concentrations ranging from 15 to 500 μM . Competition kinetic studies were conducted at a constant PNPP concentration of 50 μM with phosphate monoester varying between 20 to 1000 μM . Dodecylphosphoric acid was converted to its triethylammonium salt beforehand using triethylamine to increase solubility. Control experiments showed triethylammonium cations had no significant effect on enzyme activity. The hydrolysis reaction was initiated by the addition of AP to a concentration of 2.9 nM followed by rapid mixing. Each compound was analyzed in triplicate.

Data analysis was performed using Sigmaplot 9.0 (Systat Software, Inc.). To obtain the enzyme parameters V_{MAX} and K_M (PNPP) for PNPP hydrolysis, a non-linear regression fit to a rectangular hyperbola was used. To obtain the Michaelis constants for the phosphate monoesters, (K_M (monoester)), the general method of Kakkar et al.²¹ was used. The complete data set of [PNPP], [monoester] and initial rates including all the control data were subjected to a simultaneous non-linear regression (SNLR) fit to the Michaelis-Menten equation for competition kinetics. The output consisted of the V_{MAX} (PNPP), K_M (PNPP) and K_M (monoester) and their standard errors. Using SNLR with simulated data consistently worked well in extracting the correct parameters, validating this analysis method. All K_M (monoester) values were subsequently normalized to the K_M (PNPP) obtained during the same set of experiments to obtain the ratio $R = K_M$ (monoester) / K_M (PNPP).

5.3.5 Determination of enzymatic turnover and enzymatic efficiency for phosphate monoester hydrolysis

To find k_{cat} / K_M (monoester), kinetic runs were carried out at relatively low substrate concentrations to simplify the Michaelis-Menten equation to $v_0 = (k_{cat} / K_M)[E][S]$, assuming $[S] \ll K_M$. All reactions were carried out in disposable 2 mL polypropylene centrifuge tubes (VWR Scientific). The total reaction volumes were 1.0 mL, consisting of 50 mM Tris buffer pH 8.5 at 22°C. Substrate concentrations ranged from 100 to 400 nM for the monoPAPs and 1130 to 4520 nM for hexyl phosphate. To initiate the reactions, AP was added to a final concentration of 2.14 nM (hydrogenated phosphate experiments) or 0.214 nM (monoPAP experiments) followed by vigorous mixing. At a desired timepoint (15, 30, 45 and 60 s), trisodium phosphate was added to a final concentration of 1 mM to stop the reaction. In this manner, each timepoint represents a

separate experiment. Each timepoint was run in triplicate for all substrate concentrations. The reaction solution was extracted by addition of 1 mL ethyl acetate followed by vortexing. The ethyl acetate layer was then analyzed by gas chromatography-mass spectrometry (GC-MS) to quantify the alcohol produced by the enzymatic hydrolysis reaction. Spike and recovery experiments (N=3) were performed to determine the efficiency of the ethyl acetate extraction for both FTOHs and 1-hexanol. The percentage recoveries ranged from 81 to 94% ($\pm 2 - 7\%$ RSD) for the FTOHs and was 91% ($\pm 2\%$ RSD) for 1-hexanol.

Control hydrolysis experiments using PNPP were also performed after each kinetics experiment using the UV-Vis method outlined earlier to determine V_{MAX} and K_M (PNPP).

5.3.6 GC-MS analysis

To quantify the alcohol production rate from the hydrolysis reactions, an Agilent 7890A GC equipped with an Agilent 5975c-inert mass spectrometer operating in positive chemical ionization mode (methane reagent gas) was used. Chromatographic separation was achieved using a DB-1701 column (30 m $\times$ 0.25 mm $\times$ 0.15 μ m) with helium carrier gas at 0.9 mL/min flow rate. Injections were always performed in splitless mode. The oven program consisted of a 50°C initial temperature held for 2 minutes, followed by a 20°C/min ramp to 160°C and then a 35°C/min ramp to 280°C to bake out the column. The inlet temperature was held at 250°C. The MSD transfer line was held at 280°C. Quantification was carried out using selected ion monitoring for 4:2/6:2/8:2 FTOH ($m/z = 265, 365, 465$) and 1-hexanol ($m/z = 85$). For FTOH quantification, the source temperature was held at 300°C. For 1-hexanol, the source temperature was lowered to 150°C to reduce the extent of analyte fragmentation. The remaining

hydrogenated phosphates were not analyzed due to high instrumental detection limits. External calibration was performed using purified 4:2/6:2/8:2 FTOH standards (Wellington Labs, Guelph, ON) or 1-hexanol (Sigma-Aldrich). Data quality was assured by injection of solvent and method blanks. No significant matrix effects nor sample carryover were observed. Samples run in the absence of enzyme indicated no evidence of abiotic hydrolysis. Kinetic parameters were obtained using Sigmaplot 9.0. The initial rates were determined using a linear regression fit of the [alcohol] vs. time data. A Michaelis-Menten curve was then constructed by plotting initial rates at each substrate concentration vs. substrate concentration. A linear plot was obtained from which k_{cat} / K_M can be determined from its slope. The k_{cat} value was obtained using the concurrent experimental K_M (PNPP) and previously determined ratio (R) value for the desired compound. Every k_{cat} value reported herein is with respect to each active site in the AP dimer.

5.3.7 Control experiments

A series of control experiments were performed using bovine intestinal alkaline phosphatase (AP) to assure quality of results. There was no significant change in reaction rate in the presence of triethylammonium cations. It is important to note that vortexing a reaction solution with an equal volume of ethyl acetate does not denature AP. Hence, a high concentration of inorganic phosphate is needed to effectively halt the hydrolysis reaction during the experiments.

5.4 Results and Discussion

5.4.1 Michaelis constants of phosphate monoesters

The Michaelis constants (K_M (monoesters)) for all the phosphate esters in the present study have been elucidated and the results presented graphically in Figure 5.2 and tabulated in Table 5.1. Complete raw data are given in Appendix C, Table S1. It is important to recall that all values are being presented as the ratio (R) of K_M (monoester) to K_M (PNPP) as determined in a concurrent positive control. Sample Michaelis-Menten plots for 8:2 monoPAP are given in Figure 5.3.

Figure 5.2: Michaelis constants (K_M) of various phosphate monoesters relative to p-nitrophenyl phosphate ($n=3$) as determined by competition kinetics by UV-Vis. Error bars represent one standard error.

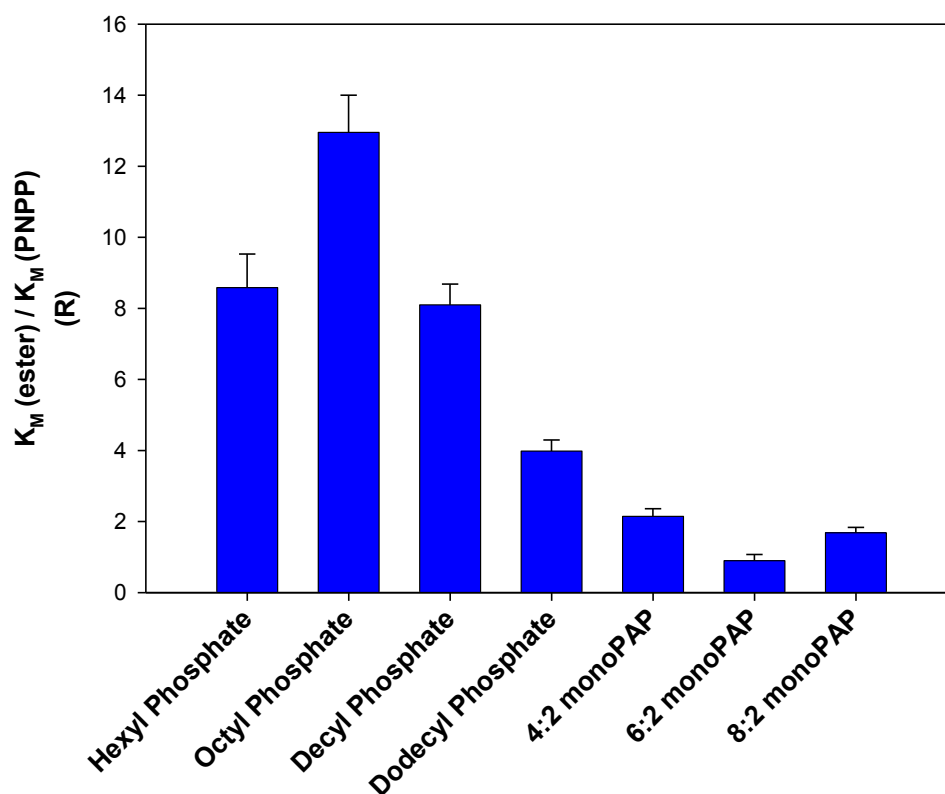


Figure 5.3: Sample Michaelis-Menten plots for competition kinetics experiments on 8:2 monoPAP ($n=3$) relative to p-nitrophenyl phosphate as determined by competition kinetics by UV-Vis. Error bars represent one standard error.

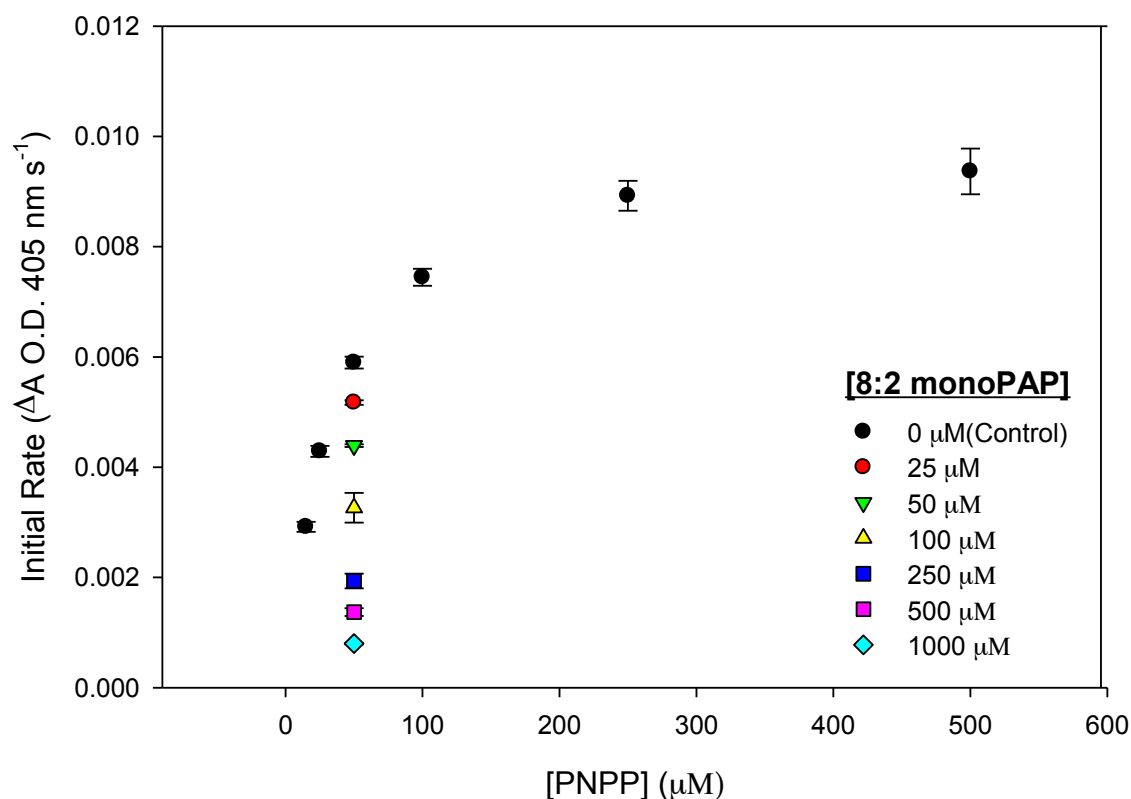


Table 5.1. Experimental enzymatic kinetic parameters for various hydrogenated and polyfluorinated phosphate esters ($n=3$). Error values represent one standard error.

Compound	R^a	k_{cat} / K_M ($\text{M}^{-1} \text{s}^{-1}$)	k_{cat} (s^{-1})
4:2 monoPAP	2.1 ± 0.2	$1.2 \times 10^7 \pm 1 \times 10^6$	1224 ± 200
6:2 monoPAP	0.9 ± 0.2	$8.9 \times 10^6 \pm 9 \times 10^5$	425 ± 100
8:2 monoPAP	1.7 ± 0.1	$1.3 \times 10^7 \pm 2 \times 10^5$	1136 ± 80
Hexyl Phosphate	8.6 ± 1	$3.8 \times 10^5 \pm 2 \times 10^4$	190 ± 25
Octyl Phosphate	13.0 ± 1	n/a ^b	n/a
Decyl Phosphate	8.1 ± 0.6	n/a	n/a
Dodecyl Phosphate	4.0 ± 0.3	n/a	n/a

^a $R = K_M$ (monoester) / K_M (PNPP).

^b n/a = not analyzed.

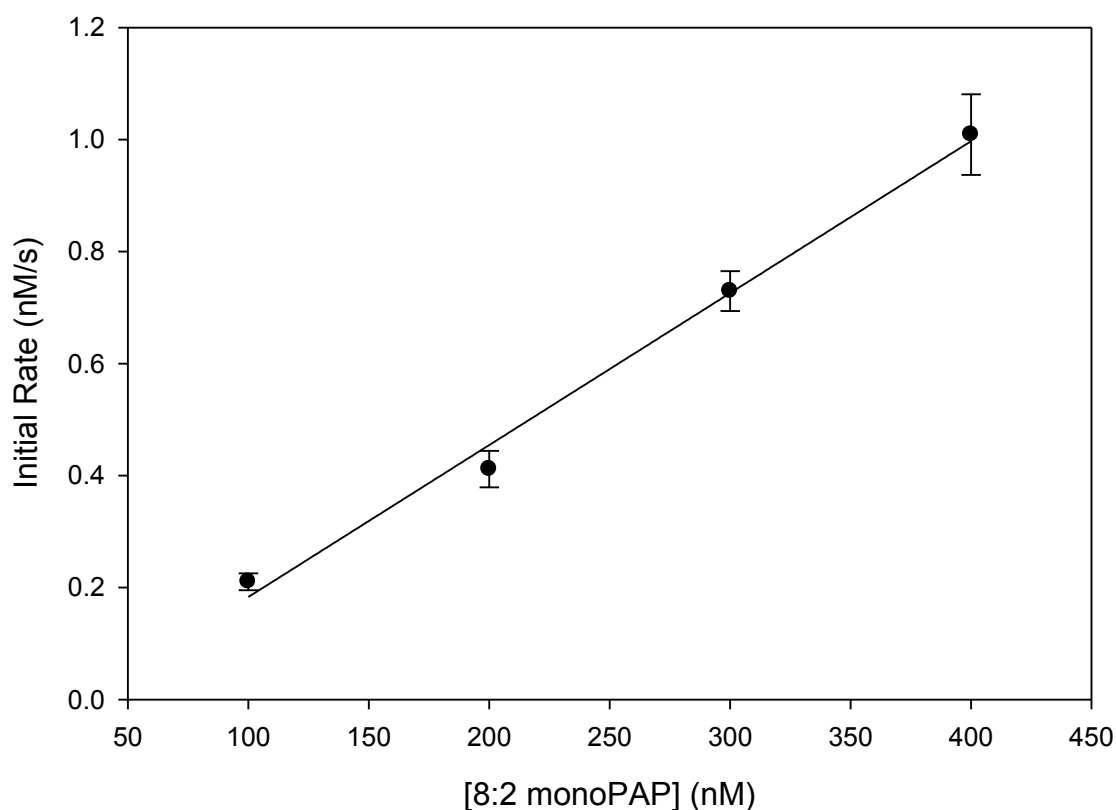
From the present study, the fluorinated monoPAPs all have lower R values than HPMEs. To a first approximation, Michaelis constants indicate how well a substrate binds to the active site of an enzyme, particularly when the catalytic steps that follow are slower than the initial non-covalent binding step. In this case, the fluorinated chains of the monoPAPs impart a slightly better binding ability to AP as indicated by their lower K_M values.

One aspect to note is the lack of an obvious chain length effect. For the hydrogenated phosphates, octyl phosphate has the highest K_M whereas 6:2 monoPAP has the lowest K_M for the fluorinated phosphates despite both having eight carbons in total. Overall, a decreasing trend is noted for the HPMEs which might indicate a slight hydrophobic effect.

5.4.2 Catalytic rate constants and enzymatic efficiency

The low concentration kinetic studies give k_{cat} / K_M which is the specificity constant of an enzymatic reaction for a particular substrate and is a measure of enzymatic efficiency. The complete set of results is summarized in Table 5.1. A sample Michaelis-Menten plot for the hydrolysis of 8:2 monoPAP is shown in Figure 5.4. For all other kinetic plots, see Appendix C. The monoPAPs all have k_{cat} / K_M of roughly $10^7 \text{ M}^{-1} \text{ s}^{-1}$ with no significant chain length effect discernable (see Table 5.1), while the most efficient enzymes have k_{cat} / K_M exceeding $10^9 \text{ M}^{-1} \text{ s}^{-1}$. This indicates that although phosphate ester hydrolysis is not diffusion controlled, it is still a rapid process representing a marked enhancement over the extremely slow uncatalyzed rate. Diffusion controlled kinetics for AP have never been observed before, probably due to the fact that AP works on a wide variety of substrates.

Figure 5.4: Example Michaelis-Menten plot obtained from the enzymatic hydrolysis of 8:2 monoPAP at low substrate concentrations through quantification of 1H,1H,2H,2H-perfluorodecanol (8:2 FTOH) by GC-MS. The slope represents $k_{\text{cat}}[E]_0 / K_M$. Error bars represent one standard error.



O'Brien et al.¹⁶ studied alkyl phosphate hydrolysis reactions using *E. coli* AP and found 2,2,2-trifluoroethyl phosphate and 2-fluoroethyl phosphate had $k_{\text{cat}} / K_M = 2.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ and $2.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ respectively. In the present study, monoPAPs were found to have values in between these two which can be explained by their differences in structure. Since k_{cat} / K_M depends on the basicity of the alkoxide leaving group, the presence of fluorine atoms causes an electron withdrawing effect by induction that diminishes with distance. In the present study, two fluorines on the γ carbon of 4:2 FTOH causes a stronger electron withdrawing effect than one fluorine in the β position of 2-fluoroethanol but not as much as having three fluorines in the β

position of 2,2,2-trifluoroethanol. This is consistent with predicted pKa values of these alcohols (4:2 FTOH = 14.2, 2,2,2-trifluoroethanol = 12.5, 2-fluoroethanol = 14.5, calculated using SPARC on-line v 4.6; <http://archemcalc.com/sparc>).¹²

The $k_{\text{cat}} / K_{\text{M}}$ of hexyl phosphate was also determined in the present study to confirm its significantly slower rate of reaction compared to monoPAPs. Its $k_{\text{cat}} / K_{\text{M}}$ was found to be $3.8 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ which is generally consistent with the value for butyl phosphate ($8.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) as found by O'Brien et al.¹⁶ Since HPMEs do not contain electron withdrawing moieties, their specificity constants are significantly smaller. This is an example of how the presence of fluorine atoms can actually increase the rate of degradation under environmental conditions.

5.4.3 Rat digestive tract modeling

The results from the present study were used to rationalize the findings of D'eon and Mabury⁹ who reported no measurable quantities of x:2 monoPAP in rat blood after an initial oral gavage dose. Assuming this lack of detection is likely due to hydrolysis, the two enzymes capable of catalyzing this reaction in vivo are acid phosphatase and alkaline phosphatase. While acid phosphatases are widely found in mammalian tissue, they are mostly prevalent in the prostate, liver, spleen and blood plasma.²² By contrast, the small intestinal mucosa possesses high levels of alkaline phosphatase.¹⁸ We therefore postulate alkaline phosphatase to be the main agent responsible for the degradation of monoPAPs in vivo.

A simple model of the rat intestinal tract was created to determine the rate at which monoPAPs would be hydrolyzed to produce the corresponding FTOH and inorganic phosphate.

Data were obtained from the literature on the dimensions of the rat small intestine, the levels of AP in a typical rat intestine and the transit time of the small intestine. Nakasaki et al.²³ homogenized intestinal mucosa from many rats and isolated approximately 250 units of AP activity per rat, where 1 unit of activity is defined as the amount of AP that can hydrolyze 1 $\mu\text{mol/min}$ PNPP. Using the Sigma-Aldrich certificate of analysis for the specific lot of AP used in the present study, it is possible to convert units of activity to molarity. Mayhew et al.²⁴ provide the dimensions of a typical rat intestine, giving a total volume as 12.6 mL. This gives an average AP concentration ($[E]_0$) of 97 nM in the intestinal mucosa. The initial substrate concentration ($[\text{monoPAP}]_0$) is also required. At the high dosing levels used by D'eon and Mabury of 6.0 mg/mL,⁹ AP will undoubtedly be saturated with substrate for the majority of the monoPAP transit through the small intestine. Hence, the reaction rate will become zero order with respect to monoPAP concentration and will simply be the V_{MAX} for the enzyme at $[E]_0 = 97 \text{ nM}$.

The time required for the hydrolysis reaction to go to completion is thus directly proportional to the initial substrate concentration. To a first approximation, the concentration of the oral gavage dose can be used as $[\text{monoPAP}]_0$ to give an upper estimate on the time required for a complete hydrolysis reaction in the small intestine. Any further dilution of the substrate in the stomach (by gastric fluids already present in the stomach for example) will only decrease the time required for the complete reaction. As an example, D'eon and Mabury⁹ dosed 8:2 monoPAP to a concentration of 6.0 mg/mL (11 mM). Using k_{cat} (8:2 monoPAP) from the present study, the V_{MAX} for a rat small intestine will be 0.11 mM/s. This gives total time for the reaction as 100 s, which is very short compared to the 2 h transit time of the rat small intestine.²⁵ It is reasonable to use V_{MAX} kinetics to approximate reaction time since reducing [8:2 monoPAP] from 11 mM to

its approximate K_M represents over 99% of 8:2 monoPAP hydrolysis. Therefore, monoPAPs are efficiently hydrolyzed by the alkaline phosphatase enzyme in the small intestinal mucosa. This is followed by uptake of the more hydrophobic FTOH into the blood along with inorganic phosphate. It should also be noted this model assumes the extremely large dose administered by D'eon and Mabury⁹ and likely does not represent typical environmental exposure.

A number of assumptions were made in this simple model. First, bovine AP was used in the present study rather than rat AP, although both being mammalian APs are expected to have similar kinetic properties. Secondly, the reactions in the present study were all performed at 22°C rather than the physiological temperature of 37°C since the UV-Vis experiments could not be performed at different temperatures. However, enzymatic kinetic parameters scale with temperature in ways that can be predicted. Changes with temperature generally follow the Arrhenius Law for k_{cat} , with an approximate doubling in rate noted for every 10 degree rise in temperature.²⁶ The effects of temperature are more difficult to predict with K_M values. Copeland et al.²⁷ found K_M decreased with increasing temperatures for human AP, with K_M halving in value as the temperature rose from 25°C to 37°C, which can be explained using the thermodynamics of the binding process. Using this information, a reasonable prediction is that monoPAPs will hydrolyze even faster at physiological temperature by a factor of four times or more. In the specific case of D'eon and Mabury⁹ the reaction time would only be halved to about 50 s since only k_{cat} is in the rate expression at saturating substrate concentrations. One final complication would be the presence of inorganic phosphate in the gut that could potentially inhibit the AP enzyme from hydrolyzing monoPAPs. Inorganic phosphate (P_i) is a part of the diet and is mostly found in food additives and preservatives as well as in soft drinks.²⁸

Depending on the diet, it might be possible to ingest enough P_i to inhibit intestinal alkaline phosphatase before it is absorbed. In these cases, the time required for monoPAP hydrolysis will likely increase. Inorganic phosphate is rapidly absorbed in the duodenum by transport proteins and passively in the jejunum and ileum.²⁹ Hence, any inorganic phosphate produced in the gut will be removed from the vicinity of alkaline phosphatase enzymes, located in the mucosa of the small intestine. This removal might alleviate any inhibition of the enzyme and allow phosphate ester hydrolysis to proceed.

One group of compounds omitted in the present study are the diPAPs which have previously been shown to be present in food packaging⁵ and in human blood⁷. Their detection in rats following oral gavage dosing along with product metabolites shows they are slower to undergo hydrolysis compared to the monoPAPs, although they still likely hydrolyze much faster than via abiotic hydrolysis alone (average half life $\sim 10^5$ years).¹⁰ The enzymatic catalysis of phosphodiester compounds is ubiquitous in biota since most DNA and RNA nucleases are classes of phosphodiesterase enzymes, along with several phospholipases.¹⁴ The lack of a non-specific phosphodiesterase enzyme may explain why diPAPs are more slowly hydrolyzed *in vivo* and can be readily detected in biological systems.

5.5 Conclusions

In the present study, monoPAPs were shown to undergo rapid hydrolysis in the presence of bovine intestinal alkaline phosphatase. This process occurs almost two orders of magnitude faster in monoPAPs than in the corresponding HPMEs, illustrating how the fluorinated portion of

these compounds acts as an electron withdrawing group even in the β position relative to the phosphate group.

Using a simple model, the kinetic results suggest monoPAPs will be rapidly degraded in vivo to produce the corresponding FTOH in a high yield. This has important toxicological implications because FTOHs have previously been shown to biotransform into PFCAs, a ubiquitous group of highly persistent organic pollutants. In addition, the degradation of FTOHs initially produces a mixture of fluorotelomer saturated and unsaturated carboxylic acids (FTCAs and FTUCAs respectively). Both classes of compounds have been shown to be orders of magnitude more toxic than the perfluorinated acid end products³⁰ and a recent study has shown them to be highly electrophilic compounds that react with cellular glutathione, inducing oxidative stress.³¹

5.6 Acknowledgments

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CHAPTER SIX

Summary, Conclusions and Future Work

Derek A. Jackson and Scott A. Mabury

Contributions – Prepared by Derek Jackson under the guidance of Scott Mabury.

6.1 Summary and conclusions

In this dissertation several new mechanisms for the formation of perfluorinated carboxylic acids (PFCAs) in the environment were presented.

In Chapter 2, a new fire fighting fluid, perfluoro-2-methyl-3-pentanone (PFMP, Novec 1230), was investigated with regards to its atmospheric fate. Based on its structure, it appeared to be capable of direct photolysis, hydrolysis and hydration but would be inert to reactions with atmospheric oxidants. The relative importance of each of the three processes was elucidated after a series of experiments at both the Ford Motor Company and the University of Toronto. While both aqueous hydrolysis and hydration are reasonable environmental reactions for PFMP, they were found to be insignificant compared to the rate of direct photolysis in the atmosphere. The mechanism of direct photolysis was elucidated using smog chamber experiments followed by offline sampling. The initial products formed are an acyl radical and a perfluorinated radical which undergo known atmospheric reactions to produce both trifluoroacetic acid (TFA) and perfluoropropanoic acid (PFPrA) as end products. While many atmospheric sources of TFA are already known, the sources of the PFPrA detected in rainwater still remains unclear. A basic calculation showed that PFMP released to the environment is capable of accounting for some, but not all, of the PFPrA that has been detected in North American rainwater. Overall, PFMP has the advantage over previous fire fighting fluids of not depleting the ozone layer nor being a long lived greenhouse gas.

A new historical source of branched PFOA to the environment was uncovered in Chapter 3. By examining the chemical reactions involved in electrochemical fluorination (ECF) along

with some legacy literature, it was postulated that the formation of perfluorooctanoyl fluoride (PFOAF) as an unintentional byproduct had significant consequences. If reacted with amines during the synthesis of commercially used sulfonamides, polyfluorinated amides (PFAMs) could be significant residuals in ECF-based materials. Since 3M voluntarily phased out production of compounds based on perfluorooctanesulfonyl fluoride (POSF) in 2001, the chemistry proposed herein would only be of historical importance but could help explain concentration trends of PFOA in human blood over the past decade. Using GC-MS and in-house synthesized standards, two representative PFAMs that are PFOA precursors by enzymatic hydrolysis were discovered in the majority of historical ECF samples tested. Therefore, PFAMs could have historically served as a branched PFOA source to human blood. Biomonitoring studies on human blood have showed a decreasing trend for PFOA over the past 10 years despite the increase in fluorotelomer compound usage, all of which should degrade to PFOA. This suggests that a significant source of PFOA was ended concurrently with 3M's phaseout of their POSF-based products, which is supported by the discovery of PFAMs as PFCA precursors.

The chemistry of the PFAMs was explored further in Chapter 4 by examining their atmospheric oxidation reactions and their potential to form PFCAs abiotically. The first phase of the experiment took place at the Ford Motor Company using the smog chamber to investigate the reaction of a model PFAM, *N*-ethylperfluorobutyramide (EtFBA), with chlorine atoms (Cl) and hydroxyl radicals (OH). Offline samples were collected using both XAD-2 cartridges and aqueous base to quantify and characterize oxidation products. The rate coefficients for the reaction of EtFBA with Cl and OH were obtained by the relative rate technique using competitors and its atmosphere lifetime was determined to be about 4 days. The offline samples

were extracted and analyzed by both GC-MS and LC-MS/MS and a plausible oxidation pathway was proposed. The atmospheric oxidation of PFAMs funnels through the formation of $\text{C}_3\text{F}_7\text{C}(\text{O})\text{N}(\text{H})$ radicals which decompose to form isocyanic acid and the perfluorinated radical C_3F_7 which can react further to produce COF_2 , TFA and PFPrA, all of which were detected products. In addition, perfluorobutanoic acid (PFBA) was detected as a major product although a pathway for its formation could not be proposed at this time. Historically, this indicates that eight carbon PFAMs could have served as atmospheric sources of branched PFOA.

In Chapter 5, the biological hydrolysis of a homologous series of polyfluoroalkyl phosphate monoesters (monoPAPs) to fluorotelomer alcohols (FTOHs) was studied using a model alkaline phosphatase enzyme. For this study, pure monoPAPs were synthesized using pyrophosphoric acid to avoid contamination of inorganic phosphate in the products. Michaelis-Menten parameters K_M and k_{cat} were measured for the 4:2, 6:2 and 8:2 monoPAP and compared to the corresponding parameters for hexyl phosphate. The results showed the fluorinated monoPAPs hydrolyzed approximately two orders of magnitude faster than hexyl phosphate, which supports earlier work done on the alkaline phosphatase mechanism. The electron withdrawing fluorinated chain assists the departure of the FTOH leaving group relative to the hexyl phosphate and accelerates the reaction. Although the metabolism of monoPAPs to FTOHs has already been determined, this study helped clarify location of hydrolysis within in the gut and explain an important result from a previous paper that failed to detect any monoPAPs in rats despite high doses being introduced. Using the Michaelis-Menten parameters from the present study, the monoPAPs were expected to hydrolyze to FTOHs in the small intestine within a matter of minutes, thus rationalizing their lack of detection. The FTOHs are then presumably

taken up by the body where they are metabolized further to PFCAs. By contrast, the rats dosed with diPAPs had detectable levels of diPAP in their tissues, demonstrating their rate of hydrolysis in vivo to be slower than the monoPAPs.

6.2 Future research

As mentioned in the introduction, the initial synthetic product from electrochemical fluorination from which all sulfonamide compounds are synthesized is a perfluorinated sulfonyl fluoride. Historically, the compound synthesized by 3M was perfluorooctanesulfonyl fluoride (POSF), however this was replaced by perfluorobutanesulfonyl fluoride (PBSF) after their voluntary phaseout of POSF in 2001. Sulfonyl fluorides are highly resistant to abiotic hydrolysis under environmental conditions of pH and are expected to be highly volatile and to partition into the atmosphere. Despite being high production volume compounds, there is a paucity in the literature concerning the environmental fate of perfluorinated sulfonyl fluorides.

Preliminary studies using the smog chamber at the Ford Motor Company found that PBSF (and therefore likely POSF) does not react with chlorine atoms or hydroxyl radicals. Therefore, POSF and PBSF have the potential to be long lived greenhouse gases. The radiative efficiency of PBSF was determined to be $0.345 \text{ W m}^{-2} \text{ ppb}^{-1}$ but without knowledge of its atmospheric lifetime a global warming potential can not be computed. The ultimate question that needs to be answered is: “What limits the lifetime of a perfluorinated sulfonyl fluoride in the atmosphere?” Since two possibilities include partitioning into water and direct photolysis, experiments need to be performed to find the rate of direct photolysis under actinic conditions to answer this question.

APPENDIX A

SUPPORTING INFORMATION FOR CHAPTER TWO

Atmospheric Degradation of Perfluoro-2-methyl-3-pentanone: Photolysis, Hydrolysis and Hydration

Computational Methods

All compounds in the present study were modelled using *Gaussian 03* with the WebMO user interface.¹ Their structures and acronyms are given in Figure 1. All computations were performed using Density Functional Theory (DFT) using the B3LYP functional. All compounds were first geometry optimized in the gas phase with the 3-21G basis set and then re-optimized using the 6-31G(d,p) basis set. Every structure's vibrational modes were examined to ensure no imaginary frequencies were found. Each optimized structure using 6-31G(d,p) was subjected to a single point molecular energy calculation in both the gas and aqueous phases using the 6-311++G(d,p) basis set. For aqueous phase calculations, the default PCM solvent model in *Gaussian 03* was used. Molecular orbital calculations were performed in regular population mode using the 6-311++G(d,p) basis set in the gas phase.

The equilibrium constants for hydration (K_{hyd}) for each compound were calculated using the relative method outlined by Gomez-Bombarelli et al.² For perfluoro-2-methyl-3-pentanone (PFMP), both the relative method of Gomez-Bombarelli et al. as well as a training set method was used. The training set consisted of fluoroacetone, trifluoroacetone and hexafluoroacetone because all three compounds have literature K_{hyd} values. In the relative method, acetone was chosen as the group reference compound for purposes of calculating $\log K_{\text{hyd}}$. In this manner, the calculated and literature K_{hyd} values for acetone are used to compute K_{hyd} for a compound of choice to minimize any systemic computational errors. The energies chosen in the present study were the computed B3LYP energies of each compound with the unscaled zero point energies (ZPEs) from the 6-31G(d,p) basis set added.

The formulas used to calculate $\log K_{\text{hyd}}$ for each compound were as follows:

$$\Delta E = E_{\text{hydrate}} + E_{\text{acetone}} - E_{\text{carbonyl}} - E_{\text{acetonehydrate}} \quad (\text{S1})$$

$$\log K_{\text{hyd}} = \log K_{\text{acetone}} - \Delta E / (\ln 10)(RT) \quad (\text{S2})$$

where $\log K_{\text{acetone}}$ is the literature hydration constant of acetone (-2.85).³ All temperatures were 298 K.

When computing $\log K_{\text{hyd}}$ for PFMP using the above relative method, all that is needed is the computed B3LYP energies of acetone, PFMP and their respective hydrates using whatever solvent is desired. However, to reduce systematic errors even further, a training set can be developed whereby $\log K_{\text{hyd}}$ is computed using the above method for similar compounds where literature values of $\log K_{\text{hyd}}$ are already available. In the present study, fluoroacetone, trifluoroacetone and hexafluoroacetone were chosen to construct the training set. Then, a “calibration” curve can be plotted to relate the literature values to the computed values. Finally, the most accurate hydration constant for PFMP can be determined.

Computational Results

The training set consisted of fluoroacetone, trifluoroacetone and hexafluoroacetone because literature values for hydration exist for these molecules (3) and they share structural similarity with PFMP. In addition, B3LYP energies were computed using the 6-311++G(d,p) basis set for both the gas phase and aqueous phase, leading to four possible values of K_{hyd} for PFMP

depending on which method and solvent model was used for the calculation. This results in the range of values for K_{hyd} as given in the body of the paper.

Figure S1. Chemical structures of all compounds modelled computationally using DFT/B3LYP

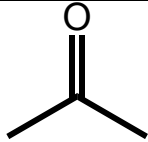
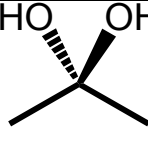
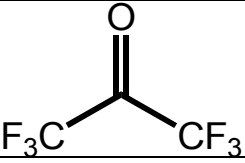
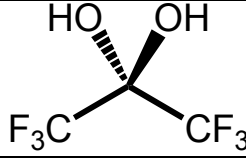
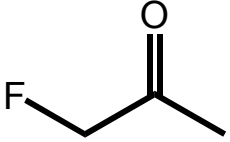
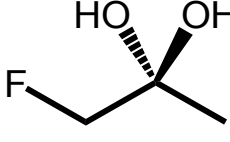
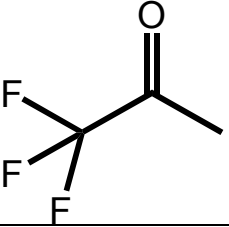
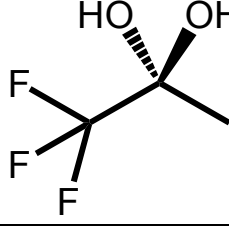
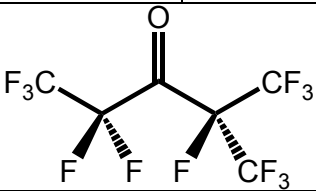
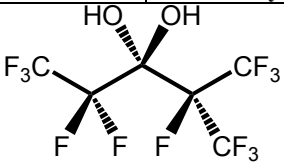
			
Acetone	Acetone Hydrate	Hexafluoroacetone	Hexafluoroacetone Hydrate
			
Fluoroacetone	Fluoroacetone Hydrate	Trifluoroacetone	Trifluoroacetone Hydrate
			
PFMP		PFMP:Hydrate	

Table S1. Computationally derived K_{hyd} values using B3LYP/6-311++G(d,p) in the gas phase.

Compound	Training Set Method $\log K_{\text{hyd}}$	Relative Method $\log K_{\text{hyd}}$	Lit. $\log K_{\text{hyd}}$
Fluoroacetone	na	-0.16	-0.78
Trifluoroacetone	na	0.80	1.54
Hexafluoroacetone	na	5.39	6.08
PFMP	-2.09	-1.76	none

Table S2. Computationally derived K_{hyd} values using B3LYP/6-311++G(d,p) in the aqueous phase using the PCM solvent model.

Compound	Training Set Method $\log K_{\text{hyd}}$	B3LYP Energy Relative Method $\log K_{\text{hyd}}$	Lit. $\log K_{\text{hyd}}$
Fluoroacetone	na	-1.73	-0.78
Trifluoroacetone	na	2.56	1.54
Hexafluoroacetone	na	7.71	6.08
PFMP	-0.43	-0.85	none

Figure S2. Computationally derived and literature $\log K_{\text{hyd}}$ values for training set compounds and PFMP using B3LYP/6-311++G(d,p) in both gas and aqueous phases.

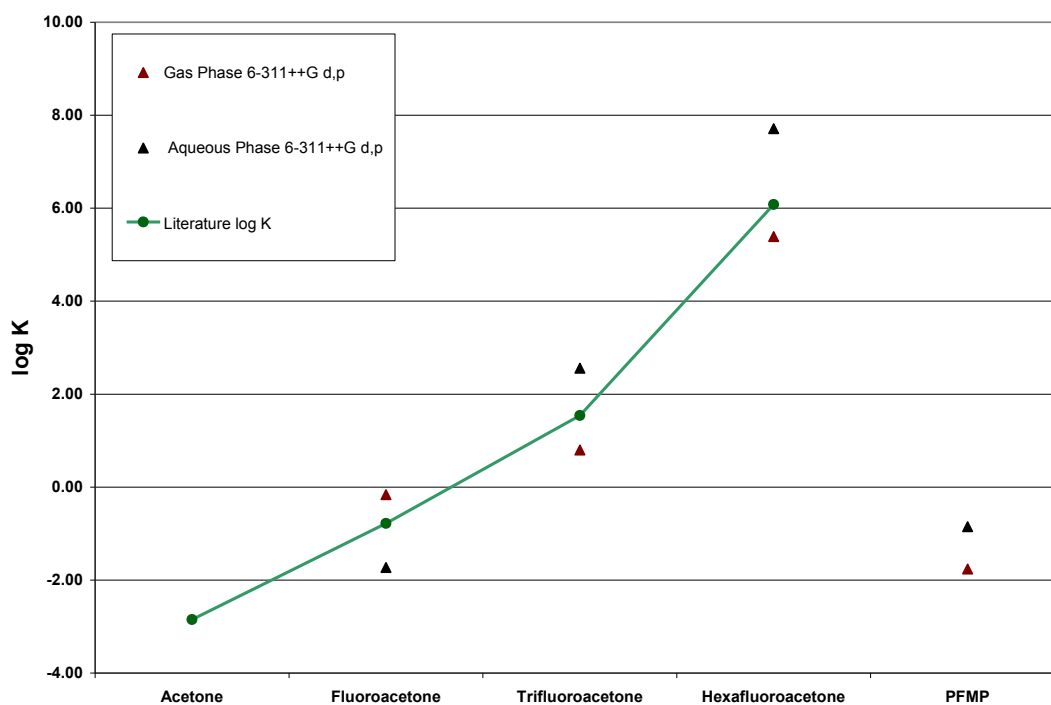
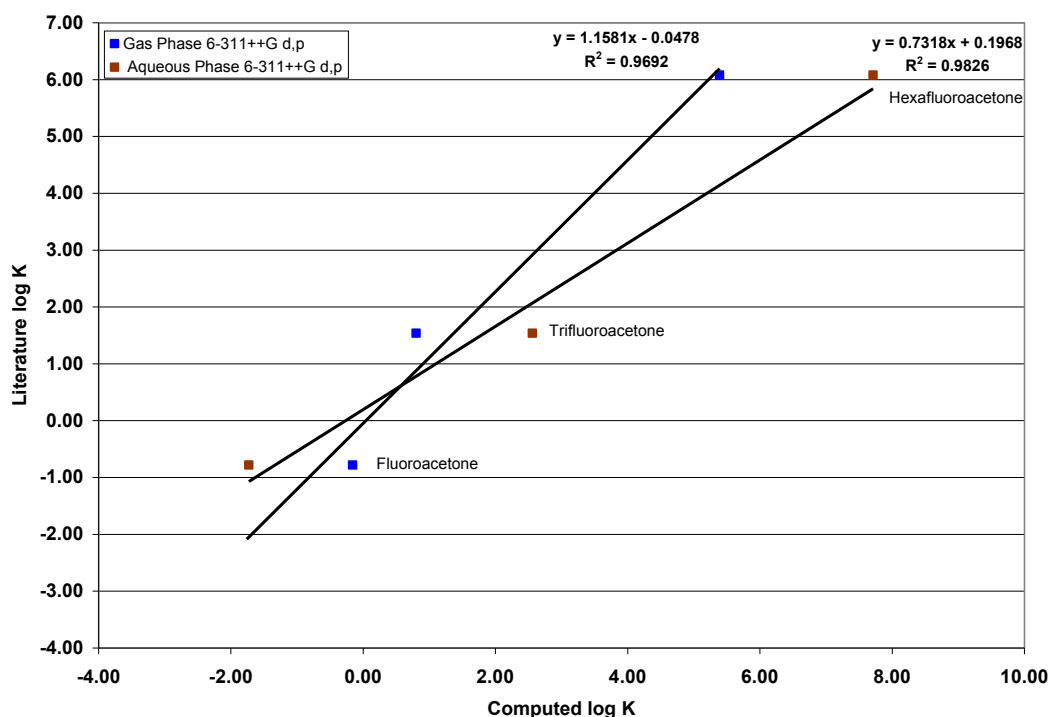


Figure S3. Linear calibrations of training set literature $\log K_{\text{hyd}}$ versus computationally derived $\log K_{\text{hyd}}$ values using B3LYP/6-311++G(d,p) in both the gas and aqueous phases.



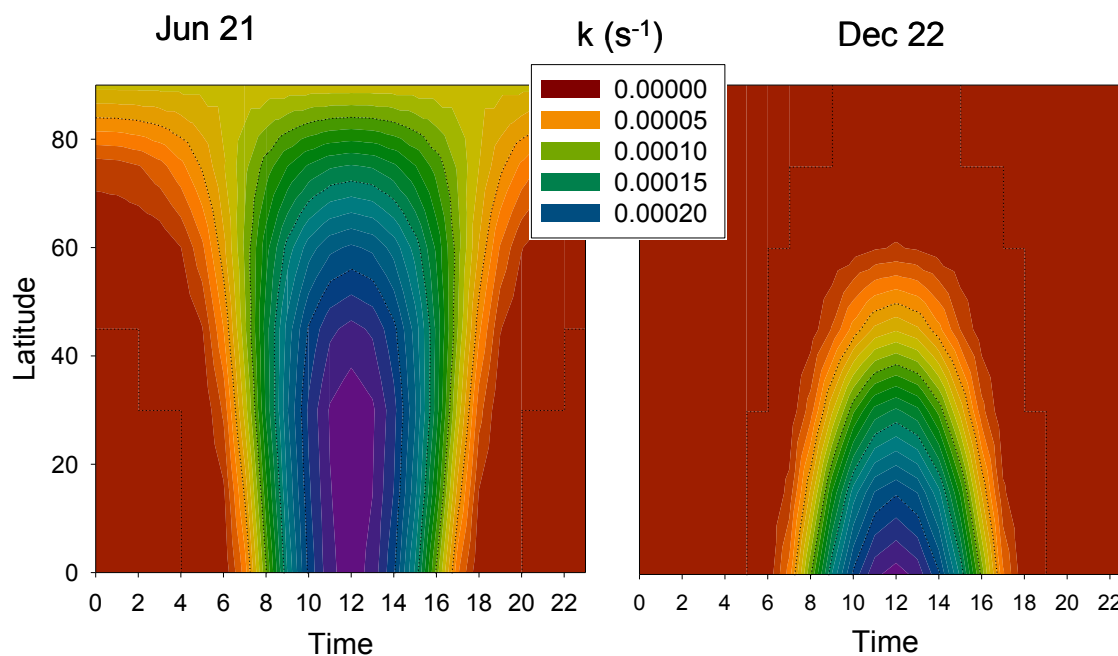
As shown in the Figure 2, the relative method of Gomez-Bombarelli et al. gives hydration constants reasonably close to the literature values for fluoroacetone, trifluoroacetone and hexafluoroacetone.

Hence the $\log K_{\text{hyd}}$ values for PFMP range from -0.43 to -2.09, showing the relative unimportance of hydration for the environmental fate of PFMP.

Table S3. Rate constants and lifetimes for PFMP based on latitude and time of year from the TUV model using the literature quantum yield of photolysis as 0.043.⁴

Latitude	24 Hour Average Rate Constant (10^{-7} s^{-1})					Annual Average
	Dec 22	Mar 22	Jun 21	Sept 23	Annual Average	Lifetime (days)
90° N	0.00	0.65	32	0.57	8.2	14
75° N	0.00	4.5	32	4.3	10	11
60° N	0.71	13	33	13	15	7.8
45° N	5.9	21	35	21	21	5.6
30° N	15	27	35	27	26	4.5
15° N	23	31	33	31	29	3.9
0°	30	32	28	32	31	3.8
15° S	35	31	22	31	30	3.9
30° S	37	27	14	27	26	4.4
45° S	38	21	5.5	21	21	5.4
60° S	36	13	0.66	13	15	7.5
75° S	34	4.3	0.00	4.4	11	11
90° S	34	0.53	0.00	0.59	9.2	13

Figure S4. Contour plots showing the photolytic rate constants of PFMP in the northern hemisphere as derived by the TUV model assuming a quantum yield of 0.043.



The Relative Importances of Photolysis and Hydrolysis: Environmental Modelling

To demonstrate the relative importances of photolysis and hydrolysis in the atmosphere, the modelling methods of Cahill and Mackay⁵ were used. In short, the rate constants of both reactions were combined with PFMP's physical properties and the amount of liquid water in the atmosphere to determine the relative rates of both.

The rate of PFMP degradation (R) in the atmosphere due to direct photolysis is given by the following equation:

$$R_{\text{photolysis}} = -C_A V_A k_{\text{photolysis}} \quad (\text{S3})$$

where C_A is the concentration of PFMP in the atmosphere, V_A is the volume of air and $k_{\text{photolysis}}$ is the first order photolytic rate constant. The value of $k_{\text{photolysis}}$ will vary depending on time of day, latitude and prevailing weather conditions. However, a typical value for a mid-latitude summer can be taken as $35 \times 10^{-7} \text{ s}^{-1}$ from the TUV modelling data.

The photolysis equation reduces to:

$$R_{\text{photolysis}} = -C_A V_A (35 \times 10^{-7} \text{ s}^{-1}) \quad (\text{S4})$$

To model the hydrolysis reaction of PFMP, it is necessary to include the air-water partitioning coefficient, K_{AW} since equilibrium conditions will be assumed for this calculation. For PFMP, $K_{AW} = 5300$. The rate of hydrolysis in the atmosphere is given by the following equation:

$$R_{\text{hydrolysis}} = -C_W (F_W V_A) k_{\text{hydrolysis}} \quad (\text{S5})$$

where C_W is the concentration of PFMP in the aqueous phase, F_W is the fraction of liquid water in the atmosphere, V_A is the volume of the air parcel and $k_{\text{hydrolysis}}$ is the pseudo first order rate constant for the hydrolysis reaction at the pH being considered. Atmospheric water typically has a pH of 5.6 so $k_{\text{hydrolysis}} = 4.2 \times 10^{-4} \text{ s}^{-1}$. A typical fraction of liquid water in the atmosphere, F_W is 4.5×10^{-8} as indicated by De Bruyn et al.⁶ The concentration of PFMP in water assuming equilibrium conditions is given by $C_W = C_A / K_{AW}$.

The rate of hydrolysis equation then becomes:

$$R_{\text{hydrolysis}} = -(C_A / 5300) (4.5 \times 10^{-8} V_A) (4.2 \times 10^{-4} \text{ s}^{-1}) \quad (\text{S6})$$

Since both the rates of hydrolysis and photolysis include only C_A and V_A , they will cancel out when the ratio is taken to find the importance of photolysis versus hydrolysis:

$$R_{\text{photolysis}}/R_{\text{hydrolysis}} = \text{approx. } 980,000,000:1 \quad (\text{S7})$$

Figure S5. ^{19}F NMR of PFMP (neat) with expansions on each signal to show nuclei coupling patterns.

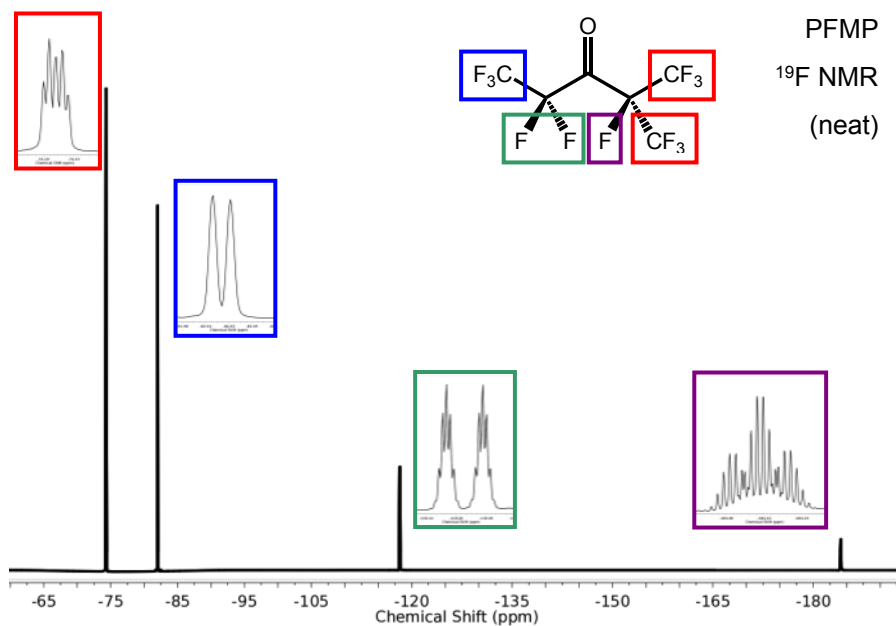
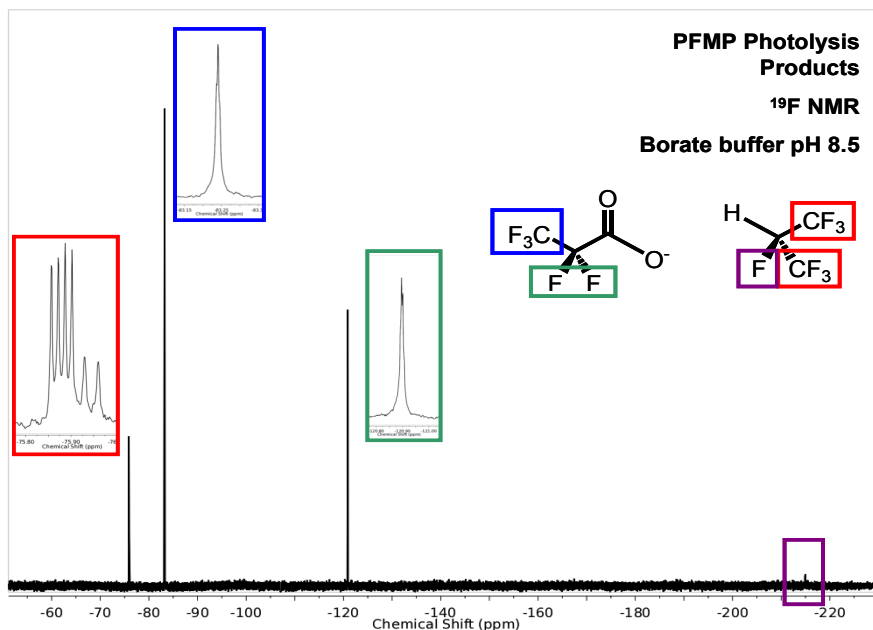


Figure S6. ^{19}F NMR of PFMP photolysate at completion of reaction (borate buffer pH 8.5) with expansions on selected signals to show nuclei coupling patterns.



Prediction of PFPrA concentrations in precipitation

This simple model makes the assumption that 1000 t of PFMP is produced each year in the United States and that 3% is emitted into the atmosphere each year, corresponding to 30 t yr⁻¹.

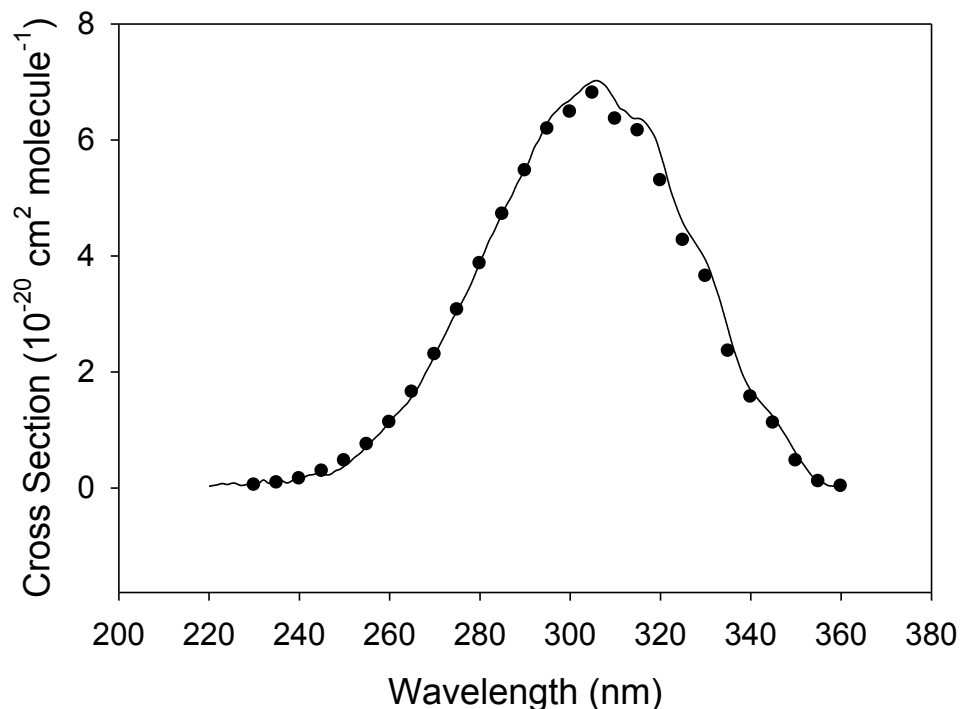
It is also assumed that due to an average atmospheric lifetime of 1 week due to photolysis, all 30 t emitted each year will degrade. The yield of PFPrA from photolysis is assumed to be 24% due to the experimental branching ratio of the $\text{C}_2\text{F}_5\text{C}(\text{O}) + \text{HO}_2$ reaction.⁷ The actual yield of PFPrA will likely be lower since a competing reaction in the presence of NO_x will drive a competing reaction that will “unzip” the perfluorinated chain and PFPrA can no longer be produced. Therefore, we will derive an upper limit for PFPrA production by photolysis.

Each year, 30 t PFMP degrades to produce PFPrA. Taking into account the molecular weights of PFMP and PFPrA as well as the 24% branching ratio, it can be shown that 3.7 t PFPrA will be atmospherically produced annually.

It can also be assumed that PFPrA, due to its low vapour pressure and high water solubility, will be quantitatively scavenged by precipitation and deposited from the atmosphere. The total annual precipitation in the continental United States is approximately 6.5×10^{15} L.⁸ This corresponds to a maximal PFPrA concentration in rainfall of 0.6 ng L^{-1} .

The above calculation assumes PFMP will only be distributed within the continental United States. With a lifetime of one week however, PFMP will be subjected to long range transport. If total precipitation in Canada is combined with the United States (annual precipitation in Canada is approximately 5.5×10^{15} L)⁹, this lowers the PFPrA concentration to 0.3 ng L^{-1} .

Figure S7. Measured UV-vis absorption cross section for PFK; 5 nm moving average of 1 nm, measured data from 218 – 382 nm (solid line); data from Taniguchi et al.¹⁰ (dots).



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APPENDIX B

SUPPORTING INFORMATION FOR CHAPTER THREE

Polyfluorinated Amides as a Historical PFCA Source by Electrochemical Fluorination of Alkyl Sulfonyl Fluorides

Table S1. List of polyfluorinated amide (PFAM) analytes and their monitored ions for GC-MS in selected ion monitoring mode using positive chemical ionization (CH₄ reagent gas).

Analyte	Acronym	Ion Monitored
<i>N</i> -methylperfluorooctanamide	MeFOA	428 [M+1] ⁺
<i>N</i> -ethylperfluorooctanamide	EtFOA	442 [M+1] ⁺
<i>N</i> -methyl- <i>N</i> -(2-hydroxyethyl)perfluorooctanamide	MeFOAE	454 [M-17] ⁺
<i>N</i> -ethyl- <i>N</i> -(2-hydroxyethyl)perfluorooctanamide	EtFOAE	468 [M-17] ⁺
<i>N</i> -methylperfluorononanamide*	MeFNA	478 [M+1] ⁺

* only in Scotchgard, pre-2001

Table S2. Mean concentrations of PFAM concentrations ± one standard deviation in electrochemical sulfonamide materials as determined by GC-MS (*n* = 3). All concentrations normalized to dry mass. n/d = not detected.

Material	Manufacturer	Amide Detected	Concentration (µg/g)
EtFOSA	Lancaster Scientific	EtFOA	150 ± 7
EtFOSE	3M, Lot A	EtFOA	604 ± 10
EtFOSE	3M, Lot B	EtFOA	5139 ± 480
EtFOSE	3B Pharmachem	EtFOA	26 ± 2
Scotchban FC-807A	3M	EtFOA	266 ± 10
di-SAmPAP	Defu	EtFOA	12 ± 1
MeFOSE	3M	MeFOA	6736 ± 448
Scotchgard, pre-2001	3M	MeFOA	260 ± 18
Scotchgard, pre-2001	3M	MeFNA	v. low
Scotchgard, post-2001	3M	n/d	n/d
EtFOSE	Wellington Labs	n/d	n/d

Figure S1. Mass spectrum of *N*-methylperfluorooctanamide (MeFOA) obtained in positive chemical ionization mode with methane reagent gas.

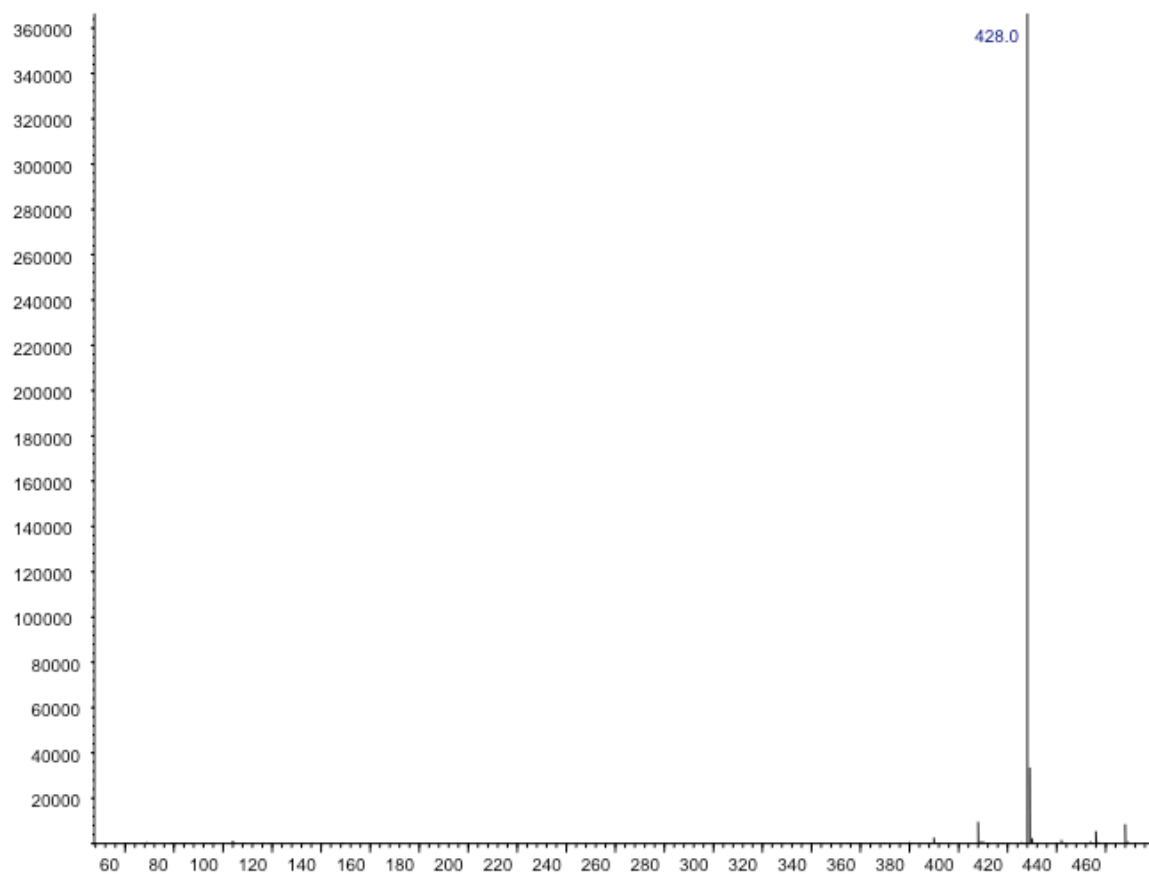


Figure S2. Mass spectrum of *N*-ethylperfluorooctanamide (EtFOA) obtained in positive chemical ionization mode with methane reagent gas.



APPENDIX C

SUPPORTING INFORMATION FOR CHAPTER FIVE

Enzymatic Kinetic Parameters for Polyfluorinated Alkyl Phosphate Hydrolysis by Alkaline Phosphatase

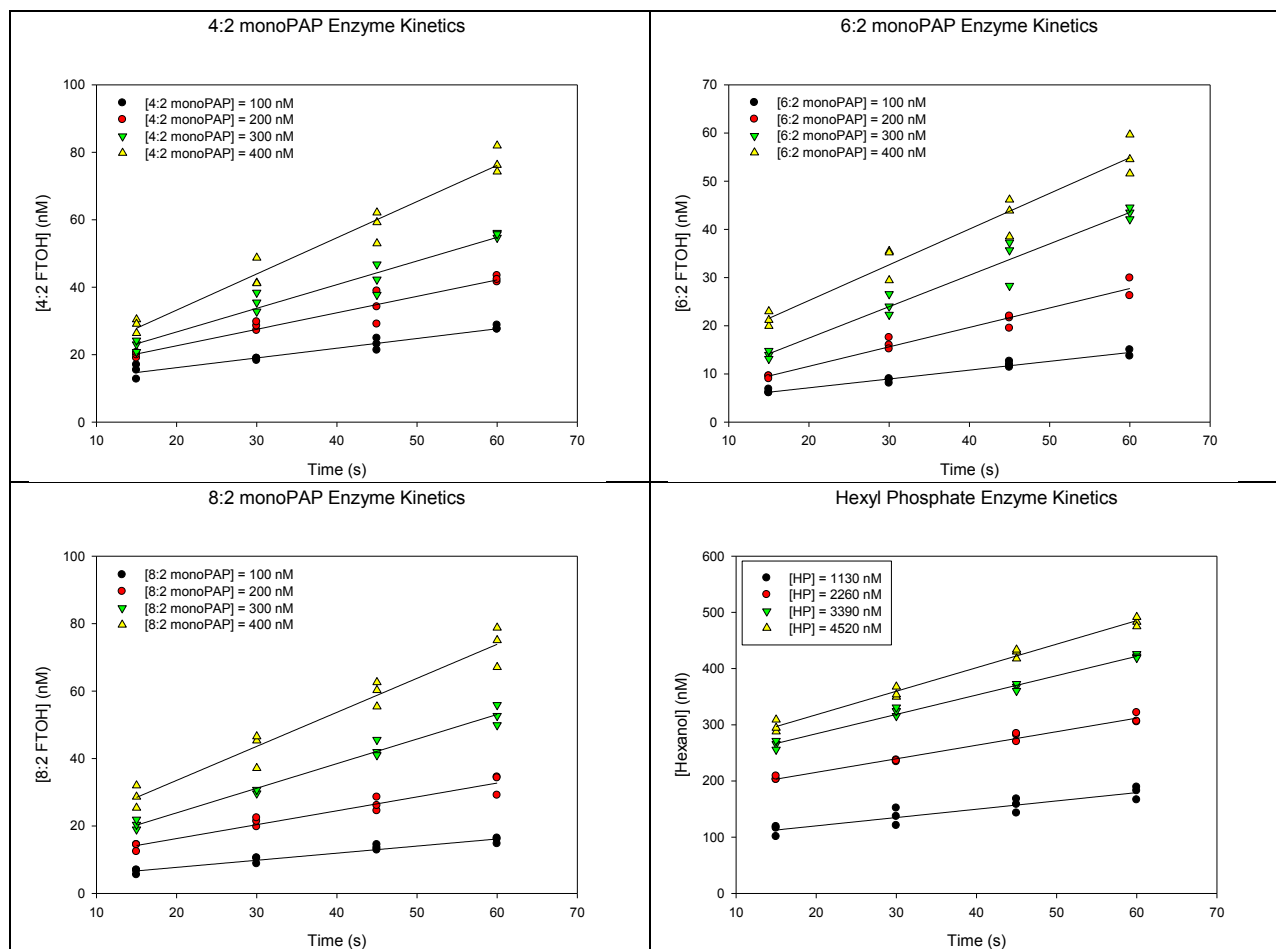
Figure S1: Concentration vs. time plots for k_{cat} / K_M experiments

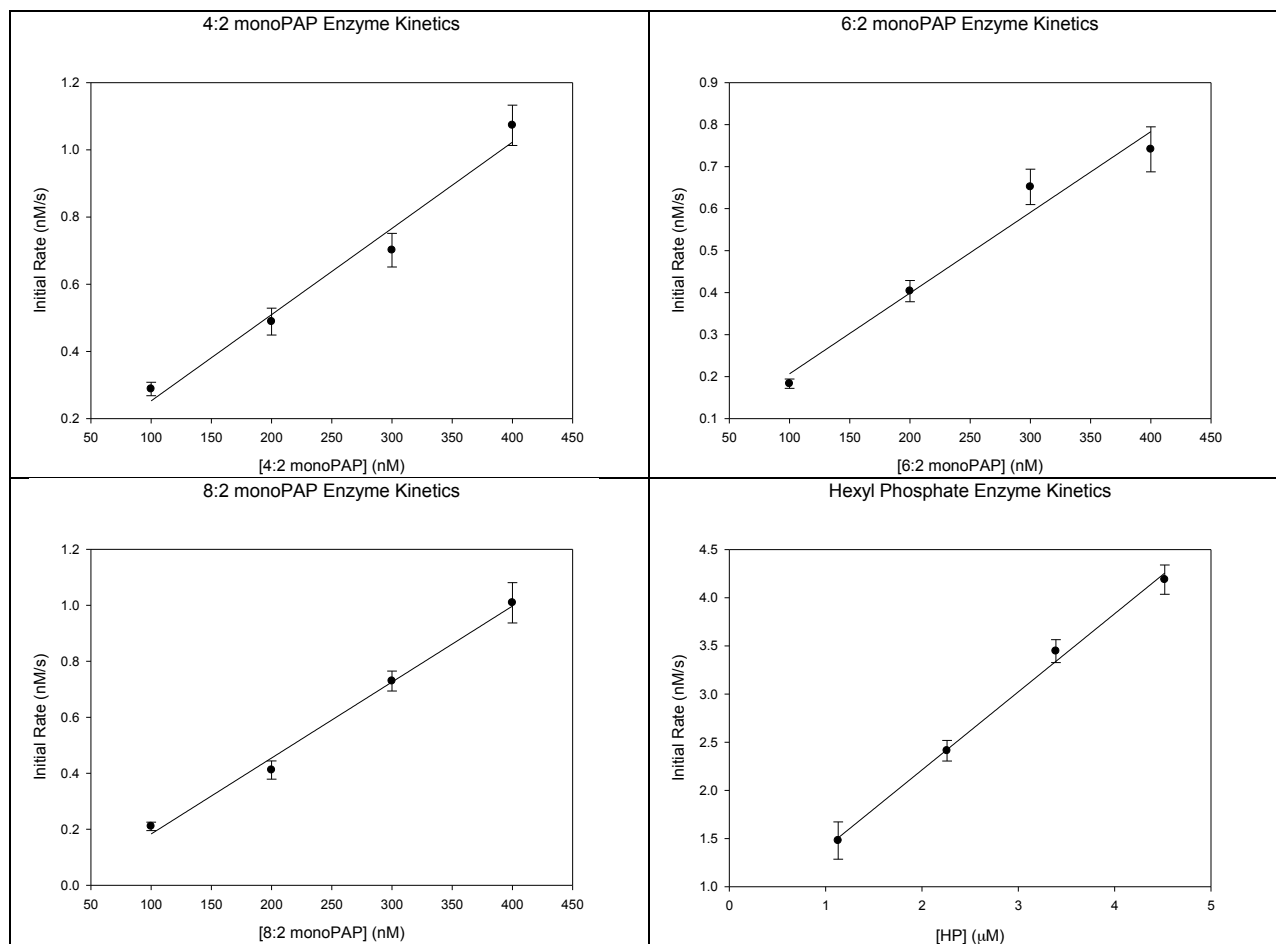
Figure S2: Initial rate vs. concentration plots for k_{cat} / K_M experiments

Table S1: Full K_M data for competition kinetics experiments.

Compound	K_M (monoester) (μM)	K_M (PNPP) (μM)	R
4:2 monoPAP	191 ± 17	89 ± 4	2.1 ± 0.2
6:2 monoPAP	80 ± 15	89 ± 4	0.9 ± 0.2
8:2 monoPAP	59 ± 4	35 ± 2	1.7 ± 0.1
Hexyl Phosphate	532 ± 53	62 ± 3	8.6 ± 1
Octyl Phosphate	803 ± 52	62 ± 3	13.0 ± 1
Decyl Phosphate	502 ± 27	62 ± 3	8.1 ± 0.6
Dodecyl Phosphate	247 ± 15	62 ± 3	4.0 ± 0.3

The K_M (PNPP) values were always obtained concurrently with the competition kinetics experiments on the desired monoester. They were converted into a relative (R) value due to enzyme activity variation over time where $R = K_M (\text{monoester}) / K_M (\text{PNPP})$.