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DEVELOPMENT OF NEW METHODS AND POLYPHOSPHAZENE CHEMISTRIES FOR ADVANCED MATERIALS APPLICATIONS

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by
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ABSTRACT

The work described within this thesis focuses on the design, synthesis, and characterization of new phosphazenes with potential in advanced materials applications. Additionally, these unique polymers required the development of novel reaction methods or the investigation of new phosphazene chemistry to achieve their synthesis. Chapter 1 lays out some of the basic principles and fundamentals of polymer chemistry. A historical overview of phosphazenes is also included along with an indepth look at the chemistry of polyphosphazenes and how they relate to advanced materials for power generation and biomedical applications.

Chapter 2 investigates the use of iodinated polyphosphazenes as x-ray opaque materials. Single-substituent polymers with 4-iodophenoxy or 4-iodophenylanine ethyl ester units as the only side groups were prepared. Although a single-substituent polymer with 3,5-diiodotyrosine ethyl ester groups was difficult to synthesize, probably because of steric hindrance, mixed-substituent polymers that contained the non-iodinated ethyl esters of glycine, alanine, or phenylalanine plus a corresponding iodinated substituent, could be synthesized. Multinuclear NMR spectroscopy was used to follow the substitution of side groups onto the phosphazene back bone and judge the ratio of substituents. Heterophase studies of the hydrolysis of iodo-amino acid/non-iodinated amino acid side group species in deionized water at 37 °C followed a bulk hydrolysis profile, with the rates dependent on the structure of the side groups. The effectiveness of these polymers as X-ray opaque materials was examined by the use of the poly(organophosphazenes) and conventional organic polymers as filters for copper Kα or rhenium-tungsten-molybdenum radiation. The phosphazene polymers that contained iodine in the side groups were opaque to X-rays, whereas the conventional organic polymers were essentially transparent to the same radiation.

Chapter 3 details the initial investigation into 3,4-dihydroxy-L-phenylalanine ethyl ester and dopamine substituted polyphosphazenes that could be applied to a number of applications. L-DOPAEE was acetonide protected to prevent crosslinking reactions by the catechole functionality. Cyclic small molecule studies and macromolecular substitution reactions on the linear high polymer
were conducted with the protected L-DOPA. After isolation of the substituted phosphazene, the acetonide protecting group was removed in acidic conditions. Attempts to acetonide protect dopamine by the same method as L-DOPA yielded 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinolinium (DTTQ) by an acid catalyzed Pictet-Spengler reaction. DTTQ was utilized in chlorine substitution reactions at both the trimer and polymer levels. Weather it was obtained as a single substituent or glycine, alanine, or phenylalanine ethyl ester cosubstituted polymer, the hydrolytic stability of DTTQ polyphosphazenes was evaluated. As a result or oxidative instability or coordinated hydrochloric acid, the DTTQ substituted phosphazenes readily hydrolyzed when exposed to deionized water. Continuing studies into protection of the dopamine catechol have elucidated a viable method for the synthesis of amino-linked dopamine polymers.

Chapter 4 describes a method for the synthesis of phosphazenes with quaternary amine complexes as potential antibacterial agents. Replacement reactions of pyridine alkoxides and chlorophosphazenes were first attempted at the small molecule level to study the reactivities of pyridine alkoxides. The formation of an insoluble product indicated the participation of pyridine alkoxides in macromolecular substitution, but a co-substituent was necessary for the formation of a soluble product. In order to obtain a soluble product at the polymer level, a typical two-step addition, side group exchange reactions between poly[(trifluoroethoxy)phosphazene] and 4-pyridine propoxide, and a three-step addition were attempted. Only the three-step addition where the solubilizing co-substituent is added first and last yielded soluble pyridine propoxy polymers. Pyridine methoxy substituted polymers were noted to be more soluble than their pyridine propoxy analogues and a homosubstituted pyridine methoxy polyphosphazene was obtained. Quaternization of the pyridine nitrogen was possible when an excess amount of 1-bromohexane was added to the reaction. Anti-bacterial studies with low polymer loadings (<900 μg/mL) did not show any therapeutic activity. Higher loadings (≥ 1500 μg/mL) should be evaluated during future studies.

Chapter 5 evaluates the potential for functionalization of polyphosphazenes by “click” chemistry with the intent of forming pendent 1-H-[1,2,3]-triazoles. Alkynoxides were co-substituted
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Chapter 6 examines the hydrophobicity and reactivity of a phosphazene system with engineered branches of well defined length occurring at precise intervals along the polyphosphazene backbone. Poly[(hexachlorophosphazo)tetrachlorophosphazene] was synthesized by the thermal ring opening polymerization of its monomer which is prepared by the treatment of hexachlorocyclotriphosphazene with ammonia followed by phosphorous (V) chloride. The polymer was treated with trifluoroethoxide and the hydrophobicity of fiber mats obtained by electrospinning were evaluated. The increased fluorine loading found in this polymer does not give an enhancement of the hydrophobic character when compared to linear trifluoroethoxy substituted polyphosphazenes. Cyclo-linear phosphazene polymers were synthesized from phosphazo precursors by adapting methods developed for the living cationic polymerization. Polymers contained 27, 2, or 1 P=N unit between each ring in the structure. Phosphazene-organic hybrid polymers were also prepared from the phosphazophosphazene cyclic monomer and were connected by reacting with a diamine. Molecular weight analysis of these cyclo-linear polymers show that with optimization, it may be possible to obtain high molecular weight species.
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Preface

Portions of this thesis have been adapted for publication. Chapter 2 was adapted for publication in Polymer Chemistry (2010, 1, 1467) and coauthored by H.R. Allcock, A.A. Soudakov, G.H. Imler, C.T. Laurencin, and L.S. Nair. The work detailed in chapter 3 and chapter 5 was intended for eventual submission to Macromolecules. Portions of chapter 6 were adapted for publication in Journal of Adhesion Science and Technology (2009, 23, 435) and coauthored by H.R. Allcock, L. Steely, and A. Singh.
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Chapter 1

Introduction to Polymer Chemistry

1.1 History of Polymers

Despite the belief that polymers and polymer chemistry are relatively new fields of chemistry, humans have used polymers for many centuries. It was not until the mid-19th century that contemporary polymer chemistry first took root. In the 1830s, the photochemical polymerization of vinyl chloride and the polymerization of styrene into a glassy solid were two of the first reported synthetic polymers. Another important milestone which occurred around the same time was the vulcanization process (sulfur-induced crosslinking) developed by Charles Goodyear in 1839. Whether accidental or intentional, these discoveries spurred corporate research and the development of polymer chemistry.

Over the next 90 years, numerous polymers based on the chemical modification of cellulose, a natural polymer found in wood and cotton, were developed. Cellulose nitrate was one such polymer obtained from the reaction of cellulose and nitric acid. The work of Christian F. Schöbein with cellulose nitrate led to the commercialization of this polymer as celluloid, one of the first man-made thermoplastics. During this time, Leo H. Baekeland formulated a synthetic phenol-formaldehyde resin. This product was widely commercialized as Bakelite beginning in 1907. Advancements in analytical methods and techniques also allowed researchers to gather data supporting the “macromolecular hypothesis”.

In 1920, Hermann Staudinger proposed that polymers were covalently bonded macromolecules rather than loosely associated clusters of small molecules. This theory was supported by his work with polystyrene, rubber and polyoxymethylene and the work of Emil
Fischer on the structure of proteins. The macromolecular theory was further supported by Carothers when he synthesized high molecular weight polyamides and polyesters from thoroughly characterized, low molecular weight molecules. Staudinger was awarded the 1953 Nobel Prize in Chemistry for his advancement of polymer chemistry.

During World War II, when traditional materials were being diverted toward the war effort, new polymers were developed rapidly to fill technological and material voids. After the war, the availability of compounds from the petrochemical industry allowed rapid development of new polymers. Now utilized as inexpensive, commercial “commodity” polymers, many of the macromolecules discovered in the short history of polymer chemistry have been studied extensively and their potential applications determined. Research in polymer chemistry now focuses on the development of novel high-performance polymer systems or architectures which are able to fill specialized markets.2,3

1.2 Structural Classifications of Polymers

The etymology of polymer is from the classical Greek words poly and meros which are roughly translated as “many parts.” A homopolymer can be defined as a macromolecule made up by a well defined repeating structure, where each identical repeat unit is covalently bound to the next unit. The small molecule repeat unit is also known as a “monomer.” One of the most important characteristics of a polymer is the molecular weight, or molar mass. Polymers of the same chemical formula have distinctly different properties when a high molecular weight polymer is compared to a low molecular weight polymer. There is a critical point where properties become independent of weight and occurs at roughly 1000 to 2000 repeat units. An oligomer is a polymer precursor with very few repeat units joined in the chain. A polymer chain is typically represented as a straight molecule. In reality, the polymer exists as a twisted and
Another factor that strongly influences polymer properties is the polymers architecture or chain structure. Examples of more common architectures are shown in Figure 1.\textsuperscript{2,3,10,11}

1.2.1 Polymer Architectures

The most common polymer structure is the linear polymer where long chains of repeat units are attached end to end. Most linear polymers are soluble in some organic solvent and the viscosity of the resulting solution is proportional to the chain length of the polymer. Physical properties of linear polymers are highly dependent on the chemical structure of the monomer unit. The resulting materials can be anything from amorphous materials to highly crystalline, glasslike materials.

Related to linear polymers are branched and brush polymers. These macromolecules are best described as linear polymers with random divergent side chains made from the same repeat unit. Many properties of branched polymers are similar to those of analogous linear polymers. However, branched polymers are less likely to crystallize and have lower solution viscosities due to their irregular structure. Brush or comb polymers are similar to branched polymers except that the divergent side chains occur at more regular intervals.\textsuperscript{3,11}

A polymer which has multiple chains interconnected by covalent bonds is known as a cross-linked or network polymer. The inter-chain bonds, or cross-links, can be formed either during polymer synthesis if an appropriate monomer is utilized or by secondary reactions after polymerization. These polymers will never dissolve in solvents, but can be swelled to various degrees depending on the density of cross-linking. Variation in the crosslink density can produce rubber like elastomers at low densities and thermally stable, rigid materials at high densities.\textsuperscript{3,11}
Figure 1-1. Architectures of homopolymers.
Star polymers and dendrimers are polymers where the chains extend from a central multifunctional core. These “arms” are linear polymers which do not have a theoretical limit to their length. Star polymers have a minimum of three “arms” which are either polymerized from the core or attached as preformed polymers with a reactive functional group at one end.\textsuperscript{3,11}

While similar to star polymers in some aspects, dendrimers are a three-dimensional structure with the chain ends forming a spherical shell around the core. Dendrimers are synthesized by sequential reactions in either a divergent or convergent process. The divergent process begins with the core and builds outward by attaching multifunctional monomers in successive layers, or generations. In the convergent method, previously synthesized dendrimeric fragments are affixed to the core molecule.\textsuperscript{3,11}

1.2.2 Copolymers

If the desired properties of a material cannot be achieved by a homopolymer, it is possible to form polymers with new properties using two or more different monomers. The actual sequence of monomer units in the polymer backbone is determined by monomer reactivities, the sequence of monomer addition to the reaction, and the polymerization mechanism. Common sequences seen when two monomers are polymerized are random, alternating, block, and graft copolymers (Figure 1-2).\textsuperscript{2,3,11}

Random copolymers, like their name suggests, have a completely random distribution of the two monomers along the polymer backbone. The crystallinity of random copolymers is greatly reduced, causing a drop in the melting temperature ($T_m$), in comparison to either of the respective homopolymers because the polymer structure is largely irregular. The glass transition temperature ($T_g$) of the copolymer is expected to fall somewhere in between the values of the two homopolymers. The other extreme is when the two monomers alternate regularly. The $T_m$ and $T_g$
values of an alternating copolymer are found in the range of the respective values of the homopolymers.\textsuperscript{2,3,11}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of AB copolymers.}
\end{figure}

Block copolymers are polymers which contain large sections synthesized from a single monomer which then abruptly changes to a different monomer. The properties of block copolymers are a combination of the properties of each homopolymer as long as each block is long enough. Graft copolymers are obtained either by polymerization of monomer B from active sites along polymer A or functional groups on preformed polymer B are reacted with polymer A. Short grafts can be used to modulate the T\textsubscript{m} of the backbone polymer by reducing crystallinity.\textsuperscript{2,3,11}

1.3 Methods of Polymer Synthesis

Another method for the classification of polymers is by the mechanism through which the polymer chain grows. There are three basic categories of polymerization mechanism with each
having many: 1) Step-growth polymerization, 2) Chain-growth Polymerization, and 3) Ring-opening polymerization. Many polymers can be synthesized using more than one polymerization mechanism. The mechanism to be used in the polymerization of each monomer depends on the type and number of functional groups present.

### 1.3.1 Step-Growth Polymerization

Step-growth polymerizations are characterized by reactions between monomer functional units which release a small molecule byproduct. These polymerizations are commonly referred to as condensation polymerizations because many of the polymers formed give off water as the byproduct. This occurs either by the reaction of a single difunctional monomer (AB monomer) with another AB monomer to yield the ABAB dimer or the coupling of two monofunctional monomers (AA and BB monomers) to give the AABB product. In order to achieve high molecular weight polymers by this polymerization mechanism, the monomer(s) must be pure and the functional group pairs must present in exactly equal molar amounts. Following either of the reaction formats, the polymer grows as the monomer is rapidly converted into oligomers. Even if precautions are taken, lengthy reaction times are needed as truly high molecular weight polymers are not formed until oligomers and other short chain species begin to couple. Many commercial polymers (Figure 1-3); such as nylons, Kevlar, poly(ethylene terephthalate) (PET), and polycarbonates; are synthesized by step-growth polymerizations.
Figure 1-3. Examples of step-growth polymers.
In contrast to step-growth polymerizations, chain-growth polymerizations are initiated by a reactive radical or ionic species and convert monomers directly into high polymers. Monomers capable of participating in these polymerizations are characterized by unsaturation and include ethylene, styrene, tetrafluoroethylene, and isobutylene (Figure 1-4).

Regardless of the initiating species; radical, cation, or anion; the mechanism follows three principle steps. First is the initiation step where the active species is generated by dissociation reactions of peroxides, azo compounds, metal halides (e.g. AlCl₃, BF₃), metal amides, or organometallic compounds. The initiated monomer species is formed from the reaction of a monomer molecule with the initiator. During the propagation step, the initiated monomer reacts with other monomers rapidly forming a high molecular weight polymer with the active site on the terminal repeat unit. Propagation will continue until a termination process quenches the active site on the polymer. This can occur by combination or disproportionation of two active
polymer chains or proton abstraction from another molecule. Living polymerizations are cases of chain-growth polymerizations where termination reactions do not occur or are reversible. These living polymerizations are of interest because the reaction can be resumed by the addition of more monomer. An example of chain-growth polymerization is the initiation of methy acrylate by 2,2’-azobis(isobutyronitrile).12-14

Figure 1-5. Reaction sequence for the chain-growth polymerization of methyl acrylate.
1.3.3 Ring-Opening Polymerization

Ring-opening polymerization (ROP) of cyclic monomers or oligomers is a versatile method which has been applied to a number of organic and inorganic systems. While similar or identical polymers can be synthesized by ring-opening polymerization and step-growth polymerizations, the ring opening does not result in the loss of a small molecule. Ring-opening polymerization also differs from chain-growth polymerizations in that no multiple bonds are lost during the reactions. The main driving force for most ring-opening polymerizations is the release of ring strain, but a catalyst or heat can be applied to facilitate the reactions. Epoxides, lactones, lactams, siloxanes, and phosphazenes are some of the polymers which utilize ring-opening polymerizations for commercial production (Figure 1-6).

![Diagram of ring-opening polymerization of selected organic and inorganic "monomers".](image)

**Figure 1-6.** Ring-opening polymerization of selected organic and inorganic "monomers".
1.4 Hybrid Inorganic-Organic Polymers

Since polymers entered the commercial market in the 20th century, the vast majority of these macromolecules are organic materials derived from petrochemicals or, more recently, biomass stocks. The low cost of the organic starting materials coupled with the breadth of organic reactions and facile processing facilitated the development of many materials. Readily available organic polymers are replacing much heavier materials like metal, glass, and wood. Despite these advantages, organic polymers have several chemical and physical limitations. The high carbon content makes many polymers chemically, thermally, oxidatively unstable. Organic polymers are limited physically by dissolution or swelling in organic solutions and narrow range of operational temperatures.

In an effort to overcome the limitations of purely organic polymers, novel polymers which contain both organic and inorganic elements are being investigated. These hybrid inorganic-organic polymers can have either an organic polymer backbone with inorganic side substituents or an inorganic backbone with organic side groups. Either of these approaches can yield polymers with improved physical and chemical properties. Two common hybrid inorganic-organic polymer systems are poly(organosiloxanes) and polyphosphazenes (Figure 1-6).

1.5 Polyphosphazenes

1.5.1 Significance

Polyphosphazenes are a type of hybrid inorganic-organic polymers with an alternating phosphorous-nitrogen backbone and two organic side groups attached to each phosphorous atom (Figure 1-7). The macromolecular replacement of chlorine atoms by organic nucleophiles to yield the final polymer is unusual in polymer synthesis. This method allows the polymer
structure and chemical properties to be highly dependent on the organic side group selected, in contrast to common organic polymers where the final properties are determined by the monomer. However, the phosphazene backbone does contribute useful properties such as thermo-oxidative stability, fire-retardance, and low glass transition temperatures. The versatility of phosphazenes has led to the synthesis of several hundred discrete polymers with a wide array of physical and chemical properties. Phosphazenes have been used as fire retardants, electro-optical materials, ion and proton conduction, and biomedical materials.\textsuperscript{15,16}

![Diagram of phosphazene synthesis](image)

**Figure 1-7.** Synthesis of poly(dichlorophosphazene) and macromolecular substitution by organic nucleophiles

### 1.5.2 Synthesis

Although the initial synthesis of a white crystalline compound was noted by Liebig\textsuperscript{17} and Rose\textsuperscript{18} in 1834, it was not until the 1870s that work by Gerhardt\textsuperscript{19}, Gladstone\textsuperscript{20}, and Wichelhaus\textsuperscript{21} elucidated the structure as hexachlorocyclotriphosphazene, a cyclic small-molecule trimer.
Stokes first polymerized hexachlorocyclotriphosphazene (trimer) and higher cyclic species in the 1890s.\textsuperscript{22} Subsequent work demonstrated that this inorganic rubber was formed by a thermal ring-opening polymerization. The polymer decomposed during exposure to the atmosphere.\textsuperscript{22-28} Progress in phosphazene chemistry was mostly stagnant until 1964 when Allcock and Kugel discovered a method for preparation of soluble polyphosphazenes which is the basis for current work with phosphazenes.\textsuperscript{29-31}

The procedure begins with the purification of hexachlorocyclotriphosphazene by re-crystallization from hexanes or heptanes and subsequent sublimation. The purified material is sealed under vacuum in a glass tube and heated to 250°C for several hours. Progress of the thermal ring-opening polymerization is determined by viscosity and is terminated after anywhere from 6 to 48 hours. The unconverted trimer (25-40\%) is separated from the poly(dichlorophosphazene) by sublimation. Low conversion during the melt polymerization is standard, but is preferential to cross-link formation at high conversion. Reclaimed trimer can be recycled in subsequent polymerizations. While the poly(dichlorophosphazene) obtained through this method is very high molecular weight, there is no direct control over polydispersity or molecular weight.\textsuperscript{15}

An alternative method of synthesizing poly(dichlorophosphazene) by a living cationic polymerization was developed by Allcock, Manners, et. al.\textsuperscript{32,33} The monomer, trichloro(trimethylsilyl)phosphoranamine, is exposed to a cationic initiator, usually phosphoros (V) chloride (PCl\textsubscript{3}), displacing the trimethylsilyl group to produce an active site for chain growth (Figure 1-7). Unlike the thermal ring-opening method, this method allows precise control over the polydispersity and resulting molecular weight. The living chain end allows poly(dichlorophosphazene) to be incorporated into complex polymer architectures such as block copolymers.\textsuperscript{15}
1.5.3 Macromolecular Substitution

The facile replacement of chlorine atoms by organic nucleophiles in phosphazene synthesis is unique in polymer chemistry. The use of alkoxides, aryloxides, or amines has yielded several hundred polyphosphazenes which contain a single side group. Even more phosphazenes which are substituted with multiple side groups are obtained by either simultaneous or sequential reactions with different nucleophiles (Figure 1-7). The co-substitution of phosphazenes allows for the optimization of the polymer properties for numerous applications. Bulk properties of the final polymer are largely determined by the chemical functionality of the side groups. Some examples are hydrophobic and super-hydrophobic surfaces from phosphazenes with highly fluorinated side groups, water soluble and hydrolytically stable polymers with multi-etheric side groups, and hydrolytically sensitive polymers for tissue engineering with amino acid side groups. The macromolecular substitution allows tuning of the polymer properties by incorporation of a secondary substituent rather than the synthesis of new monomers in organic polymers.\textsuperscript{15}

1.5.4 Polyphosphazene Architecture

The versatility of macromolecular substitution combined with the living cationic polymerization allows multiple architectures to be fashioned. While star polymers and dendrimers have been synthesized from phosphazenes, linear, graft, and block copolymers are more common (Figure 1-8).\textsuperscript{15} Any polymer which has an terminal free amine can be used in the formation of a phosphazene block copolymer. Some examples are polyphosphazene-b-polyphosphazene\textsuperscript{34,35}, polyphosphazene-b-polystyrene\textsuperscript{36,37}, and polyphosphazene-b-polyethylene oxide copolymers\textsuperscript{38,39}. The phosphazene cyclic trimers, substituted by methods similar to the
high polymer, have been incorporated into cyclo-linear polymers\textsuperscript{40} and attached as pendent groups to organic polymers\textsuperscript{41,42} as other methods for modification of the polymer properties.

![Diagram of phosphazene architectures]

**Figure 1-8.** Examples of phosphazene architectures.

### 1.5.5 Applications

The properties needed for a broad assortment of applications can usually be achieved by some combination of side groups linked to the polyphosphazene backbone. One of the most versatile classes of side groups are perfluoro-alkoxides. Polymers based on trifluoroethoxy substituents are resistant to UV or gamma irradiation and can be fabricated into super-hydrophobic surfaces.\textsuperscript{43,44} Highly fluorinated polyphosphazenes cosubstituted with trifluoroethoxy, octafluoropentoxy, and cross-linkers produce elastomers which were used by the US military for extreme temperature applications.\textsuperscript{45,46} Polyphosphazenes with etheric side groups are used as
ionic conductive membranes in batteries. The low glass transition temperature and side groups, such as 2-(2-methoxyethoxy)ethoxy, allow ionic salts to be solvated, resulting in high conductivities. Similarly, polyphosphazenes with sulfonic acid side groups are used as proton conductive materials. Membranes have been fabricated into direct methanol fuel cells. Phosphazenes with other side groups have been evaluated as electroluminescent materials, fire retardants, and biomaterials.

Figure 1-9. Examples of polyphosphazenes and potential applications.
1.6 Biomaterials

Biomaterials are relatively new materials that are used in devices for correcting defects either within or outside the human body. The devices are fabricated out of metals, ceramics, or polymers and classified as bio-stable or bio-degradable depending on the longevity of the device. Metals and ceramics are typically used as bio-stable materials because they are not intended to remodel over time. Gold, stainless steel, and titanium are used for dental replacements, orthopedic pins and screws, and joint replacements. The desirable properties of these materials are their mechanical strength, corrosion resistance, light weight. Ceramics are mostly used for materials for orthodontic repairs and bone cements. Oxide based ceramics, such as calcium hydroxyapatite, are used in favor of non-oxide ceramic analogs. Polymeric materials are used for contact lenses (poly(dimethylsiloxane), hydrophobic elastomers (polyamides), and sutures (poly(methyl methacrylate)).

Biodegradable, or bio-absorbable materials, are generally characterized by hydrolytic or enzymatic instability which allow these materials to be broken down into small molecules and eventually excreted once placed within the human body. This class of materials is almost exclusively consists of synthetic polymers; such as polyanhydrides, poly(lactic-co-glycolic acid), (PLGA), polycaprolactone, and poly(trimethylene carbonate); and several natural polymers; such as collagen, chitosan, and alginates (Figure 1-10). Many of these polymers have been studied since the 1960s and have received FDA approval for use. While most polymers are used for drug delivery and degradable sutures, some materials are being developed for more advanced applications like tissue engineering, bioadhesives, and many other applications.
Figure 1-10. Representative polymers for biomaterials with FDA approval.

1.7 Polyphosphazene Biomaterials

Phosphazene are of particular interest as biodegradable materials because they have the potential to overcome the main drawback of PLGA and other polyesters.\textsuperscript{15,68} Hydrolytic degradation of PLGA, gives products that cause a localized drop in pH, leading to irritation or tissue necrosis surrounding the implanted device.\textsuperscript{69} Phosphazenes with imidazole\textsuperscript{58,59}, amino acid esters\textsuperscript{60-64}, lactide\textsuperscript{65}, glycolide\textsuperscript{65}, glucosyl\textsuperscript{66}, and glyceryl\textsuperscript{67} side groups are hydrolytically sensitive
and degrade to benign small molecules with near-neutral pHs. The mechanism of phosphazene hydrolysis is similar for most materials and an example of an amino acid ester polyphosphazene is discussed (Figure 1-11). The initial phase is the hydrolytic displacement of an amino acid ester to form a P-OH linkage in the backbone. The P-OH rapidly isomerizes to form a phosphazane which further sensitizes the polymer to hydrolytic degradation. After the phosphazane is formed, a second hydrolysis reaction results either in chain cleavage or displacement of the second organic substituent on the phosphorous atom. Whichever route is followed, a third hydrolysis reaction results in the polymer backbone being rapidly converted to phosphate and ammonia. The side chains are released as amino acid esters. The rate of hydrolysis can be controlled by the steric hindrance along the polymer backbone or the introduction of organic side groups attached by P-O linkages. Numerous polyphosphazenes have been studied as materials for controlled drug delivery vehicles and for the formation of tissue engineering scaffolds.

In this thesis the development of new synthetic methods and phosphazene reaction chemistries for eventual use in advanced applications is discussed. The research projects focused on the design, synthesis, and structural characterization of novel polyphosphazenes for various applications. Depending on the application and structure of the phosphazene, hydrolytic sensitivity was evaluated. The following chapter will outline the use of polyphosphazenes as radio-opaque materials. For example, the incorporation of iodine into select side groups, for bio-stable and biodegradable phosphazenes, was accomplished. The initial synthesis of polyphosphazenes containing L-3,4-dihydroxyphenylalanine ethyl ester and dopamine was investigated for materials with potential as bioadhesives. Novel polyphosphazenes for antibacterial coatings based on quaternized pyridines were also synthesized. Finally, novel methods for the synthesis of triazole containing-polyphosphazenes and hydrophobic phosphazenes were investigated.
Figure 1-11. Hydrolytic degradation of amino acid substituted polyphosphazenes.
1.8 References


Chapter 2

Iodine-Containing Radio-Opaque Polyphosphazenes

2.1 Introduction

The increasing use of polymers for implantation in the human body is accompanied by the challenge of monitoring these devices and their lifetimes by standard X-ray imaging techniques. Most polymers do not absorb significantly in the X-ray region of the electromagnetic spectrum, but recent reports have shown that polymers can be made opaque to X-rays. Initially, these examples were metal-oxide-polymer composites which require large amounts of inorganic salts often with more than 25 wt % of barium sulfate or zirconium dioxide incorporated as a composite. High inorganic salt loading has a detrimental effect on the physical properties of the composite, and cytotoxicity issues arise resulting from long-term exposure and leaching.\(^1\)\(^-\)\(^6\) A second method for rendering polymers radio-opaque is via a chemical incorporation of a radio-contrast dye, typically containing bromine or iodine.\(^4\)\(^-\)\(^13\) Although the resultant polymers are substantially more biocompatible than composite polymer systems, they are hydrogels which lack the necessary physical properties\(^3\)\(^,\)\(^13\), are too susceptible to hydrolytic degradation\(^7\), or are too hydrolytically stable for implants which remodel over time\(^4\)\(^,\)\(^5\)\(^,\)\(^9\). In this paper we report the introduction of iodine into the side group structure of poly(organophosphazenes) to facilitate radiological imaging of these polymers.

Poly(organophosphazenes) are a broad class of hybrid inorganic-organic polymers usually produced by chlorine-replacement reactions carried out on poly(dichlorophosphazene) (1). The nucleophiles used for chlorine replacement include alkoxides, aryloxides, or amines, and the different side groups control the properties and final uses of the polyphosphazene\(^14\). It is also possible to generate mixed-substituent polyphosphazenes in which two or more different organic
groups are linked to the phosphazene backbone. The emerging applications for polyphosphazenes include battery and solar cell electrolytes\textsuperscript{15,16}, optical materials\textsuperscript{17,18}, bioinert elastomers\textsuperscript{19-21}, and bioerodible materials\textsuperscript{22,23}.

Previous work in our program showed that specific poly(organophosphazenes) are biocompatible while being either biostable or biodegradable. For example, the biostable polymer, poly(diphenoxyporphazene) (2), is resistant to hydrolytic degradation at body pH.\textsuperscript{24} Similarly, poly[bis(2,2,2-trifluoroethoxy)phosphazene] (6), is biostable, hydrophobic, and borders on superhydrophobic.\textsuperscript{25} On the other hand, polyphosphazenes with amino acid ethyl ester side groups linked through the amino terminus are hydrolytically sensitive and degrade to biologically benign small molecules. The steric bulk and hydrophobicity of the group at the α-position of the amino acid governs the rate of hydrolysis of these polymers.\textsuperscript{26-29} Polyphosphazenes are an attractive choice for X-ray opaque applications. The presence of phosphorus atoms in the polymer backbone, the use of various side groups that contain heavy elements such as iodine, and the demonstrated tune-ability of hydrolytic degradation provide potential starting points for polyphosphazenes to be utilized in the field of radio-opaque polymers. This study has laid the groundwork for the development of biocompatible polyphosphazenes that are radio-opaque.

Poly[bis(4-iodophenoxy)phosphazene], poly(diethoxyphosphazene), 2, and 6, were investigated initially as model systems. These polymers were exposed to Cu Kα and Re-W-Mo medical x-rays to provide a baseline of radio-opacity. Information gathered from the synthesis and characterization of these polymers was then applied to the design and synthesis of iodine-containing radio-opaque amino acid ester polyphosphazenes.
2.2 Experimental

2.2.1 Reagents and Equipment

All synthesis reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran (EMD), 1,4-dioxane (EMD), and triethylamine (EMD) were dried using solvent purification columns. Ethanol (EMD) and 2,2,2-trifluoroethanol (Aldrich) were distilled from CaH$_2$ and were stored under dry nitrogen. 3,5-Diiodotyrosine ethyl ester hydrochloride (Senn Chemicals), glycine ethyl ester hydrochloride (Bachem), alanine ethyl ester hydrochloride (Chem-Impex), phenylalanine ethyl ester hydrochloride (Chem-Impex), and phenylalanine (Bachem) were used as received. Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Japan) in evacuated Pyrex tubes at 250°C. Chemicals and polymers not mentioned above were used as received without purification. $^{31}$P, $^{13}$C, and $^1$H NMR spectra were obtained with use of a Bruker 360 WM instrument operated at 145 MHz, 90 MHz, and 360 MHz, respectively. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10°C/min and a sample size of ca. 10 mg. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-n-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards.
2.2.2 Synthesis of Polymers 2-7

Polymers 2-7 were synthesized in a similar fashion, with the synthesis of polymer 4 described as an example. Poly(dichlorophosphazene) (5.00 g, 0.0431 mol) was dissolved in 500 mL of dry 1,4-dioxane. Sodium metal (1.55 g, 0.0647 mol) was suspended in 200 mL of dry 1,4-dioxane, and phenol (6.08 g, 0.0647 mol) was added. This suspension was stirred until the sodium metal had been consumed by the reaction. Half of this solution was added dropwise to the polymer solution. The mixture was refluxed for 24 hours as the progress of the reaction was monitored by $^{31}\text{P}$ NMR spectroscopy. Sodium metal (0.99 g, 0.0431 mol) was suspended in 200 mL of dry 1,4-dioxane and allowed to react with 4-iodophenol (9.49 g, 0.0431 mol) until the sodium metal had reacted. This solution was added dropwise to the polymer reaction mixture and the solution was refluxed while the progress of substitution was monitored by $^{31}\text{P}$ NMR spectroscopy. The reaction was completed by dropwise addition of the remaining sodium phenoxide solution. When complete chlorine replacement was determined by $^{31}\text{P}$ NMR spectroscopy, most of the solvent was removed in vacuo, and the residue was precipitated into water. Polymer 4 was purified by repeated precipitations from THF into water (2x) and hexanes (2x) and was isolated as a off-white polymer (yield of 79%) soluble in THF and dioxane.

Characterization data for polymers 2-7 are shown in Table 2-1 and Table 2-2.

2.2.3 Synthesis of 4-Iodo-L-Phenylalanine (8)

This synthesis was adapted from previously published literature. L-Phenylalanine (20.07 g, 121 mmol) in 100 mL of HOAc and 15 ml of concentrated H$_2$SO$_4$ was stirred while powdered I$_2$ (12.35 g, 47.0 mmol) and NaI0$_3$ (5.09 g, 25.6 mmol) were added. The reaction mixture was heated to 70 °C and NaIO4 (1.0 g, 46.7 mmol). Reaction progress was monitored
by mass spectroscopy. The solution was concentrated and the residual oil was diluted with water. The aqueous later was extracted with 50 mL of Et₂O (x2) and CH₂Cl₂ (x2). The aqueous solution was neutralized to precipitate the crude product. After chilling, the crude product was collected by filtration and rinsed with a minimal amount of chilled water and ethanol yielding 4-iodophenylalanine (22.5 g, 64%). ¹H NMR (D₂O), ppm: δ 7.55 (d, 2H), 6.88 (d, 2H), 4.13 (t, 1H), 3.08 (dd, 1H), 3.2.95 (dd, 1H); m/z = 292 [(M+H)⁺].

2.2.4 Synthesis of 4-Iodo-L-Phenylalanine Ethyl Ester Hydrochloride (9)

Thionyl chloride (20.4 g, 0.172 mol) was added dropwise to 50 mL of ethanol chilled in an ice bath. 4- Iodophenylalanine (10.0 g, 0.0343 mol) was added and the solution slowly returned to room temperature. The reaction was heated for 12 h and the reaction progress was monitored by mass spectroscopy. When complete, the reaction was dried to yield a white solid. The crude product was dissolved in a minimum amount of hot methanol and recrystallized by the addition of ether to give 4-iodophenylalanine ethyl ester hydrochloride (11.34 g, 93%): ¹H NMR (D₂O), ppm: δ 7.53 (d, 2H), 6.85 (d, 2H), 4.12 (m, 3H), 3.07 (dd, 1H), 2.93 (dd, 1H); m/z = 320 [(M–Cl)⁺]

2.2.5 Synthesis of Polymers 10- 17.

Polymers 10-17 were synthesized in a similar manner, with the preparation of polymer 10 described as an example. Poly(dichlorophosphazene) (5.00 g, 0.0431 mol) was dissolved in dry THF (500 mL). Alanine ethyl ester hydrochloride (11.58 g, 0.0754 mol) was suspended in 200 mL of dry THF, and triethylamine (15.26 g, 0.151 mol) was added. This suspension was refluxed for 24 hours, then filtered, and half of the reaction mixture was added dropwise to the polymer
solution. The reaction mixture was refluxed and monitored by $^{31}$P NMR spectroscopy. 3,5-
Diiodotyrosine ethyl ester hydrochloride (10.72 g, 0.0216 mol) was suspended in 200 mL of dry
THF, and triethylamine (4.36 g, 0.0432 mol) was added. This suspension was refluxed for 24
hours, then filtered and added dropwise to the polymer solution. The mixture was refluxed for 24
hours, with the progress of the reaction again monitored by $^{31}$P NMR spectroscopy. Complete
chlorine replacement was then achieved by addition of the remainder of the alanine ethyl ester
solution followed by heating the reaction mixture at reflux. After confirmation of complete
halogen replacement by $^{31}$P NMR spectroscopy, the reaction mixture was filtered, concentrated in
vacuo, and the residue precipitated into hexanes. Polymer 10 was purified by dialysis against
methanol (3 days) and, after solvent removal, was isolated as a pale yellow-orange polymer (yield
of 82%). The resulting polymers are soluble in a variety of organic solvents such as methanol,
ethanol, THF, and dioxane. Characterization data for polymers 10-17 are shown in Table 2-3.

2.2.6 Hydrolytic Degradation of Polymers 10-17

Polymers 10-17 (200 mg) were dissolved in 2 mL of chloroform (10% solution g/mL). Films were solution-cast and air-dried for 24 hours, then dried under reduced pressure for 7 days.
Each film had a thickness of approximately 500 μm. Samples were distributed into 18 different
test tubes containing 10 mL of deionized water (pH=6.0). The tubes were contained in a constant
shaker bath at 37°C. Three samples were removed at each of the time points: 7, 14, 21, 28, 35,
and 42 days. The weight loss was monitored for each solid sample and the pH of each hydrolysis
medium was analyzed. $^{31}$P and $^1$H NMR techniques were utilized to follow the formation of any
small molecule hydrolysis products dissolved in the aqueous medium. Silver nitrate and
ninhydrin tests were employed to qualitatively determine the presence of phosphates and
ammonia or amino acids, respectively.
2.2.7 Radio Opacity Testing.

2.2.7.1 Soft X-rays.

Polymers 2 and 6 were solution-cast from a 10% solution (g/mL) in THF and air-dried for 24 hours. The films were further dried under reduced pressure for 5 days. Polymers 3-5 were heated to 210°C and then pressed into thin films at 3,000 lbs/ft². Polymers 10-17 were solution-cast from a 10% wt/vol solution in THF and air-dried for 24 hours followed by reduced pressure for 5 days. The films were then mounted on a support bar and placed in the path of x-rays from a Cu Kα source.

2.2.7.2 Hard X-rays (Medical X-ray Condition).

Polymers 2, 4, and 5 were processed thermally in the manner described above, with the exception that aluminum molds were used to obtain pellets of the polymers 2 cm in diameter and 4.80 mm or 1.97 mm thick. Polymers 10-12 and 14-17 were either solution-cast from 10% wt/vol solutions, to yield films 0.5-1 mm thick or thermally precessed into pellets 2cm in diameter and 4.80 mm thick. Polyethylene, poly(methyl methacrylate), polyvinyl chloride, polystyrene, poly(ethylene oxide), poly(lactic-co-glycolic acid) (50/50), and poly(dimethylsiloxane) were melt-processed in the 4.80 mm thick molds. X-ray images were obtained at The Pennsylvania State University Health Center using a Kodak 7500 DR machine with a tungsten source at 50kV and 1mAs.
2.3 Results and Discussion

The synthesis of bioerodible polyphosphazenes with iodo-aryloxy side groups presents a challenge. Other investigators\(^{32-34}\) reported a method for iodination of aryloxyphosphazenes using triflic acid and a pyridine-iodine complex, conditions that would lead to decomposition of the amino acid ester polyphosphazenes that are the focus of this present work. All the polymers used in the present work were prepared by the replacement of chlorine atoms in poly(dichlorophosphazene) (1) by organic units that already contained iodinated substituents, thus avoiding decomposition of the polymers during a subsequent iodination process. Three different classes of poly(organophosphazenes) were synthesized. The first included single-substituent and mixed-substituent polymers with phenoxy-, 4-iodophenoxy-, trifluoroethoxy-, or ethoxy side groups. These are relatively straightforward syntheses carried out to give non-bioerodible polymers for use as controls in the evaluations of X-ray opacity. The linkage of the aryl units to the skeleton via Ar-O-P linkages generates hydrolytically stable polymers. The second group included mixed-substituent polymers that contained di-iodotyrosine side groups together with non-iodinated amino acid ester substituents, all linked to the skeleton through the amino terminus of the side units. The third group of polymers contained iodophenylalanine either as single-substituent species or cosubstituted with a non-iodinated amino acid ester.

2.3.1 Synthesis and Structural Characterization of Polymers 2-7.

In the first group, polymers 2-7 were synthesized by the process shown in Figure 2-1. The progress of each reaction was monitored using \(^{31}\)P NMR spectroscopy via the disappearance of the PCl\(_2\) peak at -17 ppm and growth of the peak that corresponds to P(OR)\(_2\) (indicated in Table 2-1), which represents full chlorine replacement. Formation of the single-substituent
polymers 2, 6, and 7 usually required only 48 hours or less in refluxing THF to complete the substitution. However, the introduction of 4-iodophenoxy groups to form polymer 5 required at least a week for complete halogen replacement to be achieved even after replacing the THF solvent by refluxing dioxane at 100°C.

![Chemical structure](image)

**Figure 2-1.** Synthesis of bio-stable polymers 2-7.

The initial attempts to produce the mixed-substituent polymers 3 and 4 involved the dropwise addition of sodium 4-iodophenoxide to poly(dichlorophosphazene) in refluxing dioxane as the first substituent, followed by sodium phenoxide as the second substituent. However, loss of the $^{31}$P NMR signal after 24 hours of refluxing in dioxane indicated that the partially-substituted polymer had precipitated from solution. A change of solvent to THF or benzene did not improve the solubility of this partly-substituted polymer. Therefore, a three-step addition of the substituents was utilized for the synthesis of polymers 3 and 4 using boiling dioxane as a solvent. Half of the stoichiometrically-required sodium phenoxide was added first in a dropwise manner to ensure that a wide distribution of phenoxy groups was obtained and to maintain the solubility of the polymer during the subsequent addition of 4-iodophenoxide. The $^{31}$P NMR spectrum was monitored over the duration of the reaction to determine when substitution of each
addition was complete. For example, after 24 hours of refluxing at the first stage, substitution by the added reagent was complete and all of the stoichiometrically-required 4-iodophenoxide was then added dropwise. The remaining sodium phenoxide was added after stabilization of the chemical shifts in the $^{31}$P NMR spectrum indicated consumption of the 4-iodophenoxide. The final $^{31}$P NMR spectrum showed only one peak for polymers 2-7, which indicated complete chlorine atom replacement and a random distribution of the two side groups in the co-substituted polymers (3 and 4).

2.3.2 Thermal Characterization of Polymers 2-7.

The glass transition temperatures ($T_g$) of the iodine-bearing aryloxyphosphazene polymers 2-5 illustrate the influence of the iodine atoms. Polymers 2 and 3 share similar glass transition temperatures, but the values for 4 and 5 are much higher than those of 2 and 3, presumably due to restriction of free motion in the polymer brought about by their high loading of iodine atoms.\textsuperscript{14,35}

2.3.3 Synthesis and Characterization of 4-Iodo-L-Phenylalanine Ethyl Ester (9)

This compound was synthesized by adapting previously published methods.\textsuperscript{31} Phenylalanine was iodinated directly using $I_2$ and NaIO$_3$ in an acidic solution. The structure and purity were confirmed by mass spectroscopy and $^1$H HMR. The free amino acid was then esterified for use in phosphazene synthesis. Thionyl chloride was used to convert the iodophenylalanine into the acid chloride form and facilitate esterification. Final structure and purity of 4-iodophenylalanine ethyl ester were confirmed by $^1$H NMR and mass spectroscopy.
Table 2-1. Structural data for biostable polymers 2-7.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Group</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^{13}$C NMR (ppm)</th>
<th>$^{1}H$ NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100% OPh</td>
<td>-16.47</td>
<td>116.1, 120.8, 130.2, 151.8</td>
<td>6.87 (3H), 7.43 (2H)</td>
</tr>
<tr>
<td>3</td>
<td>75/25% OPh/OPh-I</td>
<td>-16.83</td>
<td>89.2, 121.5, 124.4, 125.6, 129.8, 140.1, 151.9</td>
<td>6.48 (1H), 6.75 (3H), 6.92 (4.5H), 7.14 (1H)</td>
</tr>
<tr>
<td>4</td>
<td>50/50% OPh/OPh-I</td>
<td>-16.64</td>
<td>88.8, 121.9, 124.2, 125.2, 130.2, 139.2, 152.3</td>
<td>6.49 (2H), 6.78 (2H), 6.90 (3H), 7.14 (2H)</td>
</tr>
<tr>
<td>5</td>
<td>100% OPh-I</td>
<td>-17.04</td>
<td>88.7, 116.9, 139.1, 152.1</td>
<td>6.52 (2H), 7.08 (2H)</td>
</tr>
<tr>
<td>6</td>
<td>100% Trifluoroethoxy</td>
<td>-7.42</td>
<td>59.1, 60.3, 62.0, 63.2 (CH$_2$), 108.2, 119.2, 128.9, 140.8 (CF$_3$)</td>
<td>4.63 (2H)</td>
</tr>
<tr>
<td>7</td>
<td>100% Ethoxy</td>
<td>-6.42</td>
<td>17.9 (CH$_3$), 58.2 (CH$_2$)</td>
<td>4.12 (2H) 1.22 (3H)</td>
</tr>
</tbody>
</table>

*OPh refers to phenoxy and OPh-I refers to 4-iodophenoxy

Table 2-2. Physical properties for biostable polymers 2–7.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Group</th>
<th>Mw (x10$^3$ g/mol)</th>
<th>Tg (lit$^{14}$) (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100% OPh</td>
<td>1042</td>
<td>-5.63 (-8)</td>
</tr>
<tr>
<td>3</td>
<td>75/25% OPh/OPh-I</td>
<td>3589</td>
<td>-4.64</td>
</tr>
<tr>
<td>4</td>
<td>50/50% OPh/OPh-I</td>
<td>1912</td>
<td>18.90</td>
</tr>
<tr>
<td>5</td>
<td>100% OPh-I</td>
<td>916</td>
<td>40.08 (43)</td>
</tr>
<tr>
<td>6</td>
<td>100% Trifluoroethoxy</td>
<td>762</td>
<td>-64.28 (-66)</td>
</tr>
<tr>
<td>7</td>
<td>100% Ethoxy</td>
<td>473</td>
<td>-85.62 (-84)</td>
</tr>
</tbody>
</table>

*OPh refers to phenoxy and OPh-I refers to 4-iodophenoxy
2.3.4 Synthesis and Structural Characterization of Polymers 10-17.

For polymers in the second group, attempts to synthesize the single-substituent polymer, poly[bis(ethyl 3,5-diiodotyrosinato)phosphazene] (13) in boiling THF or dioxane resulted in precipitation of partly-substituted derivatives and an inability to replace the remaining chlorine atoms. Moreover, the initial attempts to synthesize the mixed-substituent di-iodotyrosine polymers 10-12, which involved an initial incorporation of 3,5-diiodotyrosine ethyl ester (R₂) in boiling THF, followed by completion of the substitution with the second co-substituent (glycine ethyl ester, alanine ethyl ester, or phenylalanine ethyl ester; R₁) in a 1:1 ratio, also resulted in a loss of the ³¹P NMR signal before the second substituent was added. Again, this indicated that the partially-substituted polymers had precipitated from solution during the first phase of substitution. The use of boiling dioxane in place of THF did not change this behavior. Therefore a three-step addition of the reagents, similar to the syntheses used for polymers 3 and 4, was adopted (Figure 2-2). The chlorine replacement was monitored by ³¹P NMR spectroscopy as the first portion of R₁, followed by all of R₂, and ending with the remaining quantity of R₁ were
added to the polymer solution. For polymers 8-11, the final ratio of substituents was 0.5:1.5 (R₂:R₁).

The $^{31}$P NMR spectra for polymers 8-10 showed only one broad peak for the final product. This was attributed to the presence of amino acid residues that generated skeletal $^{31}$P signals in the 1ppm to -5ppm range and the presence of both geminal and non-geminal substitution patterns. $^1$H NMR spectroscopy was used to confirm the presence of both types of organic side groups in approximately a 0.5:1.5 ratio based on shifts unique to each substituent.

For the third group of polymers, that contained the ethyl ester of 4-iodophenylalanine, the restrictions to the syntheses were not so severe. Even the single-substituent polymer 17 could be formed in refluxing THF. Although the mixed-substituent iodophenylalanine-based polymers, 14-16, were more soluble than 10-13, the three step method was used to ensure complete substitution. Thus, half of the non-iodinated R₁ reagent was added first. When $^{31}$P NMR spectroscopy indicated that all of the R₁ nucleophile had reacted, R₂ (4-iodophenylalanine ethyl ester) was added to the reaction mixture. When R₂ had reacted completely, as determined by NMR, the remaining portion of R₁ was added to the reaction mixture. The final $^{31}$P and $^1$H NMR spectra for polymers 14-17 showed a single peak or peak integrations which indicated that all these polymers contained a random distribution of the R₁ and R₂ substituents in approximately a 1:1 ratio.
Figure 2-3. Synthesis and structures of polymers 8-15. The ratio of 3,5-diiodotyrosine ethyl ester to glycine ethyl ester, alanine ethyl ester, or phenylalanine ethyl ester was maintained at a 0.5:1.5 ratio. The ratio of 4-iodophenylalanine ethyl ester to glycine ethyl ester, alanine ethyl ester, or phenylalanine ethyl ester was held at a 1:1 ratio.
Table 2-3. Structural and physical data for bioerodible iodine-containing amino acid polyphosphazenes

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Group</th>
<th>$^3$P NMR (ppm)</th>
<th>$^1$C NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>M&lt;sub&gt;W&lt;/sub&gt; (x10&lt;sup&gt;3&lt;/sup&gt; g/mol)</th>
<th>T&lt;sub&gt;g&lt;/sub&gt; (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>25/75% I&lt;sub&gt;2&lt;/sub&gt;-Tyr/Gly</td>
<td>3.34</td>
<td>13.5 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 39.4 (1.5 CH&lt;sub&gt;2&lt;/sub&gt;), 55.8 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 61.2 (0.5 CH), 126.3, 127.9, 130.2, 137.8 (4 Ar), 174.1 (2 C=O)</td>
<td>1.24 (6H), 3.27 (1H), 3.79 (3H), 3.94 (0.5H), 4.14 (4H), 6.89 (1H)</td>
<td>123</td>
<td>-2.31</td>
</tr>
<tr>
<td>11</td>
<td>25/75% I&lt;sub&gt;2&lt;/sub&gt;-Tyr/Ala</td>
<td>1.96</td>
<td>13.2 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 19.5 (1.5 CH&lt;sub&gt;3&lt;/sub&gt;), 43.6 (2 CH/CH&lt;sub&gt;2&lt;/sub&gt;), 55.4 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 60.9 (0.5 CH) 126.6, 128.3, 129.5, 137.6 (4 Ar), 174.1 (2 C=O)</td>
<td>1.22 (6H), 1.39 (4.5H), 3.82 (0.5H), 3.60 (4.5H), 6.89 (1H)</td>
<td>137</td>
<td>20.60</td>
</tr>
<tr>
<td>12</td>
<td>25/75% I&lt;sub&gt;2&lt;/sub&gt;-Tyr/Phe</td>
<td>0.72</td>
<td>14.1 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 41.1 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 55.7 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 60.8 (2 CH), 126.5, 128.2, 129.9, 137.8 (4 Ar), 174.1 (2 C=O)</td>
<td>0.88 (6H), 3.01 (4H), 3.82 (4H), 4.30 (2H), 7.11 (9.5H)</td>
<td>199</td>
<td>52.52</td>
</tr>
<tr>
<td>13</td>
<td>50/50% I-Phe/Gly</td>
<td>-2.93</td>
<td>13.5 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 39.4 (CH&lt;sub&gt;2&lt;/sub&gt;), 56.5 (CH&lt;sub&gt;2&lt;/sub&gt;), 61.2 (CH&lt;sub&gt;2&lt;/sub&gt;), 92.6, 131.4, 137.1 (3 Ar), 174.1 (2 C=O)</td>
<td>1.24 (6H), 3.31 (2H), 3.59 (2H), 4.09 (4H), 6.93 (2H), 7.47 (2H)</td>
<td>246</td>
<td>34.91</td>
</tr>
<tr>
<td>14</td>
<td>50/50% I-Phe/Ala</td>
<td>-1.86</td>
<td>13.2 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 19.5 (CH&lt;sub&gt;3&lt;/sub&gt;), 43.6 (CH/CH&lt;sub&gt;2&lt;/sub&gt;), 55.4 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 61.1 (CH), 92.6, 131.4, 137.1 (3 Ar), 174.1 (C=O)</td>
<td>1.23 (6H), 1.42 (3H), 3.31 (2H), 3.59 (2H), 4.09 (4H), 6.93 (2H), 7.50 (2 H)</td>
<td>126</td>
<td>35.81</td>
</tr>
<tr>
<td>15</td>
<td>50/50% I-Phe/Phe</td>
<td>-2.31</td>
<td>14.1 (2 CH&lt;sub&gt;3&lt;/sub&gt;), 41.1 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 55.7 (2 CH&lt;sub&gt;2&lt;/sub&gt;), 60.8 (2 CH), 92.5, 128.2, 129.9, 137.8 (4 Ar), 174.1 (2 C=O)</td>
<td>1.25 (6H), 3.49 (4H), 3.74 (2H), 4.09 (4H), 7.02-7.80 (9H)</td>
<td>102</td>
<td>37.65</td>
</tr>
<tr>
<td>16</td>
<td>100% I-Phe</td>
<td>-2.47</td>
<td>14.2 (CH&lt;sub&gt;3&lt;/sub&gt;), 40.3 (CH&lt;sub&gt;2&lt;/sub&gt;), 55.7 (CH&lt;sub&gt;2&lt;/sub&gt;), 61.4 (CH), 92.6, 131.4, 137.1 (3 Ar), 174.1 (C=O)</td>
<td>0.98 (3H), 3.00 (2H), 3.93 (3H), 6.92 (2H), 7.49 (2H)</td>
<td>120</td>
<td>38.75</td>
</tr>
</tbody>
</table>

∞ I<sub>2</sub>-Tyr refers to ethyl 3,5-diiodotyrosinyl, I-Phe refers to ethyl 4-iodophenylalanyl, Gly refers to ethyl glycinyl, Ala refers to ethyl alanyl, and Phe refers to ethyl phenylalanyl.
2.3.5 Thermal Characterization of Polymers 10 – 17.

The glass transition temperatures (Tg) of polymers 10-17 are shown in Table 2-3. With one exception (50%/50% (ethyl diiodotyrosinyl/ethyl glycinyl)) the glass transition temperatures are at or above room temperature. This provides a range of properties for different medical applications. The values for polymers 10-12 cover a range from -2.31°C (10) to 52.52°C (12). The Tg's of these polymers are governed by the high level of incorporation of R1 rather than the minority 3,5-diiodotyrosine ethyl ester. The Tg range is wide because the steric size of the substituents directly influences the thermal properties of the polymer. Poly[(ethyl glycinato)1.62(ethyl tyrosinato)0.38phosphazene] has a glass transition temperature of 5.4°C which is similar to the Tg value of 10 (-2.31°C).36

With polymers 14-17, the Tg is dependent on both the 4-iodophenylalanine ethyl ester and R1 because the substituents are present in roughly equal amounts. The Tg’s of 14 and 15 are much higher than the values for poly[bis(ethyl glycinato)phosphazene] or poly[bis(ethyl alaninato)phosphazene] (-20°C and -15°C respectively), but lower than the Tg of poly[bis(ethyl phenylalaninato)phosphazene] (68°C).26 However, with 16 and 17, the measured Tg’s are lower than for the phenylalanine single-substituent polymer as the result of the increased free volume from 4-iodophenylalanine ethyl ester units and the elimination of crystallinity which had previously been detected.

2.3.6 Hydrolytic Degradation of Polymers 8-10 and 12-15.

Solution cast films of 10-12 are insoluble in water. Previously reported studies have shown that complete hydrolytic degradation of amino acid substituted polyphosphazenes yields ammonia, phosphates, free amino acid, and ethanol.26-29,37-39 The high solubility of these products
in water allows “sink” conditions to be achieved using the procedure described in the experimental section. Thus, a heterogeneous hydrolytic degradation profile was generated over a period of 6 weeks. The initial mass of each film was recorded before the film was immersed in water. Each week, a set of samples was removed and the remaining portion of the film was freeze-dried for at least one week. Figure 2-4A shows the mass retention for polymers 10-12. Despite polymers 10 and 11 losing 25% of their original mass after only 7 days, by the end of 6 weeks, these polymers retained 65% and 62% of their initial weight. Polymer 12 showed very little mass loss over the duration of the study. The incorporation of 25% of the bulky, hydrophobic 3,5-diiodotyrosine ethyl ester as the side group is not sufficient to slow the rate of degradation. Thus, the co-substituent (glycine, alanine, or phenylalanine ethyl ester) controls the rate of hydrolysis. The rates of hydrolysis are consistent with the general trend that the hydrolytic half-life of polyphosphazenes substituted with bulky, hydrophobic amino acid residues (phenylalanine ethyl ester) is much longer than the half-life of polyphosphazenes that contain less sterically hindered amino acids, such as glycine or alanine residues. When the mass loss of polymers 14-17 (Figure 2-4B) is compared to that of polymers 10-12, the 4-iodophenylalanine polymers retained significantly more of their initial mass over the 6 week period with the maximum mass loss of 30%. Although polymers 16 and 17 might be expected to have slower rates of hydrolysis than polymers 14 and 15, they were in fact found to hydrolyze faster. The 1:1 ratio of side groups in polymers 14-17 allows the 4-iodophenylalanine to influence the rate of hydrolysis, resulting in the similar mass loss profiles for the polymers.

The hydrolysis media were analyzed in an attempt to assess the degradation mechanism for polymers 10-17. The presence of phosphates was first detected after 2 weeks as a sharp peak at 0 ppm in the $^{31}\text{P}$ NMR spectrum. The addition of silver nitrate to the hydrolysis medium yielded a yellow precipitate of silver phosphate, confirming the presence of phosphates. Free amino acid residues of glycine, alanine, and phenylalanine and ethanol were present in the $^{1}\text{H}$
NMR spectrum of the hydrolysis medium after 1 week. The free 3,5-diiodotyrosine or 4-iodophenylalanine residues were not detected by $^1$H NMR spectroscopy until week three. The presence of ammonia or the free amine termini of the amino acids was further confirmed by a positive ninhydrin test.

**Figure 2-4.** A) Mass loss profile of polymers 10-12 during a 6 week hydrolysis study. B) Mass loss profile of polymers 12-15 during a 6 week hydrolysis study. C) pH measurements of the hydrolysis media for polymers 8-10. D) pH measurements of the hydrolysis media for polymers 12-15.
These results are consistent with a bulk erosion mechanism where the least sterically hindered amino acid ethyl ester is cleaved from the polymer backbone. The order in which the ester functionality is hydrolyzed and the side group is cleaved from the phosphazene backbone cannot be determined from these results. However, the presence of phosphates in the aqueous medium is consistent with a complete hydrolytic degradation of the phosphazene backbone.

The pH of each hydrolysis medium (Figures 2-4C & 2-4D) remained constant for the duration of the 6 week study, with the exception of polymers 16 and 17. Hydrolysis of the polymer backbone yielded ammonia and phosphates which form a buffered solution that causes little change in the pH of the hydrolysis medium. The decrease in the pH of the hydrolysis medium for polymers 16 and 17 is caused by the liberation of trace amounts of hydrochloric acid during hydrolytic degradation. Small molecule model studies have shown that two competing equilibria exist for the hydrogen chloride byproduct of the macromolecular substitution of poly(dichlorophosphazene) with an amino group. The hydrogen chloride can either be absorbed by the triethylamine hydrochloride acceptor or complexed with the basic nitrogen atoms in the phosphazene, the latter making complete removal of the hydrochloride salt during purification difficult. The concentration of trapped hydrochloride salt necessary to affect the observed changes in pH is well below the limit of detection by $^1\text{H}$ NMR spectroscopy. The acidic hydrolysis medium also explains the accelerated hydrolysis of polymers 16 and 17. Previous studies have shown that when phosphazenes are exposed to an acidic solution, the degradation is accelerated when compared to hydrolysis in deionized water or basic solutions.

The 3,5-diiodotyrosine and 4-iodophenylalanine residues released as a result of hydrolysis are expected to have minimal effect on biocompatibility. 3,5-Diiodotyrosine is a natural product which is used in the synthesis of Thyroxine, a thyroide hormone, and regulator of thyroid peroxidase. 4-Iodophenylalanine residues have been used in numerous studies as a non-natural amino acid for fluorescence and bioluminescence modification. During its use as a
radiological tag in brain tumor imaging, animal testing showed no acute physiological response to doses of 10 mg·kg⁻¹. Despite this evidence, further studies are needed to confirm the biocompatibility of these polymers.

2.3.7 Radio Opacity Testing and Medical Imaging.

Small samples of the thermally fabricated polymers 2-5 were characterized after fabrication utilizing ¹H and ³¹P NMR, GPC, and DSC methods. The results were identical to the initial characterization, which confirmed that no degradation occurred as a result of the processing. As a preliminary test, polymers 2, 4-6, 10-12, and 14-17 were exposed to a copper Kα X-ray source. Their ability to block these “soft” X-rays was judged relative to the source being completely blocked or unblocked. Although all the biostable polymers (2-6) showed some ability to block this radiation, those polymers with iodinated side groups were the most opaque. Similarly, the thin films of the biocompatible polymers which averaged one iodine per repeat unit were also opaque to the x-rays. All the polymers were then characterized a final time to confirm that short term exposure to “soft” x-rays, such a copper Kα, do not cause detectable degradation of the polymer.

X-ray images were then obtained using a rhenium-tungsten-molybdenum target and a protocol employed for the imaging of a broken finger. The x-ray image of polymers 2, 4, and 5 at two different thicknesses [(A) 4.80mm and (B) 1.97mm] was obtained. Polymer 2, which contained no iodine, was transparent at both thicknesses. Incorporation of one or more iodine atoms per repeating unit (polymers 4 and 5) is sufficient to render the polymers opaque to tungsten x-rays at either thickness. This series of polymers also shows that image contrast is proportional to the amount of iodine incorporated into the polymer backbone and the thickness of the polymer sample. The radiologic opacity of the biocompatible polymers 10-12 and 14-17 were
evaluated as both solution cast thin films and pressed pellets. The thin films and pellets were clearly visible in the image, which demonstrates the possibility for these polymers to be used on their own as a bulk material or applied as a coating to a compatible substrate. To further illustrate the uniqueness of the biostable and biocompatible polymer systems, Figure 2-5 shows an X-ray image of selected polymers (5, 12, 16, and 17) alongside several common organic polymers. Only two of the polymers imaged, poly(vinyl chloride) and poly(dimethylsiloxane), come close to the opacity of the reference poly(organophosphazenes) and neither is as good a candidate for most biomedical applications due to the need for plasticizers and cross-linkers, the toxicity of the additives, or their mechanical properties. The polymer samples were again tested several times to ensure that no degradation occurred as a result of the processing or exposure to “hard” x-rays.
2.4 Conclusions

To the best of our knowledge this is the first reported synthesis of poly(organophosphazenes) that contain 3,5-diiodotyrosine ethyl ester, or 4-iodophenylalanine ethyl ester side groups for use as x-ray opaque materials. The synthesis of single-substituent 4-iodophenoxy polymer had been previously reported, but had not been evaluated for X-ray opacity. The new mixed-substituent polymers were obtained through a three-step replacement of the chlorine atoms in poly(dichlorophosphazene) by sodium phenoxide or an amino acid ethyl ester and a similar iodinated derivative. A series of biostable poly[bis(aryloxy)phosphazene] derivatives with an increasing amount of iodine incorporated into the polymer were synthesized. 4-Iodophenoxy side groups have a marked influence on increasing the $T_g$ values. Two sets of amino acid ester polymers were synthesized with 3,5-diiodotyrosine ethyl ester or 4-iodophenylalanine ethyl ester and glycine ethyl ester, alanine ethyl ester, or phenylalanine ethyl ester as the co-substituents. The physical and thermal properties of polymers 10-12 are controlled by the non-iodinated co-substituent due to the low incorporation of the iodine-containing side group. Conversely, polymers 14-17 have very similar physical and thermal properties resulting from the 1:1 ratio of 4-iodophenylalanine and the co-substituent. All polymers with an average of one iodine per repeat unit were opaque to both copper Kα and rhenium-tungsten-molybdenum x-rays.
2.5 Acknowledgments

This work was supported by NIH grant number RO1EB004051. We thank Mark Angelone at The Pennsylvania State University Materials Research Institute for his help testing synthesized polymers with the copper Kα x-ray source. We also thank Melanie Harris and the Radiology Center at The Pennsylvania State University Student Health Center for their assistance obtaining images on the Kodak 7500 DR x-ray unit.

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Chapter 3

Synthesis and Characterization of L-DOPA and Dopamine Substituted Polyphosphazenes

3.1 Introduction

The adhesion of marine mussels has long been an issue for the maritime community. Investigations into the adhesion of these organisms revealed that mussel adhesive proteins (MAPs) are excreted and within seconds form water-resistant bonds to a variety of surfaces. Of the species studied, five unique MAPs have been isolated from the distal threads of *Mytilus edulis* and are referred to as Mefp’s. Protein sequencing has shown that Mefp-3 and Mefp-5 contain up to 30 mol% of 3,4-dihydroxy-L-phenylalanine (L-DOPA), an uncommon amino acid. Numerous studies have since shown that the catechol functionality in L-DOPA is the primary point of adhesive reactions.\(^1\)\(^-\)\(^9\) Whether the reaction mechanism follows the oxidative coupling, metal chelation, or hydrogen bonding pathways, L-DOPA and other catechol-containing biomolecules are ideal compounds for development into bio-adhesives. This chapter examines the initial synthesis and characterization of poly(organophosphazenes) derived from L-DOPA and dopamine for potential use as bioadhesive polymers.

Poly(organophosphazenes) are a highly versatile class of organic-inorganic hybrid polymers. Nucleophilic replacement of the chlorine atoms in poly(dichlorophosphazene) by alkoxides, aryloxides, or amines govern the properties and potential applications of the polyphosphazene. Mixed-substituent polymers, obtained when two or more different nucleophiles are used during chlorine atom replacement, allow the properties of the polyphosphazene to be further tuned. During the development of novel macromolecular systems, it is often helpful to initially develop synthetic methods utilizing a simpler small molecule model.
system. Polyphosphazenes have been used in a number of fields including power generation, optical materials, and biodegradable materials.\textsuperscript{10}

Two properties of amine-substituted polyphosphazenes make the phosphazene system a good base on which to build a bioadhesive material. The hydrolytic sensitivity of amino terminus linked amino acid ethyl ester phosphazenes and the biologically benign hydrolysis products of these polymers will minimize concerns about long term exposure of a patient to biostable parent polymers used in other systems. Another advantage of polyphosphazenes is the inherent flexibility of the polymer backbone which should aid the polymer in remaining pliable once cross-linked. By combining the versatility of phosphazenes and the adhesive properties of DOPA, it is possible to generate a biodegradable adhesive material which may have distinct advantages over other DOPA based bioadhesives.\textsuperscript{10,11}

In this study, novel phosphazenes with catechol-containing natural products were synthesized. Hexachlorocyclotriphosphazene, (NPCl\textsubscript{2})\textsubscript{3}, was used as a model system for the substitution of DOPA and dopamine onto phosphazenes. Before these substitution reactions can be carried out an esterification of DOPA and the acetonidization of the catechol in DOPA and dopamine were necessary.\textsuperscript{12,13} This is required because catechol functionalities are known to react with phosphazenes to form spirocyclic compounds.\textsuperscript{14} The acetonide protecting group can then be removed yielding the free catechol functionalities.\textsuperscript{15}

### 3.2 Experimental

#### 3.2.1 Reagents and Equipment

All synthesis reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran (EMD) and triethylamine (EMD) were dried using
solvent purification columns.\textsuperscript{16} Glycine ethyl ester hydrochloride (Bachem), alanine ethyl ester hydrochloride (Chem-Impex), and phenylalanine ethyl ester hydrochloride (Chem-Impex) were used as received. Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Japan) in evacuated Pyrex tubes at 250°C. Chemicals and polymers not mentioned above were used as received without purification. \textsuperscript{31}P, \textsuperscript{13}C, and \textsuperscript{1}H NMR spectra were obtained with use of a Bruker 360 WM instrument operated at 145 MHz, 90 MHz, and 360 MHz, respectively. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10°C/min and a sample size of ca. 10 mg. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-n-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards. Mass spectrometric data was collected using turbo spray ionization technique on an Applied Biosystems API 150EX LC/MS mass spectrometer.

3.2.2 3,4-Dihydroxy-\textit{L}-phenylalanine ethyl ester hydrochloride (L-DOPAEE-HCl, 1)

This procedure was adapted from published literature.\textsuperscript{12} 3,4-Dihydroxy-\textit{L}-phenylalanine (10.0 g, 50.72mmol) was suspended in 200 mL of anhydrous ethanol and the solution was cooled in an ice bath. Thionyl chloride (30.17 g, 0.25357 mol) was diluted with anhydrous ethanol (75 mL) and was added dropwise to the L-DOPA suspension over 30 min. The mixture was stirred at 0°C for 2 hours and then slowly warmed to room temperature. The progress of the reaction was monitored by mass spectroscopy. When complete, the reaction solution was dried by solvent evaporation to yield a dense yellow oil (97 %) which was used without further purification. 1H
NMR (CDCl$_3$), ppm: $\delta$ 6.62 (1H, d, Ar), 6.56 (1H, s, Ar), 6.44 (1H, d, Ar), 4.13 (2H, q, -CH$_2$CH$_3$), 3.68 (1H, m, $\alpha$-CH), 3.18 (2H, m, $\beta$-CH$_2$), 1.25 (3H, t, -OCH$_2$CH$_3$); MS (ESCI+) $m/z = 226 ([M–Cl]^+)$. 

3.2.3 Acetonide protection of L-DOPAEE·HCl (L-DOPA(Ac) EE·HCl, 2)

This procedure was adapted from published literature.$^{13}$ 3,4-Dihydroxy-L-phenylalanine ethyl ester hydrochloride (13.27 g, 50.7 mmol) was dissolved in iso-propanol (100 mL) and acetone (50 mL). $p$-Toluenesulfonic acid monohydrate (0.964g, 5.07 mmol) was added and the solution was heated to 80°C for 24 hours. The reaction progress was monitored by mass spectroscopy. When complete, all solvents were removed under vacuum and a white powder was obtained. This was purified by recrystallization from methanol/hexane (94 %). $^1$H NMR (MeOD), ppm: $\delta$ (6.80 1H, m, Ar), 6.68 (1H, m, Ar), 4.51 (1H, dd, $\alpha$-CH), 4.33 (2H, q, -OCH$_2$CH$_3$), 3.27 (1H, dd, $\beta$-CH$_2$), 3.08 (1H, dd, $\beta$-CH$_2$), 1.74 (3H, s, -CH$_3$(Ac), 1.59 (3H, s, -CH$_3$(Ac), 1.30 (3H, t, -OCH$_2$CH$_3$); MS (ESCI+) $m/z = 266 ([M–Cl]^+)$. 

3.2.3 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-isoquinolinium (DTTQ·HCl, 4)

Dopamine hydrochloride (10g, 50.34 mmol) was dissolved in iso-propanol (100 mL) and 2,2-dimethoxy propanol (26.21g, 0.2517 mol). $p$-Toluenesulfonic acid monohydrate (0.9576 g, 5.034 mmol) was added and the reaction was heated to 80°C while the reaction progress was monitored by mass spectroscopy. When complete, the solvent was removed and the white precipitate was dried under vacuum. 6,7-Dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-isoquinolinium (DTTQ·HCl) was obtained in 93% yield. $^1$H NMR (MeOD), ppm: $\delta$ 6.67 (1H, s,
Ar), 6.51 (1H, s, Ar), 3.28 (2H, t, -HNCH₂CH₂⁻), 2.81 (2H, t, -HNCH₂CH₂⁻), 1.47 (6H, s, 2-C(CH₃)₂); MS (ESCI+) m/z = 194 ([M–Cl]⁺).

3.2.4 Synthesis of hexa(L-DOPA(Ac)EE)cyclotriphosphazene (5)

L-DOPA(Ac)EE (6.076 g, 0.02013 mol) was suspended in a solution of THF (100 mL) and triethylamine (4.366 g, 0.04314 mol). The reaction mixture was refluxed for 24 hrs and filtered into a solution of hexachlorocyclotriphosphazene (1.00 g, 28.7 mmol) in THF (10mL). The reaction progress was monitored by ³¹P NMR spectroscopy, and when complete, the solvent was removed under vacuum. The resulting solid was dissolved in dichloromethane and extracted with water. The organic layer was dried with magnesium sulfate, filtered, and all the solvent was removed. After drying at reduced pressure, the yield was 73% based on hexachlorocyclotriphosphazene. ³¹P NMR (CDCl₃), ppm: δ +11.13 (3P, s); ¹H NMR (CDCl₃), ppm: δ 7.09 (2H, m, Ar), 6.56 (1H, m, Ar), 4.20 (2H, q, -OCH₂CH₃), 3.74 (1H, m, α-CH), 2.83 (2H, m, β-CH₂), 1.45 (6H, s, 2-C(CH₃)₂), 1.28 (3H, t, -OCH₂CH₃); MS (ESCI+) m/z = 1721 ([M+H]⁺).

3.2.5 Synthesis of hexa(DTTQ)cyclotriphosphazene (6)

The synthesis of hexa(DTTQ)cyclotriphosphazene followed a procedure similar to that of hexa(L-DOPA(Ac)EE)cyclotriphosphazene. After drying at reduced pressure, the yield was 35% from hexachlorocyclotriphosphazene. ³¹P NMR (CDCl₃), ppm: δ +9.27 (3P, s); ¹H NMR (CDCl₃), ppm: δ 6.68 (1H, s, Ar), 6.51 (1H, s, Ar), 3.65 (2H, t, -HNCH₂CH₂⁻), 2.95 (2H, t, -HNCH₂CH₂⁻), 1.52 (6H, s, 2-C(CH₃)₂); MS (ESCI+) m/z = 1289 ([M+H]⁺).
3.2.6 Deprotection of hexa(L-DOPA(Ac)EE)cyclotriphosphazene (7)

Hexa(L-DOPA(Ac)EE)cyclotriphosphazene (0.500 g, 0.291 mmol) was dissolved in a solution of trifluoroacetic acid : ethanol (80:20, 5 mL) and allowed to react for 24 hrs at 25°C. The reaction solution was dried and redissolved in methanol. The solution was passed through a short silica gel column using ethyl acetate : hexanes (80:20) as the mobile phase. The product was dried under vacuum to give a viscous oil (76%). $^{31}$P NMR (CDCl₃), ppm: $\delta$ +11.13 (3P, s); $^1$H NMR (CDCl₃), ppm: $\delta$ 7.09 (2H, m, Ar), 6.56 (1H, m, Ar), 4.20 (2H, q, -OCH₂CH₃), 3.74 (1H, m, $\alpha$-CH), 2.83 (2H, m, $\beta$-CH₂), 1.28 (3H, t, -OCH₂CH₃); MS (ESCI+) $m/z = 1481 ([M+H]^+)$.

3.2.7 Synthesis of polymers 8–15

The synthesis of polymer 12 is given here as a representative example. Poly(dichlorophosphazene) (2.00 g, 17.25 mmol) was dissolved in THF (200mL). L-DOPA(Ac)EE (4.57 g, 17.25 mmol) was suspended in THF (100 mL) and triethylamine (5.23 g, 51.77 mmol), and the solution was refluxed for 24 hrs. The reaction solution was filtered and added dropwise to the polymer solution. The reaction mixture was then refluxed and the reaction progress was monitored by $^{31}$P NMR spectroscopy. Glycine ethyl ester hydrochloride was suspended in a solution of THF (100 mL) and triethylamine (5.23 g, 51.77 mmol) and the reaction mixture was refluxed for 24 hrs. This was filtered into the polymer solution and the mixture was refluxed for an additional 24 hrs. The solvent was evaporated and the residual solid was redissolved in methanol or THF. The polymer was purified by dialysis against methanol for 3 days to give yields in the range of 63 – 76%. Characterization data can be found in table 3-1 (polymers 8-11) and table 3-2 (polymers 12-15).
3.2.8 Hydrolitic degradation of DTTQ substituted polyphosphazenes (8-11)

Films of polymers 8-11 were solution cast from THF (100mg/mL) and air dried for 24 hrs. The films were then dried an additional 5 days at reduced pressure. The films were divided among test tubes (ca 10 mg each) and each test tube was filled with 5 mL of de-ionized water. The test tubes were incubated at 37°C in a shaker bath. Samples were removed from the hydrolysis media, in triplicate, at 1 week intervals to measure weight loss and solution pH.

3.2.9 Deprotection of acetonide protected polymers (16-19)

The deprotection of polymer 11 is given here as a representative example. Poly[bis(L-DOPA(Ac)EE)phosphazene] (0.500 g, 0.873 mmol) was dissolved in a trifluoroacetic acid : ethanol solution (80:20, 10 mL) and allowed to react for 24 hrs at 25°C. The reaction solution was neutralized with NaHCO₃, dried under reduced pressure, and redissolved in methanol. The solution was then dialized against methanol for 3 days. The polymer was isolated and dried at reduced pressure.

3.3 Results and Discussion

3.3.1 3,4-Dihydroxy-L-phenylalanine protection and DTTQ synthesis

Formation of an acetonide is usually an effective method for the protection of 1,2-diols. 3,4-Dihydroxy-L-phenylalanine was prepared for phosphazene substitution by protecting the free carboxylic acid as the ethyl ester. The reactive catechol functionality of L-DOPA was protected as the acetonide. The acetonide was formed either with acetone or 2,2-dimethoxypropane (Figure 3-1). 12,13,15
This method of acetonide protection of the catechol functionality was adopted for the attempted protection of dopamine. Despite mass spectrometric data which was consistent with the desired dopamine(acetonide) (3), proton NMR spectroscopy revealed that an isoquinolininium (DTTQ·HCl, 4) was formed instead. This is consistent with previous attempts at direct acetonidization of dopamine (Figure 3-2).17,18,19

One of the first instances where the condensation of dopamine and acetone formed 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-isoquinolinium (DTTQ) was reported in 1971.20 The acid catalyzed ring closing that occurs between β-phenethylamines and carbonyl compounds is
known as a Pictet-Spengler reaction.\textsuperscript{21} A similar reaction is also known to occur when 2-phenylethanol is exposed to acetone and other carbonyls in an acidic environment.\textsuperscript{22,23} The mechanism (Figure 3-3) proceeds via formation of a Schiff base and subsequent Friedel-Crafts cyclization.\textsuperscript{22,24,25}

![Figure 3-3. Mechanism of Pictet-Spengler reaction resulting in the formation of DTTQ (4).](image)

This cyclization is a very thermodynamically favored product as the reaction occurs preferentially regardless of temperature. The reaction can not be prevented by simply treating dopamine with an excess of hydrogen chloride or bromide which is enough to prevent formation of the isoquinoline product during the acetodination of L-DOPA.\textsuperscript{15,17,18} This reaction can be prevented if an acid stable amino-protecting group is selected. When N-phthaloyl- (Phth), Fmoc-, and trifluoroacetate (Tfa) protecting groups were first introduced to dopamine hydrochloride, the acetonide-protected dopamine was obtained. However, if the Boc- protecting group is utilized for protection of the amine, isoquinoline is the only product.\textsuperscript{17}

### 3.3.2 Small Molecule Model System

The simplest phosphazene system is the cyclic trimeric species which was used as a small molecule analog to investigate the feasibility of substituting dopamine and L-DOPAEE. This was
accomplished by treating hexachlorocyclotriphosphazene with an excess of L-DOPA(Ac)EE or DTTQ in the presence of triethylamine. A single signal in the $^{31}$P NMR spectrum is indicative of complete chlorine replacement to yield hexa(L-DOPA(Ac)EE)cyclotriphosphazene (5) and hexa(DTTQ)cyclotriphosphazene (6). These species were isolated as oils which were soluble in common organic solvents.

Hexa(L-DOPA(Ac)EE)cyclotriphosphazene was used as a model for the acidic cleavage of the acetonide protecting group in the L-DOPA side groups. Complete deprotection was achieved when trimer 5 was treated with an excess of trifluoroacetic acid. The absence of peaks in the $^1$H NMR spectrum previously attributed to the acetonide protecting group indicated that the desired product was obtained. This was further confirmed by mass spectrometry. A $^{31}$P NMR peak at +11.13 ppm indicated that an acid catalized hydrolytic degradation did not occur during the deprotection reactions.

3.3.3 Initial attempts at the synthesis of dopamine and L-DOPA phosphazenes without catechol protection

Initial attempts at the synthesis of Dopamine and L-DOPA substituted polyphosphazenes utilized the substituents with free catechol functionalities. Dopamine and 3,4-dihydroxy-$L$-phenylalanine ethyl ester were allowed to react with poly(dichlorophosphazene) in an attempt to obtain the respective polymers. A polymeric material precipitated from solution and was insoluble in organic solvents. It is suspected that some combination of two cross-linking methods is responsible for this observed insolvability. The first is the formation of P-N linkages to one polymer chain and P-O linkages to another polymer chain by the reactive catechol functionalities in both dopamine and L-DOPA.$^{14}$ The second method of cross-linking is by the oxidative dimerization of L-DOPA and dopamine.$^4$ Previous studies have shown that the catechol
functionality can be converted to a reactive ortho-quinone in moderately basic reaction conditions.\cite{4,8,19} Thus it is necessary to protect the catechol portion of dopamine and L-DOPA.

### 3.3.4 Synthesis and characterization of 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinolinium substituted polyphosphazenes

DTTQ was synthesized during the attempted acetonide protection of dopamine and was utilized in the macromolecular replacement of chlorine atoms on poly(dichlorophosphazene) (Figure 3-4). Some of the physical and chemical properties of polymers 8-11 are given in Table 3-1. After isolation, these polymers were initially soluble in organic solvents such as methanol, THF, and acetone. There are two reactive functionalities which can potentially substitute the phosphazene backbone. Based on the observed \(^{31}\text{P}\) NMR shifts (Table 3-1), and when compared to previously synthesized polymers, it is believed that the primary attachment is through the aryloxide unit (Figure 3-4).\cite{26-29} The \(^{31}\text{P}\) NMR shift reported for an analog of polymer 8; were it amine substituted, poly[bis(piperidino)phosphazene], is -7.7 ppm, which is significantly different from the observed -15.58 ppm.\cite{28,29} The observed value is more closely related to those seen during polymer substitution through an aryloxide unit.

![Figure 3-4. Synthesis of DTTQ substituted polyphosphazenes](image)

\[ 8: x:y = 2:0 \\
9: R = H, x:y = 1:1 \\
10: R = \text{CH}_3, x:y = 1:1 \\
11: R = \text{CH}_2\text{C}_6\text{H}_5, x:y = 1:1 \]
Table 3-1. Structural and physical properties of DTTQ substituted polyphosphazenes (Polymers 8-11).

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>$M_w$ (x10$^4$ g/mol)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>-15.85</td>
<td>6.70 (1H), 6.53 (1H), 3.62 (2H), 2.98 (2H), 1.45 (6H)</td>
<td>5.32</td>
<td>38.82</td>
</tr>
<tr>
<td>9</td>
<td>-5.68</td>
<td>6.72 (1H), 6.58 (1H), 4.25 (3H), 3.62 (4H), 2.93 (2H), 1.47 (6H), 1.33 (3H)</td>
<td>6.87</td>
<td>27.43</td>
</tr>
<tr>
<td>10</td>
<td>-7.23</td>
<td>6.74 (1H), 6.55 (1H), 4.25 (3H), 3.62 (3H), 2.93 (2H), 1.47 (9H), 1.33 (3H)</td>
<td>4.32</td>
<td>26.34</td>
</tr>
<tr>
<td>11</td>
<td>-6.82</td>
<td>7.25 (5H), 6.70 (1H), 6.53 (1H), 4.13 (2H), 3.76 (3H), 2.98 (2H), 1.53 (6H), 1.31 (3H)</td>
<td>7.23</td>
<td>31.73</td>
</tr>
</tbody>
</table>

3.3.5 Hydrolytic instability of DTTQ substituted polyphosphazenes

The hydrolytic stability of a polymer targeted for biological applications is important. Therefore the stability of polymers 8-11 was evaluated against de-ionized water. Based on the structure proposed in Figure 3-4, the polymers were expected to be relatively hydrolytically stable. However, this was not the case and films of polymers 8-10 lost 100% of their initial mass after less than one week (Figure 3-5a). On the other hand, polymer 11 only showed 50% mass loss over the duration of the 6 week study. In an attempt to determine if the polymers were solubilized or underwent hydrolytic degradation, the hydrolysis media from select samples was dried and any solid redisolved in D$_2$O. For polymers 8-10, only a sharp peak was observed at 0 ppm by $^{31}$P NMR spectroscopy, but polymer 11 contained a sharp peak at 0 ppm and a broad peak at -0.8 ppm in the $^{31}$P NMR spectrum which is consistent with a phosphorous-N-phenylalanine linkage.
The pH of the hydrolysis media also provides some insight to the mechanism and reason for hydrolysis. Polymers 8 and 9 showed an increase of more than 1 pH unit, to a maximum of 7.20, while polymer 10 decreased by 1.5 units, to a minimum of 4.6, over the course of the study. In both cases, the change in pH correlates to their mass loss. Polymer 11 again was unique among the 4 samples evaluated. Over the first two weeks, the pH rose to 7, but then declined over time (Figure 3-5b).

These results indicate that rapid hydrolytic degradation occurred in polymers 8-10. The DTTQ may have been oxidatively cleaved from the polymer backbone or protonation of the secondary amine solubilized the polymer leading to the rapid degradation of 8 and 9. The decrease in pH observed with polymer 10, indicates that DTTQ or other free amine formed a hydrochloride salt during the initial polymer synthesis that was not removed. Upon exposure to the hydrolysis media, the hydrochloride salt was liberated accelerating the mass loss of the polymer. Polymer 11 appears to have undergone a similar loss of DTTQ as polymers 8 and 9, but the hydrophobicity of phenylalanine retarded hydrolytic degradation of the remaining polymer.
3.3.6 Synthesis of L-DOPA(Ac)EE/amino acid ethyl ester co substituted polyphosphazenes

Poly[bis(L-DOPA(Ac)EE)phosphazene] and co-substituted polymers were synthesized by the macromolecular substitution of the poly(dichlorophosphazene) reactive intermediate. L-DOPA(Ac)EE was added first to the reaction mixture and the progress was monitored by $^{31}$P
NMR spectroscopy. The respective amino acid ethyl ester; glycine (13), alanine (14), or phenylalanine (15); was added to the polymer reaction when roughly 50% of the chlorine atoms had been replaced by L-DOPA. Structural and physical properties of polymers 12-15 are given in Table 3-2. The peak at 1.43 ppm in the $^1$H NMR spectrum of polymers 12, 13, and 15 was assigned as the protons in the acetonide protecting group on the catechol. The analogous peak in the $^1$H NMR spectrum of polymer 14 is shifted to 1.65 ppm and includes the β-methyl group of alanine.

**Figure 3-6.** Synthesis of L-DOPA(Ac)EE substituted polyphosphazenes.
Table 3-2. Structural and physical properties of L-DOPA(Ac)EE substituted polyphosphazenes (Polymers 12-15).

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$^3$P NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>$M_w$ (x10^5 g/mol)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>-4.21</td>
<td>7.09 (2H), 6.56 (1H), 4.20 (2H), 3.75 (1H), 2.88 (2H), 1.45 (6H), 1.25 (3H)</td>
<td>0.85</td>
<td>48.23</td>
</tr>
<tr>
<td>13</td>
<td>-1.55</td>
<td>6.96 (2H), 6.57 (1H), 4.22 (4H), 3.75 (3H), 2.95 (2H), 1.41 (6H), 1.29 (6H)</td>
<td>1.16</td>
<td>26.10</td>
</tr>
<tr>
<td>14</td>
<td>-5.32</td>
<td>7.28 (2H), 6.73 (1H), 4.31 (4H), 3.86 (2H), 3.06 (2H), 1.65 (9H), 1.27 (6H)</td>
<td>1.22</td>
<td>26.89</td>
</tr>
<tr>
<td>15</td>
<td>-2.13</td>
<td>7.21 (5H), 6.58 (2H), 6.51 (1H), 4.10 (4H), 3.80 (2H), 3.07 (4H), 1.45 (6H), 1.22 (6H)</td>
<td>1.57</td>
<td>38.67</td>
</tr>
</tbody>
</table>

3.3.7 Acetonide Deprotection of Polymers 12-15

Polymers 12-15 were subsequently deprotected to yield the free catechol functional group. This was achieved by the acidic cleavage of the acetonide using trifluoroacetic acid (TFA). The ease with which amino acid substituted polyphosphazenes undergo acid catalyzed hydrolysis can make deprotections in acidic media difficult. It was necessary to optimize the acid concentration, reaction temperature, and time of the reaction in order to minimize polymer degradation and maximize deprotection of the catechol. Optimal deprotection was achieved using TFA: ethanol (80:20) at room temperature for 24 hrs to 48 hours. The deprotection ratios of nearly 100% were confirmed by the absence of peaks in the $^1$H NMR spectrum. For polymers 16, 17, and 19, the signal near 1.43 ppm was absent from the $^1$H NMR spectra. In the case of polymer 18, the integration of the peak at 1.65 ppm in the $^1$H NMR spectrum decreased according
to the loss of 6 protons from the protecting group. Acidic cleavage of the polymer backbone was negligible as determined from molecular weight data and $^{31}$P NMR spectroscopy.

![Chemical structures](image)

**Figure 3-7.** Acidic deprotection of acetonide protected 3,4-dihydroxy-\(L\)-phenylalanine ethyl ester substituted polyphosphazenes.

### 3.4 Conclusions

The study of small molecule analogs is an important step in the development of macromolecules which require protection and deprotection reactions. This is the first study where DTTQ and 3,4-acetonide-\(L\)-phenylalanine ethyl ester were utilized in the synthesis of small molecule cyclotriphosphazenes and linear high polymers. Hexa(\(L\)-DOPA(Ac)EE)cyclotriphosphazene was deprotected by TFA resulting in the complete removal of the acetonide protecting group without side reactions. Polymers were synthesized with DTTQ as the only side group and were also co-substituted with glycine, alanine, or phenylalanine ethyl ester. A second series of polymers containing L-DOPA(Ac)EE, glycine ethyl ester, alanine ethyl ester, and phenylalanine ethyl ester were also synthesized. The acetonide protecting group in
these polymers was removed by the use of TFA while minimal degradation of the polymer backbone was observed.

Additional work is needed in the future to bring about the acetonide protection of dopamine.\textsuperscript{17} The dopamine(Ac) can then be used in the synthesis of both model compounds and polymers similar to those with L-DOPA(Ac)EE. The dopamine(Ac) will be deprotected to yield polymers with the free catechol functionality. These dopamine and L-DOPAEE polymers can then be screened to evaluate their potential as bioadhesive materials.\textsuperscript{5,7-9}
3.5 References


Chapter 4

Synthesis and Characterization of Poly[(4-(1'-(n-hexyl)pyridinium bromide)alkoxy)phosphazenes] as Potential Antibacterial Agents

4.1 Introduction

Bacterial infection is a common complication of surgery is. In 1998, during recovery, 293,000 hospital patients developed infections at the surgical site with a 4% mortality rate. Another 1,076,000 patients, with a 6% mortality rate, developed secondary infections while hospitalized after surgery. These infections are commonly caused by *Staphylococcus aureus* and *Streptococcus pneumoniae* which are rapidly becoming resistant to common antibiotics such as penicillin. To remedy this problem, new materials are needed to keep surfaces free of bacterial growth. Recently developed polymers utilize bactericidal side groups instead of classic antibacterial drugs. These polymers possess side groups such as quaternary amines, antibacterial peptides, or nitroxide releasing groups.

Quaternary amine complex (QAC) polymers show promise as antibacterial agents. QAC polymers are pyridine or amine based side groups which are attached to a polyethylene backbone. The bactericidal activity is created by quaternizing the amine with a bromoalkane. Studies have shown that pyridine based QACs are better bactericidal agents than other amine-based QACs. QAC polymers are able to maintain antibacterial efficiency over an extended period of time because these polymers do not rely on the release of antibacterial agents into the surrounding medium. Instead, the QAC polymers rely on a process which causes severe physical damage to a bacterial cell wall. The bacteria adhere to the polymer coated surface, assisted by the positive charge of the quaternary amine. The long aliphatic tail on the side group is then able to penetrate...
the cell wall. Motion of the polymer backbone and aliphatic tail cause the bacterial cell wall to rupture, lysing the cell. Studies have shown that QAC polymers are selective for bacterial cells. When tested with a mixture of mammalian and bacterial cells, the QAC polymers killed the bacterial cells while leaving the mammalian cells intact. Polyphosphazenes have the potential to contribute to the advancement of antibacterial polymers.

Polyorganophosphazenes are a type of hybrid organic-inorganic polymer with a phosphorous-nitrogen backbone and pendent organic side groups. Although the phosphazene backbone does not possess any inherent antibacterial activity, the highly tailorable substituents can potentially impart significant activity. This work aims to generate antibacterial polyphosphazenes based on QAC’s from pyridine-containing side groups. Model studies were conducted with hexachlorocyclotriphosphazene and this information was incorporated into the planned polymer synthesis. Pyridine alkoxides were linked to the phosphazene backbone and, if necessary, co-substituted with a second side group to enhance polymer solubility for fabrication. The pyridinepropoxy and pyridinemethoxy groups were then treated with 1-bromohexane to give the quaternary pyridine complex. The activity of the polymers was then evaluated at different concentrations against *Escherichia coli*.

### 4.2 Experimental

#### 4.2.1 Reagents and Equipment

All synthesis reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran (EMD) and toluene (EMD) were dried using solvent purification columns. Ethanol was dried over calcium hydride, distilled from sodium metal, and stored over molecular sieves. Poly(dichlorophosphazene) was prepared by the thermal ring-
opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Japan) in evacuated Pyrex tubes at 250°C. Chemicals and polymers not mentioned above were used as received without purification. $^{31}$P, $^{13}$C, and $^1$H NMR spectra were obtained with use of a Bruker 360 WM instrument operated at 145 MHz, 90 MHz, and 360 MHz, respectively. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10°C/min and a sample size of ca. 10 mg. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-n-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards.

4.2.2 Attempted synthesis of pyridinealkoxy cyclotriphosphazenes (2-4)

A similar method of preparation was used for all the pyridinealkoxy cyclotriphosphazenes, and the synthesis of trimer 3 is given here as a representative example. 4-pyridinepropanol (7.99 g, 58.3 mmol) was added to a suspension of sodium (1.29 g, 56.1 mmol) in THF (100 mL). Hexachlorocyclotriphosphazene (3.00 g, 8.629 mmol) was dissolved in THF (100 mL) and the 4-pyridinepropoxide was added drop-wise. The reaction mixture was stirred at 25°C for 24 hours and then heated to reflux. During this time the reaction was monitored by $^{31}$P NMR spectroscopy. After 48 hours, the partially substituted trimer had precipitated from solution. The precipitate was collected and could not be redisolved in any solvents. No further characterization was attempted.
4.2.3 Poly[bis-(2,2,2-trifluoroethoxy)phosphazene] (5)

Sodium metal (3.34 g, 0.1452 mol) was suspended in THF (200 mL) and 2,2,2-trifluoroethanol (15.10 g, 0.1509 mol) was added to the reaction mixture.
Poly(dichlorophosphazene) (5.50 g, 0.0476 mol) was dissolved in THF (500 mL) and the trifluoroethoxide solution was added drop-wise. The reaction mixture was refluxed for 24 hours at which time the reaction was complete by $^{31}$P NMR spectroscopy. The reaction was concentrated and purified by repeated precipitation into either water (3x) or hexanes (3x). A white polymer was obtained (73%). $^{31}$P NMR (THF-d$_8$), ppm: $\delta$ -9.83; $^1$H NMR (THF-d$_8$), ppm: $\delta$ 4.42 (2H, CH$_2$).

4.2.4 Attempted exchange reaction between polymer 5 and 4-pyridinepropan-1-ol

Sodium hydride (60%, 0.164 g, 4.10 mmol) was suspended in THF (50 mL) and 4-pyridinepropanol (0.637 g, 4.64 mmol) was added drop-wise. Polymer 5 (1.00 g, 4.116 mmol) was dissolved in THF (25 mL) and the 4-pyridinepropanoxide solution was added. Reaction progress was monitored by $^{31}$P NMR spectroscopy for 4 days at 25°C. The mixture was then heated to reflux for an additional 4 days. During the course of the attempted reaction, no side group exchange was detected. $^{31}$P and $^1$H NMR spectra were identical to those from polymer 5.

4.2.5 Synthesis of pyridinealkoxy polyphosphazenes (8-13)

The preparation of polymers 8-13 all followed a similar method and the synthesis of polymer 9 is given here as a representative example. Sodium metal (1.07 g, 0.0466 mol) was suspended in THE (150 mL) and 2,2,2-trifluoroethanol (5.18 g, 0.0518 mol) was added. A solution of poly(dichlorophosphazene (3.00 g, 0.02589 mol) in THF (300 mL) was prepared and
approximately half of the trifluoroethoxide solution was added drop-wise. The reaction progress was monitored by $^{31}$P NMR spectroscopy and was complete after 24 hrs. Sodium hydride (60%, 0.517 g, 0.01295 mol) was suspended in THF (100 mL) and 3-pyridinepropanol (1.78 g, 0.0130 mol) was added. The pyridinepropoxide was added drop-wise to the polymer reaction and the mixture was heated. After 36 hrs, the remaining portion of the trifluoroethoxide solution was added to the reaction mixture. Once complete as assessed by $^{31}$P NMR spectroscopy, the solvent was removed and the residual solid was dissolved in methanol. The polymer was purified by dialysis against methanol for 3 days. The polymer solution was removed from dialysis and dried to give a yellow-orange solid (63-81%). Characterization data for polymers 8-13 are given in Table 4-1.

4.2.6 Synthesis of 1-hexyl-4-(methanol)pyridinium bromide as a model system

4-Pyridinemethanol (0.50 g, 4.58 mmol) was dissolved in ethanol (100 mL) and 1-bromohexane (1.13 g, 6.86 mmol) was added. The reaction mixture was heated to reflux and the reaction was monitored by $^1$H NMR spectroscopy. After 16 hrs, the product was dried under vacuum to give an yellow-orange oil (87%) which formed yellow crystals on standing. $^1$H NMR (MeOH-d4), ppm: δ 8.60 (2H, d, 2CH), 7.83 (2H, d, 2CH), 4.79 (2H, s, CH$_2$), 4.41 (2H, t, CH$_2$), 1.84 (2H, m, CH$_2$), 1.10 (6H, m, 3CH$_2$), 0.67 (3H, t, CH$_3$).

4.2.7 Quaternization of polymers 8-13 with 1-bromohexane (14-19)

The quaternization of polymers 8-13 all followed a similar method, and the synthesis of polymer 15 is given as a representative example. Poly[(3-pyridinepropoxy)$_{0.5}$(2,2,2-trifluoroethoxy)$_{1.5}$phosphazene] (9, 3.00 g, 0.0121 mol) was dissolved in ethanol (200 mL). 1-
Bromohexane (6.035 g, 0.0366 mol) was added and the reaction was heated. After 48 hrs, the mixture was dried and the resulting solid was dissolved in methanol. The polymer was purified by dialysis against methanol for 3 days and was isolated as an orange solid (73-87%). Characterization data are given for polymers 14-19 in Table 4-2.

4.2.8 Antibacterial testing of polymers 14-19 with *Escherichia coli*

Solutions of polymers 14-19 in methanol were prepared. This solution was added to sterile test tubes to give a series of concentrations (100 μg/mL, 200 μg/mL, 300 μg/mL, 700 μg/mL, and 900 μg/mL) after 1 mL of solution was added. The methanol was evaporated and dried under vacuum so that the bottom of the test tube was coated with a thin film of each polymer. An *Escherichia coli* solution (1 mL) was added and the test tubes were incubated in a shaker at 37°C for 18 hrs. The turbidity of the solution was evaluated qualitatively and a small amount of the solution was spread on an agar filled petri dish.

4.3 Results and Discussion

4.3.1 Synthesis of cyclic trimer model compounds

The synthesis of small molecule phosphazenes was attempted to study the relative reactivities of pyridine containing alkoxides to hexachlorocyclotriphosphazene (1). A stoicheometric excess of the respective alkoxide (4-pyridinepropoxide, 3-pyridinepropoxide, or 4-pyridinemethoxide) was added to a solution of 1 in THF or benzene (Figure 4-1). The reaction progress was monitored by 31P NMR spectroscopy and after 24 hrs at room temperature partial substitution was detected. After another 24 hours, both at room temperature or refluxing, the
products precipitated from solution and no signal was detected in the $^{31}$P NMR spectrum. These experiments showed that the alkoxides were able to participate in the replacement of chlorine atoms, but that co-substitution was necessary to obtain a soluble product.

![Reaction Scheme](image)

**Figure 4-1.** Synthesis of (a) (4-pyridinealkoxy)$_x$(chloro)$_{6-x}$cyclotriphosphazenes and (b) (3-pyridinepropoxy)$_x$(chloro)$_{6-x}$cyclotriphosphazene which yielded an insoluble product after 48 hours.

### 4.3.2 Attempted synthesis of pyridinepropoxide substituted phosphazene polymers

Initial attempts at the macromolecular substitution of poly(dichlorophosphazene) (7) by pyridinealkoxides to obtain homo-substituted polymers and co-substituted polymers were unsuccessful. When the polymer was treated with 4-pyridinepropoxide or 3-pyridinepropoxide, the polymer precipitated from solution. Spectrographic $^{31}$P NMR data revealed that roughly 25% of the chlorine atoms were replaced before the polymer became insoluble. The addition of a second nucleophile, 2,2,2-trifluoroethoxide or phenoxide, did not solubalize the precipitate. With the knowledge obtained through the cyclic trimer model studies and these initial polymer reactions, two methods for obtaining pyridinepropoxide co-substituted polymers were devised.
The first planned route involved side group exchange reactions and the second was a three step sequential addition of the desired side groups.

Several side groups on homo-substituted polyphosphazenes are known to be labile and replaceable through solution reactions with some nucleophiles.\(^8,12-15\) Thus an attempt was made to replace the side groups in poly[bis-(2,2,2-trifluoroethoxy)phosphazene] (5) by 4-pyridinepropoxide (Figure 4-2). Solutions of polymer 5 and the propoxide were stirred for 4 days at 25°C and the reaction was monitored by \(^{31}\text{P}\) NMR spectroscopy. No replacement of the 2,2,2-trifluoroethoxy side groups was evident at the end of this period so the reaction was heated to reflux. After an additional 4 days, there was still no indication that any exchange reaction had occurred either by \(^{31}\text{P}\) or \(^1\text{H}\) NMR spectroscopy. It was concluded that, even if substitution were possible, this method for the synthesis of poly[(4-pyridinepropoxy),\(_x\)(2,2,2-trifluoroethoxy),\(_y\)phosphazene] would be impractical due to the high nucleophile concentrations and length of time required for any substantial replacement.

![Figure 4-2](image.png)

**Figure 4-2.** Attempted synthesis of poly[(4-pyridinepropoxy),\(_x\)(2,2,2-trifluoroethoxy),\(_y\)phosphazene] by a side group exchange reactions between poly[bis-(2,2,2-trifluoroethoxy)phosphazene] and 4-pyridinepropoxide.
4.3.3 Synthesis of pyridinealkoxy substituted polyphosphazenes

A three step addition was the used for the synthesis of polymers 8-12 (Figure 4-3). This method can be utilized if several different substituents are to be included in the final polymer or if one of the substituents causes insolubility at an intermediate stage. In this case, phenoxy and 2,2,2-trifluoroethoxy substituents were used as solubilizing groups for the pyridinealkoxy groups. Half of the stoichiometrically desired phenoxy or 2,2,2-trifluoroethoxy (R₁) was added drop-wise to a solution of 7, and the reaction progress was monitored by 31P NMR spectroscopy. The total amount of the pyridinealkoxide (R₂) was then added drop-wise and the reaction mixture was heated. When substitution of the second nucleophile was complete based on 31P NMR spectroscopy, the remaining chlorine atoms were replaced with additional quantities of R₁. The final 31P NMR spectrum of polymers 8-10 showed two peaks: one corresponding to phosphorous atoms bearing R₁ groups and the other phosphorous atoms substituted with R₂. The integrations of the peaks indicate complete chlorine atom replacement by the two nucleophiles in the desired ratios (Table 4-1). Polymers 11 and 12 appear to contain a random distribution of the side groups based on the number and integration of peaks in the 31P NMR spectra.

During the course of these reactions, it was noted that 4-pyridinemethoxide and 4-pyridinemethoxy polyphosphazenes are more soluble than their pyridinepropoxy analogs. Therefore the synthesis of poly[bis-(4-pyridinemethoxy)phosphazene] was attempted by the drop-wise addition of the alkoxide into a solution of polymer 7 (Figure 4-3c, 16). Unlike the situation at the small molecule level, the polymer remained in solution throughout the reaction period. Complete chlorine replacement was evident from a single peak in the 31P NMR spectrum at -4.36 ppm.
Table 4-1. Characterization data for pyridinealkoxy substituted polyphosphazenes.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Group*</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>$M_w$ (x 10$^5$ g/mol)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>TFE</td>
<td>-7.63</td>
<td>4.28 (2H)</td>
<td>8.53</td>
<td>-68</td>
</tr>
<tr>
<td>8</td>
<td>4PP/TFE (1:3)</td>
<td>-7.69, -9.14</td>
<td>8.30 (2H), 7.15 (2H), 4.29 (6H), 3.95 (2H), 2.64 (2H), 1.87 (2H)</td>
<td>3.15</td>
<td>-55.73, 22.43</td>
</tr>
<tr>
<td>9</td>
<td>3PP/TFE (1:3)</td>
<td>-7.78, -9.61</td>
<td>8.28 (2H), 7.12 (2H), 4.30 (6H), 3.95 (2H), 2.62 (2H), 1.86 (2H)</td>
<td>3.65</td>
<td>-53.53, 22.16</td>
</tr>
<tr>
<td>10</td>
<td>4MP/TFE (1:3)</td>
<td>-6.81, -7.77</td>
<td>8.25 (2H), 7.23 (2H), 5.07 (2H), 4.40 (6H)</td>
<td>1.64</td>
<td>-32.71, 47.66</td>
</tr>
<tr>
<td>11</td>
<td>4MP/OPh (1:3)</td>
<td>-15.13, -16.97</td>
<td>8.22 (2H), 6.81 (17H, br), 5.03 (2H)</td>
<td>1.04</td>
<td>17.43</td>
</tr>
<tr>
<td>12</td>
<td>4MP/OPh (1:1)</td>
<td>-15.21</td>
<td>8.20 (2H), 6.95 (7H, br), 5.02 (2H)</td>
<td>1.25</td>
<td>17.76</td>
</tr>
<tr>
<td>13</td>
<td>4MP</td>
<td>-4.36</td>
<td>8.21 (2H), 7.20 (2H), 5.05 (2H)</td>
<td>1.13</td>
<td>37.66</td>
</tr>
</tbody>
</table>

*4PP refers to 4-pyridinepropoxy, 3PP refers to 3-pyridinepropoxy, 4MP refers to 4-pyridinemethoxy, TFE refers to 2,2,2-trifluoroethoxy, and OPh refers to phenoxy.
Figure 4-3. Three step addition of nucleophiles utilized in the synthesis of (a) 4-pyridinepropoxy polyphosphazenes (8), (b) 3-pyridinepropoxy polyphosphazenes (9), and (c) 4-pyridinemethoxy polyphosphazenes (10-13).
4.3.4 Thermal characterization of polymers 8-13

The thermal transitions recorded for polymers 8-10 indicate that substitution is blocky in nature because two distinct transitions are seen. However, the glass transition temperature ($T_g$) which corresponds to the trifluoroethoxy portion of the polymer is shifted to higher temperatures than the observed $T_g$ for polymer 5. In addition, the $T_g$ attributed to the pyridinemethoxy (47.66°C) or pyridinepropoxy (22.43°C) portions of the polymer is significantly higher than $T_g$’s observed for phenylmethoxy (-31.4°C) or 3-phenylpropoxy (-47°C) species. The single thermal transitions seen in polymers 11-13 are indicative of randomly substituted polymers, but are still significantly higher than expected from work with the analogous phenyl or phenoxy polymers.

4.3.4 Quaternization of the pyridine ring

A model study for the quaternization of pyridinealkoxy polyphosphazenes was conducted using 4-pyridinemethanol and 1-bromohexane in ethanol. After 16 hrs, the only isolated product was the hexyl 4-pyridinemethanol salt. This method was then applied to the quaternization of polymers 8-13 with an increase in the reaction time. Initially, only a light stoicheometric excess (1.2 molar equivalents) of the bromohexane was added to the reaction. These reactions resulted in only partial quaternization (30-52%) of the pyridine groups. This was not unexpected because secondary reactions at the polymeric level do not always give yields as high as the small molecule reactions. Thus, the quaternization reactions were attempted with a significant excess (12 molar equivalents) of the bromohexane. After purification, $^1$H NMR spectroscopy indicated that quaternization of the pyridine side groups was quantitative. The $^{31}$P NMR spectrum of the quaternized polymer showed no significant difference when checked against that of the initial polymers. The spectral data of the quaternized polymers is given in
Table 4-2. The thermal transitions of the polymers were lowered as a result of the quaternization (Table 4-2). This is possibly due to the additional free volume generated by the addition of the hexyl tail to the pyridine.

Table 4-2. Characterization data for bromohexane quaternized pyridinealkoxy substituted polyphosphazenes.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Group*</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Q4PP/TFE (1:3)</td>
<td>-7.69, -9.14</td>
<td>8.30 (2H), 7.15 (2H), 4.29 (6H), 3.95 (4H), 2.64 (2H), 1.87 (4H), 1.35 (6H), 0.93 (3H)</td>
<td>-2.58</td>
</tr>
<tr>
<td>15</td>
<td>Q3PP/TFE (1:3)</td>
<td>-7.59, -9.62</td>
<td>8.28 (2H), 7.67 (1H), 7.36 (2H), 4.40 (6H), 4.07 (4H), 2.74 (2H), 1.95 (4H), 1.32 (6H), 0.86 (3H)</td>
<td>-49.42, 17.38</td>
</tr>
<tr>
<td>16</td>
<td>Q4MP/TFE (1:3)</td>
<td>-6.81, -7.77</td>
<td>8.66(2H), 7.64 (2H), 4.54 (2H), 4.31 (6H), 3.59 (2H), 1.64 (2H), 1.28 (6H), 0.86 (3H)</td>
<td>-48.00, 36.57</td>
</tr>
<tr>
<td>17</td>
<td>Q4MP/OPh (1:3)</td>
<td>-15.13, -16.97</td>
<td>8.66(2H), 7.82 (8H), 4.82 (2H), 3.59 (2H), 1.65 (2H), 1.31 (6H), 0.86 (3H)</td>
<td>13.87</td>
</tr>
<tr>
<td>18</td>
<td>Q4MP/OPh (1:1)</td>
<td>-15.26</td>
<td>8.67(2H), 7.85 (8H), 4.31 (2H), 3.62 (2H), 1.59 (2H), 1.27(6H), 0.84 (3H)</td>
<td>14.37</td>
</tr>
<tr>
<td>19</td>
<td>Q4MP</td>
<td>-4.36</td>
<td>8.21 (2H), 7.20 (2H), 5.05 (2H), 3.57 (2H), 1.62 (2H), 1.30 (6H), 0.92 (3H)</td>
<td>30.61</td>
</tr>
</tbody>
</table>

*Q4PP refers to 4-(1'-(n-hexyl)pyridinium bromide)propoxy, Q3PP refers to 3-(1'-(n-hexyl)pyridinium bromide)propoxy, Q4MP refers to 4-(1'-(n-hexyl)pyridinium bromide)methoxy, TFE refers to 2,2,2-trifluoroethoxy, and OPh refers to phenoxy.
Figure 4-4. Quaternization of pyridinealkoxy polypshophazenes by 1-bromohexane
4.3.5 Antibacterial testing

The polymers were evaluated for their antibacterial activity against *Escherichia coli* using standard techniques. A series of test tubes with various amounts of the respective polymer were prepared in triplicate to minimize any false results. The polymer samples were dosed with the bacterial broth solution and incubated at physiological conditions for 18 hrs. At the end of this period, all the solutions were turbid, indicating that none of the polymers were active at the concentrations which were tested (<900 μg/mL). This was confirmed by spreading some of the solution from the incubated test tube on an agar plate and observing the bacterial growth after 24 hrs incubation (Figure 4-5).

![Figure 4-5](image-url)

**Figure 4-5.** Results of antibacterial testing of quaternized polymers were determined by (a) solution trubidity and (b) agar plates were prepared by brushing with solution from test tubes.
4.4 Conclusions

Novel polyphosphazenes with pendant pyridinealkoxy groups were synthesized by the macromolecular substitution of poly(dichlorophosphazene). With the exception of one polymer, the polymers were co-substituted with either 2,2,2-trifluoroethoxy or phenoxy groups through a three step method to increase the solubility of the final polymers. During the synthesis of poly[bis-(4-pyridinemethoxy)phosphazene], the polymer remained soluble and a homo-substituted polymer was obtained. Test reactions were carried out on 4-pyridinemethanol to determine conditions best suited for quaternization of the pyridinealkoxy phosphazenes. The polymers were quaternized by a reaction with 1-bromohexane. Solution turbidity tests with *Escherichia coli* were performed on the quaternized polymers, but none were active at the low concentrations tested.

Additional studies are required to truly determine the antibacterial activity of the polymers synthesized in this work. Based on published literature, the side groups that are incorporated into these polymers are antibacterial at some concentration.\(^3,7\) This includes polyphosphazenes were previously tested for antimicrobial activity.\(^8-10\) Significantly higher concentrations of polymer need to be evaluated as well as their efficacy against other bacterial strains. In previous studies with polyphosphazenes, *Escherichia coli* was the one strain tested which the polymers were ineffective against at high concentrations.\(^8,18,19\)
4.5 References


Chapter 5

Polyphosphazenes Bearing Pendent 1-H-[1,2,3]-Triazole Groups via Macromolecular “Click” Chemistry

5.1 Introduction

In the recent years, interest in bringing fuel cell technology to the general public market has driven research to develop better performing and more cost effective membrane materials. One of the primary stepping stones to developing a better material is to reduce or eliminate the dependence of proton conductive membranes on water for the main mechanism of proton conduction.\(^1,2\) Water dependent membranes are intrinsically limited in their maximum operating temperature (≤ 100°C).\(^2\) One group of polymers that have been studied for this application are macromolecules that contain heteroaromatic species such as imidazole, pyrazole, or benzimidazole.\(^1,3,4\)

Another aromatic heterocycle that is being investigated for this purpose is the triazole.\(^5-7\) When the conductivity of poly(vinylimidazole) and poly(vinyltriazole) are compared, the triazole based polymer has a substantially higher conductivity. The reason for the improved conduction is the lower pKa of triazole and the fewer conformational changes that are needed in the conduction mechanism.\(^5\) Additionally, these studies revealed that the glass transition temperature (Tg) of a polymer also plays an important role in the efficiency of proton transport across a membrane.\(^5,8\)

When the inherent backbone flexability (corresponding low T_g’s) and the thermo-oxidative stability are combined with the versatility of macromolecular substitution, polyphosphazenes become an attractive platform for polymer electrolyte membrane fuel cells (PEMFCs).\(^9\) Previously studied polyphosphazenes have shown potential for use as proton...
exchange membranes (PEM’s). However, these polymers contain sulfonic acid, phosphonic acid, or sulfonamide functional groups and rely heavily on water for the conduction of protons across the membrane. Few attempts have been made to introduce either imidazole or triazole units into a phosphazene system. The problems arise from the nucleophilic imidazole nitrogen atoms which compete for linkage to a phosphazene chain if a linking group is used. In addition, when the imidazole is attached directly to the phosphazene, the product is susceptible to rapid hydrolysis. This chapter describes the preparation of 1-H-[1,2,3]-triazole substituted phosphazenes by a macromolecular “click” reaction.

Hexachlorocyclotriphosphazene was used as a model for chlorine-replacement reactions by sodium 5-hexyn-1-oxide. The information gathered during this small molecule reaction was then applied to the synthesis of poly[(5-hexyn-1-oxy)(2-(2-methoxyethoxy)ethoxy)phosphazene] and poly[(4-pentyn-1-oxy),(alkoxy),phosphazene]. These polymers were then used as macromolecular intermediates in “click” reactions designed to give 4-(1-H-[1,2,3]-triazole)alkoxy substituted polyphosphazenes by two different reaction methods.

5.2 Experimental

5.2.1 Reagents and Equipment

All synthesis reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran (EMD) was dried using solvent purification columns. Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of reerystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Japan) in evacuated Pyrex tubes at 250°C. Chemicals and polymers not mentioned above were used as received without purification. $^{31}$P, $^{13}$C, and $^1$H NMR spectra were obtained with use of a Bruker
360 WM instrument operated at 145 MHz, 90 MHz, and 360 MHz, respectively. Glass transition temperatures were measured with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10°C/min and a sample size of ca. 10 mg. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1100 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-n-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards. Conductivity measurements were made on a Karl Suss PM5 probe station with AC and DC measurement capabilities.

5.2.2 Synthesis of cyclic trimer analog (4)

5-Hexyn-1-ol (1.69 g, 0.01726 mol) was added to a suspension of sodium hydride (60%, 0.414 g, 0.01726 mol) in THF (50 mL) and the reaction mixture was stirred for 16 hrs. A solution of hexachlorocyclotriphosphazene (1, 2.00 g, 5.752 mmol) in THF (10 mL) was added drop-wise to the hexynoxide reaction mixture and the combination was heated at 60°C. The reaction progress was monitored by $^{31}$P NMR spectroscopy. Sodium hydride (60%, 1.15 g, 0.02877 mol) was suspended in THF (50 mL), and 2,2,2-trifluoroethanol (2.88 g, 0.02877 mol) was added slowly. The trifluoroethoxide solution was then added to the phosphazene reaction mixture which was then refluxed for 48 hrs. The solvent was removed and the residual oil was disolvent in ethyl acetate. The organic solution was then extracted with water and the combined organic layers were dried over magnesium sulfate. The solvent was removed to give a yellow oil (63% by 1). $^1$H NMR (CDCl$_3$), ppm: δ 4.22 (3H, m, -OCH$_2$CF$_3$), 3.99 (2H, m, -OCH$_2$(CH$_2$)$_3$C≡CH), 2.21 (2H, m, -O(CH$_2$)$_3$CH$_2$C≡CH), 1.94 (1H, m, -OCH$_2$(CH$_2$)$_3$C≡CH), 1.79 (2H, m, -OCH$_2$(CH$_2$)$_2$CH$_2$C≡CH), 1.61(2H, m, -OCH$_2$(CH$_2$)$_2$CH$_2$C≡CH); MS (ESCl+) m/z = 724
([M+H]+, N₃P₃(5-hexyn-1-oxy)₃(2,2,2-trifluoroethoxy)₃, C₂₄H₃₅F₉N₃O₆P₃), 726 ([M+H]+, N₃P₃(5-hexyn-1-oxy)₂(2,2,2-trifluoroethoxy)₄, C₂₀H₂₅F₁₂N₃O₆P₃).

5.2.3 Synthesis of alkynoxy polyphosphazenes (6-10)

Polymers 6-10 were synthesized by a similar method, and the preparation of polymer 6 is given here as an example. 4-Pentyn-1-ol (1.45 g, 0.01725 mol) was added drop-wise to a suspension of sodium metal (0.396 g, 0.01725 mol) in THF (100 mL) and the reaction mixture was stirred for 16 hrs. Poly(dichlorophosphazene) (2.00 g, 0.01725 mol) was dissolved in THF (200 mL) and the 4-pentyn-1-oxide solution was added drop-wise over 1.5 hrs. The mixture was heated to reflux and progress of the reaction was monitored by ³¹P NMR spectroscopy. Sodium metal (0.595 g, 0.0259 mol) was suspended in THF (100 mL), allowed to react with 2,2,2-trifluoroethanol (2.59 g, 0.0259 mol), and the mixture was stirred for 14 hrs. The trifluoroethoxide solution was then added to the polymer solution which was then returned to reflux. After 24 hrs, the reaction was complete and was concentrated at reduced pressure. The polymer was purified by alternating precipitations from THF between water and hexanes (3x each). Yields were between 63-82%, and characterization data are given in Table 5-1.

5.2.4 Synthesis of Triphenylmethyl azide (Tr-N₃, 11)

The synthesis of triphenylmethyl azide followed published literature procedures. Sodium azide (5.00 g, 0.0769 mol) was dissolved in a chloroform:water solution (4:1, 25 mL). Triphenylmethanol (5.00 g, 0.0192 mol) was dissolved in chloroform (40 mL), and was combined with the sodium azide solution. The reaction mixture was cooled to 0°C, and concentrated sulfuric acid (5 mL) was added drop-wise. After 1.5 hrs, the mixture was warmed
to 25°C and neutralized with sodium hydroxide (aq). The organic layer was extracted and the aqueous layer washed with chloroform. The combined organic layers were evaporated to yield the product as a yellow oil. The oil was purified by recrystallization from hexane to give yellow crystals of triphenylmethyl azide (92%). ¹H NMR (CDCl₃), ppm: δ 7.26 (15H, m, Ar); mp: 64-66°C (lit. 64-65°C)¹²,¹³.

5.2.5 “Click” reactions with triphenylmethyl azide (Tr-N₃) (12-16)

The method for the synthesis of polymers 12-16 was similar and 13 is given here as an example. Polymer 8 (1.50 g, 6.85 mmol) was dissolved in a minimum of CHCl₃. Triphenylmethyl azide (2.92 g, 10.27 mmol), Copper Iodide (0.615 g, 3.42 mmol), and tetramethylethylenediamine (0.796 g, 6.85 mmol) were added and the mixture was refluxed for 48 hrs. The reaction progress was monitored by IR spectroscopy. A solution of ethelenediaminetetraacetic acid disodium salt dihydrate (EDTANa₂·2H₂O, 3.00 g, 8.06 mmol) in water (10 mL) was added and the reaction mixture was stirred for 24 hrs. Volatile solvents were removed under vacuum and the polymer was purified by dialysis against THF/methanol (80:20) for 3 days.

5.2.6 Deprotection of 1-Tr-[1,2,3]-triazole

Polymers 12-16 were dissolved in a minimum amount of a trifluoroacetic acid:methanol:water (8:1:1) solution. The polymers were stirred at 25°C for 24 hrs and the solution was neutralized. The polymer was purified by dialysis against methanol/THF for 3 days. Yields were 73-82% based on polymers 7-10. Characterization data are given in Table 5-2.
5.2.7 Click reactions with trimethylsilyl azide (TMS-N\textsubscript{3}) (17-21)

This procedure was adapted from published literature.\textsuperscript{14} The synthesis of polymer 17 is given here as a representative example. Poly[(4-pentyn-1-oxy)(2,2,2-trifluoroethoxy)phosphazene] (6, 0.300 g, 1.37 mmol) was dissolved in a DMF:methanol solution (9:1, 10 mL). Trimethylsilyl azide (0.456 g, 3.96 mmol) and copper iodide (0.0261 g, 0.137 mmol) were added and the reaction mixture was heated for 48 hrs. The reaction was dried under reduced pressure and the residual solid was dissolved in ethyl acetate. An excess of EDTANa\textsubscript{2} (aq, 0.325 g, 10.0 mmol) was added and the reaction mixture was stirred for 16 hrs. The aqueous layer was removed and the organic layer placed in dialysis against methanol for 2 days. The polymer solution was removed from dialysis and dried to give the 4-(1-H-[1,2,3]-triazole)alkoxy substituted polyphosphazene (83-92%). Structural characterization data is given in Table 5-3.

5.2.8 Conductivity testing of polymers

The polymers were dissolved in a suitable solvent and solution cast to give films. The films were air dried for 48 hrs and then dried further for 5 days under vacuum. Polymers 6, 8, and 17-21 formed self supporting polymer films that were cut into small strips that were roughly 0.5 cm x 2.0 cm. The film thickness was directly measured with a caliper. Polymers 7, 9, and 10 did not form self supporting films and were recast on glass slides. Film thickness was determined by the difference between the slide supported film and a cleaned portion of the slide. Conductivity measurements were made on a Karl Suss PM5 probe station with AC and DC measurement capabilities.
5.3 Results and Discussion

5.3.1 Model study for the synthesis of alkynoxy phosphazenes

When developing new synthetic routes for macromolecules, it is often beneficial to begin with the study of a model system. The system which is most often used to model the substitution reactions of poly(dichlorophosphazene) (5) is the cyclic trimer, hexachlorocyclotriphosphazene (1). Initial studies attempted to obtain complete chlorine atom replacement by either 5-hexyn-1-oxide or 4-pentyn-1-oxide, but the compounds 2 and 3 precipitated from solution before full substitution (Figure 5-1a). The insoluble material could not be redisolved in any common organic solvents. Analysis of $^{31}$P NMR spectra obtained before product precipitation indicated that 3 or 4 of the chlorine atoms had been replaced, while the compounds still remained soluble in THF. Therefore, the next synthetic target was a co-substituted molecule, (5-hexyn-1-oxy)$_3$(2,2,2-trifluoroethoxy)$_3$cyclotriphosphazene, in order to maintain solubility of the trimer for replacement of all the chlorine atoms. Sodium 5-hexyn-1-oxide was added drop-wise to a solution of 1 and the reaction progress was monitored by $^{31}$P NMR spectroscopy. When no further change was detected, sodium 2,2,2-trifluoroethoxide was added to the reaction mixture to replace the remaining chlorine atoms. The fully substituted trimer was then purified by liquid/liquid extractions. Mass spectrometry and integrations from the $^1$H NMR spectrum revealed that the purified product contained a mixture of di- and tri-alkynoxy substituted phosphazenes (Figure 5-1b). Separation of the products was attempted by column chromatography with ethyl acetate/hexanes as the mobile phase, but this did not resolve the $^1$H or $^{31}$P NMR spectra.
Figure 5-1. Synthesis of phosphazene small molecule analogues: (a) homo-substitution of 1 resulted in precipitation of the product prior to complete substitution. (b) Co-substitution resulted in di- and tri-alkynoxy substituted phosphazenes.

5.3.2 Synthesis and characterization of polymers 6-10

Initial attempts to synthesize fully alkynoxy substituted polymers were unsuccessful. After roughly 80% of the chlorine atoms had been replaced, the polymers precipitated from solution and could not be resolubilized. Thus, two common side groups, which are known to give excellent solubility, were selected to be co-substituted with the alkynoxide onto the polymer backbone.

The synthesis of polymers 6-10 was accomplished by the macromolecular substitution of the chlorine atoms in 5 (Figure 5-2). Substitution by the alkynoxide was monitored by changes in the $^{31}$P NMR. When no further shift was observed, the second alkoxide was added. Stabilization of the $^{31}$P NMR spectra of each polymer as a single peak indicated that complete chlorine substitution had occurred as a random distribution of side groups along the polymer backbone.
Confirmation of the substitution ratios for the side groups was obtained by comparison of unique shifts in the $^1$H NMR spectrum of the polymers.

**Figure 5-2.** Synthesis of poly[(alkynoxy)$_x$(alkoxy)$_y$phosphazenes].
### Table 5-1. Physical and chemical characterization data of polymers 6-10.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Side Groups (x:y)*</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H HMR (ppm)</th>
<th>Mw ($\times 10^5$ g/mol)</th>
<th>Tg (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Pentyn:OTFE 1:1</td>
<td>-7.50</td>
<td>4.49 (2H), 4.17 (2H), 2.20 (2H), 1.89 (1H), 1.79 (2H)</td>
<td>7.92</td>
<td>-76.17</td>
</tr>
<tr>
<td>7</td>
<td>Pentyn:OMEE 1:1</td>
<td>-7.35</td>
<td>4.05 (2H), 3.93 (2H), 3.62 (2H), 3.51 (2H), 3.34 (2H), 2.12 (2H), 1.83 (1H), 1.70 (2H)</td>
<td>6.17</td>
<td>-72.63</td>
</tr>
<tr>
<td>8</td>
<td>Pentyn:OTFE 1.5:0.5</td>
<td>-5.73</td>
<td>4.45 (1H), 4.16 (3H), 2.21 (3H), 1.88 (1.5H), 1.79 (3H)</td>
<td>4.66</td>
<td>-56.77</td>
</tr>
<tr>
<td>9</td>
<td>Pentyn:OMEE 1.5:0.5</td>
<td>-7.09</td>
<td>4.05 (1H), 3.94 (3H), 3.63 (1H), 3.50 (1H), 3.35 (1H), 2.10 (3H), 1.83 (1.5H), 1.70 (3H)</td>
<td>8.11</td>
<td>-63.13</td>
</tr>
<tr>
<td>10</td>
<td>Hexyn:OMEE 1:1</td>
<td>-7.03</td>
<td>4.01 (2H), 3.89 (2H), 3.60 (2H), 3.47 (2H), 3.32 (2H), 2.04 (2H), 1.95 (1H), 1.56 (2H), 1.41 (2H)</td>
<td>8.78</td>
<td>-79.19</td>
</tr>
</tbody>
</table>

*Pentyn refers to 4-pentyn-1-oxy; hexyn refers to 5-hexyn-1-oxy; OTFE refers to 2,2,2-trifluoroethoxy; OMEE refers to methoxyethoxyethoxy.
5.3.3 Thermal characterization of polymers 6-10

The glass transition temperatures ($T_g$) for polymers 6-10 are given in Table 5-1. All the polymers have $T_g$'s in the range of -55° to -80°C which indicated that these polymers have a high degree of molecular flexibility in both the polymer backbone and side groups. The low $T_g$'s are consistant with the literature values of poly[bis-(2,2,2-trifluoroethoxy)phospha-zene (-66°C) and poly[bis-(2-(2-methoxyethoxy)ethoxy)phosphazene] (-84°C). The observed decrease in $T_g$ when the alkynoxy chain length is increased (polymer 7 and 10) is also consistent with previous observations.

5.3.4 Triazole synthesis by macromolecular “click” reactions

The “click” reaction is a relatively new concept in chemistry which was first introduced in 2001 by Sharpless. The “click” reaction was first used as a generic term referring to any reaction which is easy to perform and work up, is high yielding, and tolerant of oxygen and water. Recently, the term has become synonymous with the Huisgen 1,3-dipolar cycloaddition. This is a regiospecific [3+2] cycloaddition reaction between a terminal alkyne and an azide to yield the 1,4-disubstituted 1,2,3-triazole. This class of reactions has been adopted by materials chemistry due to its versatility and high yields.

![Figure 5-3](image)

**Figure 5-3.** [1,2,3]-Triazole regioisomers obtained from the thermal [3+2] cycloaddition.
5.3.4.1 Preparation of triphenylmethyl azide (Tr-N₃)

Triphenylmethyl azide (trityl azide, Tr-N₃) was synthesized according to published literature techniques.¹²,¹³ The addition of sulfuric acid to a solution of triphenylmethanol and sodium azide readily yielded the desired Tr-N₃ (Figure 5-4). Proton NMR spectroscopy was not particularly helpful to determine the purity of the product. However, the purity could be readily verified by simple melting point determination. The melting point of the triphenylmethanol starting material is significantly higher (161-163°C) than that of the desired product (64-66°C).

![Figure 5-4. Synthesis of triphenylmethyl azide for use in macromolecular "click" reactions.](image)

5.3.4.2 "Click" reactions with Tr-N₃

Initially, the synthesis of polymers 17-21 was attempted by the “click” reaction between the respective polymer and sodium azide with a copper (I) catalyst. These reactions were unsuccessful for two reasons. The terminal alkyne is insufficiently activated by electron withdrawing groups for the reaction to occur. Additionally, the mechanism of ring closing relies on thermal initiation rather than on a catalyzed process. To date, there are no reports of
copper(I)-catalyzed “click” reactions optimized for the synthesis of 1,2,3-triazoles with sodium azide.

Thus, polymers 7-10 were used as intermediates for the synthesis of polymers containing pendant triazole functionalities by “click” reactions between the polymer and Tr-N₃ (Figure 5-5a). The reaction is catalyzed by a copper(I)-TMEDA complex and produces the Tr-protected triazole in relatively high yields. The reaction was confirmed by ¹H NMR and infrared spectroscopy. In the proton NMR spectrum, a new signal was detected in the aromatic region (7.27 ppm), where no signal was observed previously, and was attributed to the Tr-protecting group and the triazole CH. The signal assigned to the terminal alkyne (C≡CH) was no longer detected. In the IR spectrum of polymers 7-10, two alkyne stretching vibrations were observed: one band at 3305-3280 cm⁻¹ (C≡C-H stretching) and another band at 2120-2110 cm⁻¹ (C≡C-H stretching). Although the intensity of these signals in polymer spectra is muted when compared to small molecule analogs, they still serve as qualitative markers. After the reaction was complete, a broad new band is observed above 3400 cm⁻¹ and neither of the alkyne stretching vibrations are seen. Excess azide remaining after purification can be qualitatively estimated by the intensity of a sharp band at 2095 cm⁻¹. No degradation, normally indicated by a sharp peak at δ 0.00 ppm, was found in the ³¹P NMR spectra at any point in the reactions.
**Figure 5-5.** Two methods toward the formation of 4-(1-H-[1,2,3]-triazole)alkoxy polyphosphazenes: (a) Ph$_3$CN$_3$, CuI, TMEDA, CH$_2$Cl$_2$, Δ. (b) TFA, H$_2$O, MeOH. (c) TMS-N$_3$, CuI, DMF, MeOH, Δ
Table 5-2. Structural characterization of 4-(1-Tr-[1,2,3]triazole)alkoxy substituted polyphosphazenes.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Original Side Groups*</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H HMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Pentyn:OTFE 1:1</td>
<td>-6.15</td>
<td>7.29 (16H), 4.40 (2H), 4.12 (2H), 2.29 (2H), 1.85 (2H)</td>
</tr>
<tr>
<td>14</td>
<td>Pentyn:OTFE 1.5:0.5</td>
<td>-5.99</td>
<td>7.29 (24H), 4.38 (1H), 4.13 (3H), 2.29 (3H), 1.85 (3H)</td>
</tr>
<tr>
<td>15</td>
<td>Pentyn:OMEE 1.5:0.5</td>
<td>-7.11</td>
<td>7.24 (24H), 3.98 (1H), 3.85 (2H), 3.55 (1H), 3.43 (1H), 3.28 (1.5H), 2.23 (3H), 1.76 (3H)</td>
</tr>
<tr>
<td>16</td>
<td>Hexyn:OMEE 1:1</td>
<td>-7.06</td>
<td>7.31 (16H), 4.03 (2H), 3.91 (2H), 3.61 (2H), 3.49 (2H), 3.34 (2H), 2.21 (2H), 1.60 (2H), 1.42 (2H)</td>
</tr>
</tbody>
</table>

*Pentyn refers to 4-pentyn-1-oxy; hexyn refers to 5-hexyn-1-oxy; OTFE refers to 2,2,2-trifluoroethoxy; OMEE refers to methoxyethoxyethoxy.

5.3.4.3 Deprotection of 4-(1-Tr-[1,2,3]-triazole)alkoxy polyphosphazenes

The triphenylmethyl group can be used to protect a wide variety of functional groups and is a common protecting group for imidazoles and other nitrogen containing aromatic heterocycles.\(^{21}\) When the trityl group is used as a protecting group for hetero aromatic rings, it can be removed by treating the compound with acid.\(^{21-23}\) Polymers 12-16 were deprotected with trifluoroacetic acid and were purified by dialysis against methanol (Figure 5-5b). Both the $^1$H NMR and $^{31}$P NMR spectra were essentially unchanged except for the decrease in integration of
the aromatic peak near 7.27 ppm. In polymers 12-16, the proton signal assigned to the trityl protecting group also contains the signal for the triazole C5-H. When the protecting group was eliminated in polymers 17-21, only the signal for the triazole C5-H was seen. In some instances, a broad, weak peak at 10.88 ppm was observed and this can be attributed to the 1-H proton on the triazole ring.

5.3.4.4 Direct synthesis of 1-H-[1,2,3]-triazoles via “click” reactions with TMS-N3

Although the two step method shown in Figure 5-5a,b yields the 1-H-[1,2,3]-triazole functionality, it is advantageous to eliminate the need for the deprotection reaction (Figure 5-5b). A second method for the synthesis of the 1H-[1,2,3]-triazole is the direct formation during the [3+2] cycloaddition. Historically, this method relies upon the thermal initiation of activated species.24,25 However, recent work has led to the development of methods for the synthesis of 1H-[1,2,3]-triazoles from less active components at low temperatures using a copper(I) catalyst.14,24,26

The exact method selected was the CuI catalyzed [3+2] cycloaddition of a terminal alkyne (polymers 6-10) and trimethylsilyl azide (TMS-N3). The mechanism for this reaction, shown in Figure 5-5, consists of four stages. The catalytic cycle is initiated by the activation of the terminal alkyne through the formation of the copper acetylide (Figure 5-6A). Hydrazoic acid is generated in situ by the reaction of TMS-N3 and methanol (Figure 5-6B). Any hydrazoic acid produced in B is rapidly consumed in a regiospecific [3+2] cycloaddition to give the copper-triazole intermediate (Figure 5-6C). The final step involves the protonolysis of the C5-Cu by another terminal alkyne, methanol, or HI to produce the copper acetylide and the 1H-[1,2,3]-triazole product.14
Polymers 17-21 were readily synthesized by this method. However, removal of the copper catalyst was at times problematic. The particulate copper could not be removed by filtration and was removed after complexation with EDTA to isolate the copper in the aqueous phase. The polymers were characterized by $^{31}$P NMR, $^1$H NMR, and IR spectroscopy. The $^{31}$P NMR spectra of the polymers were unchanged when compared to polymers 6-10 and the $^1$H NMR spectra were consistent with those obtained from the deprotection reactions (Table 5-3). The IR spectra of polymers 12-16 and 17-21 were almost identical except the peak seen at 3400 cm$^{-1}$ (polymers 12-16) had shifted to above 3450 cm$^{-1}$ (polymers 17-21). The glass transition temperatures of polymers 17-21 are higher than those of their alkyne counterparts (Table 5-3). This is probably due to the introduction of hydrogen-bonding between the triazole groups present in the polymers.

**Figure 5-6.** Mechanism for Cu(I) catalyzed click reactions between TMS-N$_3$ and polymers 6-10$^{14}$
Table 5-3. Structural and thermal characterization of 4-(1-H-[1,2,3]triazole)alkoxy substituted polyphosphazenes.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Original Side Groups*</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H HMR (ppm)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Pentyn:OTFE 1:1</td>
<td>-6.04</td>
<td>7.29 (1H), 4.40 (2H), 4.12 (2H) 2.29 (2H), 1.85 (2H)</td>
<td>16.48</td>
</tr>
<tr>
<td>18</td>
<td>Pentyn:OMEE 1:1</td>
<td>-7.38</td>
<td>7.24 (1H), 3.98 (2H), 3.85 (2H), 3.55 (4H), 3.43 (2H), 3.28 (3H), 2.23 (2H), 1.76 (2H)</td>
<td>46.53</td>
</tr>
<tr>
<td>19</td>
<td>Pentyn:OTFE 1.5:0.5</td>
<td>-6.31</td>
<td>7.29 (1.5H), 4.40 (1H), 4.13 (3H) 2.29 (3H), 1.85 (3H)</td>
<td>25.63</td>
</tr>
<tr>
<td>20</td>
<td>Pentyn:OMEE 1.5:0.5</td>
<td>-7.12</td>
<td>7.28 (1.5H), 4.05 (1H), 3.93 (3H), 3.61 (1H), 3.51 (1H), 3.33 (1.5H), 2.29 (3H), 1.83 (3H)</td>
<td>-127.86, 47.16</td>
</tr>
<tr>
<td>21</td>
<td>Hexyn:OMEE 1:1</td>
<td>-6.98</td>
<td>7.31 (1H) 4.03 (2H), 3.91 (2H), 3.61 (2H), 3.49 (2H), 3.34 (2H), 2.21 (2H), 1.60 (2H), 1.42 (2H)</td>
<td>-67.16</td>
</tr>
</tbody>
</table>

*Pentyn refers to 4-pentyn-1-oxy; hexyn refers to 5-hexyn-1-oxy; OTFE refers to 2,2,2-trifluoroethoxy; OMEE refers to methoxyethoxyethoxy.
5.3.5 Conductivity testing of Polymers

The conductivity of dried polymers 6-10 has been evaluated. These polymers were evaluated to act as a control in future studies of triazole containing phosphazenes and no proton conductivity was expected for these polymers. No proton conduction was detected in these polymers due to the lack of significantly acidic protons on the alkynoxy, 2,2,2-trifluoroethoxy, or 2-(2-methoxyethoxy)ethoxy side groups.

5.4 Conclusions

This chapter includes two novel methods for the synthesis of 4-(1-H-[1,2,3]-triazole)alkoxy polyphosphazenes by macromolecular “click” reactions. A small molecule model system, hexachlorocyclotriphosphazene, was studied first, and information about the solubility of alkyn-1-oxy phosphazenes was gathered. The first macromolecular intermediate in the synthesis of the target polymer was a polymer containing 4-pentyn-1-oxy or 5-hexyn-1-oxy cosubstituted with 2,2,2-trifluoroethoxy or 2-(2-methoxyethoxy)ethoxy side groups in different ratios. Two methods to obtain pendent 1-H-[1,2,3]-triazole polymers were then investigated. The first route was a more traditional copper (I) catalyzed “click” reaction where an activated azide is allowed to react with the terminal alkyne by a [3+2] cycloaddition. In this case, the triphenylmethyl activating group on the azide also serves as a protecting group which can be removed from the triazole, affording polymers 17-21. The second method of synthesis was also catalyzed by copper (I), but allowed the use trimethylsilyl azide with a terminal alkyne. Hydrazoic acid is generated in situ and reacts with the copper acetylide intermediate during the cycloaddition. As a result, polymers 17-21 were synthesized directly without the need for an additional deprotection step.
Additional work is needed to fully evaluate the polymers discussed here. The temperature and hydration dependence of proton conductivity needs to be studied. Problems could arise when the conductivity of these polymers is studied at different hydration levels. The polymers co-substituted with 2-(2-methoxyethoxy)ethoxy side groups are either soluble in water or are swelled so that all mechanical stability is lost. Even 2,2,2-trifluoroethoxy polymers were swelled significantly in water once the free triazole was present. Crosslinking by γ-irradiation could provide the needed stability, but perhaps at the expense of conductivity by restricting the polymer chain and side group motion. Apart from the future development of this method for the production of proton-conductive membranes, this study has laid the groundwork for a new method of functionalizing polyphosphazenes with species that have prospective utility in metal coordination chemistry as well as in other areas.
5.5 References


Chapter 6
Synthesis and Characterization of Novel Phosphazene Polymer Systems Based on Phosphazocyclophosphazenes

6.1 Introduction

Although many phosphazenes based on hexachlorocyclotriphosphazene and poly(dichlorophosphazene) are known, there are other phosphazene backbone structures which provide the possibility of enhanced materials properties. These include structures where phosphorus atoms have been replaced with carbon or sulfur atoms and phosphazenes with engineered branches of a well defined length (Figure 6-1).\textsuperscript{1} A phosphazophosphazene is a phosphazene derivative with two geminal phosphazenyl groups (-N=PCl\textsubscript{3}). These species have been studied extensively at the small molecule level\textsuperscript{2-6}, but limited information is available about the polymers beyond their synthesis and standard characterization techniques.\textsuperscript{1,7-9}

![Phosphazene analogs with backbone substitutions or engineered branches](image)

Figure 6-1. Phosphazene analogs with backbone substitutions or engineered branches

Previous work with polyphosphazenes has shown that polymers substituted with certain side groups are hydrophobic and borderline super-hydrophobic.\textsuperscript{10-13} The degree of
hydrophobicity of a material is due to a combination of processing (surface roughness) and surface chemistry. While there is no clear delineation, a material is considered to be hydrophobic or superhydrophobic when the water contact angle (WCA) is greater than 90° or 150°, respectively.

This work began as an investigation into the hydrophobicity of 2,2,2-trifluoroethoxy substituted poly(phosphazophosphazenes) and its comparison to the hydrophobicity found in processed poly[(bis-2,2,2-trifluoroethoxy)phosphazene]. During the synthesis of small molecule polymer precursors, interesting reactivity was noted. Cyclo-linear polymers based on phosphazenes and phosphazene-organic hybrids were designed to exploit the reactivity of the phosphazenyl units.

6.2 Experimental

6.2.1 Reagents and Equipment

All synthesis reactions were carried out using a dry argon atmosphere and standard Schlenk line techniques. Dichloromethane (CH$_2$Cl$_2$), diethyl ether, 1,4-dioxane, tetrahydrofuran (THF), and triethylamine were dried using solvent purification columns. Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Japan) in evacuated Pyrex tubes at 250°C. Chlorophosphoranamine (Cl$_3$P=N-TMS, Cl-monomer) and bromophosphoranamine (Br(OCH$_2$CF$_3$)$_2$P=N-TMS, Br-monomer) were synthesized and purified by literature procedures. Phosphorous (V) chloride (PCl$_3$) was purified by sublimation and was stored under inert atmosphere in a dry box. Chemicals and polymers not mentioned above were used as received without purification. $^{31}$P, $^{13}$C, and $^1$H NMR spectra were obtained with use
of a Bruker 360 WM instrument operated at 145 MHz, 90 MHz, and 360 MHz, respectively. Molecular weights were determined using an Agilent 1100 liquid chromatograph equipped with Phenomenex columns and a HP 1047A refractive index detector calibrated against polystyrene standards. Samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-n-butylammonium nitrate in THF. Glass transition temperatures were determined from a TA Instruments Q10 differential scanning calorimetry (DSC) apparatus with a heating rate of 10°C/min under an inert atmosphere. Electrospinning was accomplished with the setup described previously with the applied voltage potential, working distance at 20 cm, and flow rate of polymer solution at 1 mL/h held constant for all samples. The solution concentration was varied to produce fiber mats with different morphologies. SEM was conducted using a FEI–Philips XL-20. Water contact angle measurements were obtained using a Rame'Hart contact angle goniometer. Water was dispensed from a needle attached to a Gilmont microliter syringe filled with ultrapure water (Millipore system, 18 MΩ cm). Water droplets were placed on the surface and images of the drop silhouette were captured digitally and stored for later analysis.

6.2.2 Synthesis of gem-diaminotetrachlorocyclotriphosphazene (2)

This procedure is adapted from previous literature. Hexachlorocyclotriphosphazene (50g, 0.144 mol) was dissolved in ether (1 L) and cooled to 0°C. The flask was fitted with a dry ice/isopropanol condenser and ammonia (NH₃, g) was bubbled through the reaction mixture for 1 hr. The mixture was stirred for an additional hour and allowed to gradually warm to room temperature. The precipitate was removed by filtration and the solid was washed with ether. The solvent was evaporated to yield a white solid obtained (95%). $^{31}$P NMR (CDCl₃), ppm: δ 19.75 (2P, d), 10.80 (1P, t); MS (TOF-EI+) $m/z = 309$ ([M+H]$^+$, $C_4H_4Cl_4N_5P_3$).
6.2.3 Synthesis of gem-bis(trichlorophosphazo)tetrachlorocyclotriphosphazene (3)

This procedure is adapted from previous literature. Compound 2 (20g, 0.0646 mol) was suspended in hexane (100mL) together with phosphorous (V) chloride (28.32 g, 0.136 mol). The mixture was heated to 50°C and was stirred for 16 hrs. Any particulate material was removed by hot filtration, and the filtrate was cooled yielding a white solid (89 %). $^{31}$P NMR (CDCl$_3$), ppm: δ 19.05 (2P, d), -15.32 (2P, d), -18.85 (1P, m); MS (TOF-EI+) m/z = 578 ([M+H]$^+$, Cl$_{10}$N$_5$P$_3$).

6.2.4 Synthesis of Poly[(hexa-2,2,2-trifluoroethoxy phosphazo)(tetra-2,2,2-trifluoroethoxy)phosphazene] (5)

Compound 3 (10g, 0.0173 mol) was placed in a flask under vacuum. The flask was lowered into a 155°C oil bath and the polymerization was stirred for 2 hrs. The mixture was cooled and the solidified impure polymer was dissolved in 1,4-dioxane (400 mL). Sodium metal (4.76 g, 0.2072 mol) was suspended in 1,4-dioxane (200 mL), 2,2,2-trifluoroethanol (20.72 g, 0.2072 mol) was added, and the mixture was stirred for 24 hrs. The trifluoroethoxide solution was added to the polymer solution and the mixture was heated to 60°C for 48 hrs. The solvent was removed under vacuum and the concentrated reaction solution was purified by dialysis against acetone/water (9:1) for 5 days. $^{31}$P NMR (THF-d8), ppm: δ 0.31 (2P), -9.83 (3P); $^1$H NMR (THF-d8), ppm: δ 4.51-4.24 (br, m, -OCH$_2$CF$_3$); $M_w$ = 6.85 x10$^{4}$.

6.2.5 Synthesis of poly[bis-(2,2,2-trifluoroethoxy)phosphazene] (TFE Polymer)

Sodium metal (3.34 g, 0.1452 mol) was suspended in THF (200 mL) and 2,2,2-trifluoroethanol (15.10 g, 0.1509 mol) was added. After reacting for 16 hrs, the trifluoroethoxide was added to a solution of poly(dichlorophosphazene) (5.50 g, 0.04746 mol) dissolved in THF
(400 mL). The reaction mixture was refluxed for 24 hrs and the mixture was concentrated at reduced pressure. The polymer was purified by repeated precipitations from THF into water or hexane (3x each). \(^{31}\)P NMR (THF-d8), ppm: \(\delta -6.84\) (s, 1P); \(^1\)H NMR (THF-d8), ppm: 4.32 (2H, br, s, -OCH\(_2\)CF\(_3\)); GPC (HP1100/1049A RI): M\(_w\) = 8.53 \times 10^5\) g/mol.

6.2.6 Synthesis of phosphazophosphazene cyclo-linear polymers (6-8)

The synthesis of polymer 6 is given here as a representative example. Compound 3 (0.100 g, 0.173 mmol) was dissolved in CH\(_2\)Cl\(_2\) (50 mL) and phosphorous (V) chloride (0.0721 g, 0.346 mmol) was added. After 8 hrs, chlorophosphoranamine (1.94 g, 8.63 mmol) was added and the reaction mixture was stirred for 48 hrs at 25°C. Compound 2 (0.0534 g, 0.173 mmol) was dissolved in THF (50 mL) and triethylamine (0.0525 g, 0.519 mmol) was added, followed by bromophosphoranamine (0.151 g, 0.381 mmol). The reaction mixture was warmed gently for 48 hrs and then the solvent was replaced with CH\(_2\)Cl\(_2\) (25 mL). The reactions containing 2a and 3a were combined and heated gently for 48 hrs. The solvent was removed and replaced with THF (50 mL). Sodium metal (0.239 g, 10.40 mmol) was suspended in THF (25 mL) and 2,2,2-trifluoroethanol (1.13 g, 13.10 mmol) was added. The solution of trifluoroethoxide in THF was then added to the solution containing coupled 2a and 3a in THF and the mixture was refluxed for 24 hrs. The solvent was removed and the resulting material was purified by dialysis against acetone/water (8:2) for 4 days. Structural characterization data are available in Table 6-2.

6.2.7 Synthesis of a cyclo-linear phosphazophosphazene-organic hybrid polymer (9)

Compound 3 (1.00, 1.726 mmol) was dissolved in THF (100 mL) and triethylamine (0.524 g, 5.18 mmol) was added. 1,4-Diaminobutane (0.1522 g, 1.726 mmol) was added
dropwise over 1 hr and the reaction mixture was stirred for an additional 24 hrs. Sodium metal (0.357 g, 15.50 mmol) was suspended in THF (50 mL), 2,2,2-trifluoroethanol (1.64 g, 16.40 mmol) was added, and the mixture was stirred for 24 hrs. The solution of sodium trifluoroethoxide was added to the polymer solution and the mixture was heated for 24 hrs. The solvent was removed and the product was purified by dialysis against methanol for 4 days. $^{31}P$ NMR (THF-D8), ppm: $\delta$ 16.56 (br, m), 9.29 (br, m), -0.91 (br, m); $^1H$ NMR (THF-d8), ppm: 4.22 (8H, br), 2.81 (4H, br), 1.60 (4H, br); GPC (HP1100/1049A RI): $M_w = 4.69 \times 10^6 \text{ g/mol}$, $M_w = 4.20 \times 10^5 \text{ g/mol}$, $M_w = 3.25 \times 10^5 \text{ g/mol}$.

6.3 Results and Discussion

6.3.1 Synthesis of gem-bis(trichlorophosphazo)tetrachlorocyclotriphosphazene (3)

The phosphazophosphazene monomer (3) was synthesized in relatively high yield by the two step reaction shown in Figure 6-2. The synthesis of the aminocyclotriphosphazene (2) can be achieved with the use of either ammonia gas or a standard solution of ammonia in hexane. The geminal substitution of the substituent groups is unusual in phosphazene chemistry. Several factors influence the substitution pattern of an amine in a given reaction. Although most are directly related to the nature of the side group; such as the type of amine (primary or secondary), steric bulk, or nucleophilicity; other external factors; such as solvent and reaction temperature; play a part in determining the resultant substitution pattern. Evidence of the single diaminocyclotriphosphazene product is provided by the resolved doublet and triplet which is seen in the $^{31}P$ NMR spectrum, suggesting an AB$_2$ spin system. The substitution pattern of the diaminophosphazene cannot be readily proved until the phosphazophosphazene derivative is formed.
The aminophosphazene was readily converted to the phosphazocyclotriphosphazene by the addition of phosphorous (V) chloride. The purified product (3) was obtained by crystallization as the reaction mixture cooled. It is at this stage when the geminal nature of 2 and 3 is proved. If 3 were non-geminal, the $^{31}$P NMR shifts for the point of attachment to the phosphazene ring and the phosphazo group should be similar to the analogous phosphorous atom in monophosphazophosphazene. However, large differences in the observed chemical shifts proved that this is not the case.$^{25}$ A mechanism similar to the substitution of t-butylamine was proposed by Feistel and Moeller and is shown in Figure 6-3.$^{25,26,29}$

**Figure 6-2.** Synthesis of gem-bis(trichlorophosphazo)tetrachlorocyclotriphosphazene (3).

**Figure 6-3.** Mechanism for the geminal substitution of aminocyclotriphosphazene.
6.3.2 Polymerization and substitution of poly(diphosphazophosphazenes)

The polymerization of monomer 3 occurs at a significantly reduced temperature compared to the temperature required to initiate the thermal polymerization of 1. This is due to the facile dissociation of a chloride ion from the phosphazo groups occurring more readily than dissociation from the phosphazene ring. Thus, the polymerization to yield 4 can be carried out at reduced pressure using standard laboratory practice. Unreacted monomer can be recovered from the polymerization reaction by washing the material with hexanes or heptanes. However, this may expose the polymer to water and result in hydrolytic degradation. It can be avoided by substituting the crude unseparated polymer/monomer mixture. The substituted monomer is then subsequently removed during the polymer purification.

![Chemical structure](image)

**Figure 6-4.** Synthesis of poly[(hexa-2,2,2-trifluoroethoxy phosphazo)(tetra-2,2,2-trifluoroethoxy)phosphazene] (5).

During the macromolecular substitution of polymer 4, preferential substitution of the phosphazo branches was noted (Figure 6-5). The $^{31}$P NMR signal at -26 ppm, attributed to the branched –PCl$_3$ groups, shifted first to a broad signal at 0.31 ppm followed by a pattern consistent with substitution of the remaining chlorine atoms.
6.3.3 Hydrophobicity of highly fluorinated polyphosphazophosphazene

Previous work has shown that poly[bis(2,2,2-trifluoroethoxy)phosphazene], a highly fluorinated polymer, forms hydrophobic free standing films.\textsuperscript{11,12} Hydrophobicity in highly fluorinated polymers is not uncommon. This is the result of the fluorine-bearing groups concentrating at the polymer surface and minimizing the surface free energy.\textsuperscript{31,32} When poly(trifluoroethoxyphosphazene) is electrospun to form nanofiber mats, the polymer shows superhydrophobic properties. When compared to trifluoroethoxy substituted polymer, poly[(hexa-2,2,2-trifluoroethoxy phosphazo)(tetra-2,2,2-trifluoroethoxy)phosphazene] (5) has a significantly higher localized concentration of fluorine atoms and may exhibit even more superhydrophobic behavior. Fiber mats of 5 were fabricated by electrospinning from a THF solution. Decreases in solution viscosity are mirrored by declining fiber diameter, until only a beaded morphology is formed.\textsuperscript{33} The result of solution concentration on fiber morphology for electrospun samples of 5 is shown in Figure 6-6.
One unusual characteristic of these nanofiber mats is the unusually concentrated solutions of 5 which were needed to obtain stable fibers. By comparison solution concentrations of 5% (wt/v) or less were needed to obtain nanofiber mats of poly(trifluoroethoxyphosphazene).\textsuperscript{11,12} The most likely explanation for the difference in solution concentrations necessary to obtain similar morphologies is the significant difference in $M_w$, two orders of magnitude, between poly(trifluoroethoxyphosphazene) and 5. When electrospinning, a polymer with a lower $M_w$ would require higher solution loading to obtain the solution viscosity required for a specific fiber morphology when all other parameters are held constant.\textsuperscript{13} The static water contact angle (WCA) was obtained for each of the electrospun morphologies and for a spun-cast film of 5 (Figure 6-7). The WCA’s measured for fiber mats of 5 were in the range of 120°-155° and found to be inversely proportional to fiber diameter, similar to the behavior of trifluoroethoxy substituted polyphosphazenes.\textsuperscript{11}
6.3.4 Phosphazocyclotriphosphazene based cyclo-linear polymers

6.3.4.1 Phosphazene cyclo-linear polymers

In an attempt to exploit the reactivity observed during the synthesis of polymer 5, cyclo-linear polymers were designed with 2 and/or 3 as the main components in each monomer. These polymers are unusual because the entire polymer system is composed of phosphazenes rather than...
an organic-phosphazene system. The main distinguishing feature between the three cyclo-linear polymers, Figure 6-8, is the length of the linear portion used to link the parent monomers.

The first method, Figure 6-8a, used 3 as an initiator for the living cationic polymerization of chlorophosphoranamine (Cl-monomer).\textsuperscript{19-22} Compound 3 was treated with phosphorous (V) chloride to form the -N=PCl\textsuperscript{2+}/PCl\textsubscript{6} active site on the phosphazo side chains. The Cl-monomer was added to form a 26-repeat unit oligomer at each phosphazo branch. Integration of the new signal at -17.53 ppm combined with the disappearance of the signal at -15.32 ppm in the \textsuperscript{31}P NMR spectrum was used to verify formation of 3b. The growth of a 26-repeat unit chain was used to minimize any steric interactions which may prevent formation of the desired polymer.

The second component, which was used to form the polymer, was 2 which had been treated with bromophosphoranamine (Br-monomer).\textsuperscript{19-22} Formation of 2b was verified by integration of the shift at -33.69 ppm in the \textsuperscript{31}P NMR spectrum which corresponds to the Br-monomer. The coupling of 3a and 2b to yield polymer 6 (Figure 6-8a) is an AB step-growth polymerization.

Step growth polymerizations are often plagued by low conversions and lengthy reaction times. Molecular weight analysis by GPC revealed that the major product was an oligomer calculated to have 4.5 repeat units per chain (Table 6-1). Despite the low conversion, the 27 P=N units between each of the phosphazene rings in the repeat unit give the isolated polymer significant molecular weight. Increasing the length of the coupling reaction or controlling the quantities of each monomer could give higher conversion.
Figure 6-8. Cyclo-linear phosphazene polymers 6-8: (a) additional P=N spacers attached to phosphazophosphazene 3 by the living cationic method. (b) bromophosphoranamine functionalized aminocyclotriphosphazene. (c) monophosphazomonoaminecyclotriphosphazene coupling.

The second method (Figure 6-8b) did not use any additional P=N spacers between 3 and the Br-monomer functionalized aminocyclotriphosphazene (2b). NMR spectroscopy was again used to verify the formation of 2b, and shifts similar to those in method 1 were seen.

Phosphazophosphazene 3 was treated with PCl₅ to form the activated phosphazo groups and reacted with 2b in a step-growth polymerization to obtain polymer 7. The low number of repeat units per polymer chain (calculated 2.5) could be the result of several factors, including the short coupling time and the stoicheometric ratios were not exact.
Table 6-1. Structural characterization of cyclo-linear phosphazene polymers 6-9.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>$^{31}$P NMR (ppm)</th>
<th>$^1$H NMR (ppm)</th>
<th>$M_w$ (g/mol)</th>
<th>PDI</th>
<th>% Area</th>
<th># of Repeat Units</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>21.61, 5.04 – 5.93 (br, m), -8.68 (m)</td>
<td>4.34 (br)</td>
<td>6.33 x10$^4$</td>
<td>1.40</td>
<td>62.36</td>
<td>4.5</td>
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<tr>
<td>7</td>
<td>18.73, -4.26 (m), -9.05 (m)</td>
<td>4.35 (br)</td>
<td>5.47 x10$^3$</td>
<td>1.18</td>
<td>61.72</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>19.62, -3.50 (br), -9.90 (br)</td>
<td>4.37 (br)</td>
<td>9.19 x10$^4$</td>
<td>1.31</td>
<td>6.51</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.71 x10$^3$</td>
<td>1.03</td>
<td>36.33</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.35 x10$^3$</td>
<td>1.00</td>
<td>31.29</td>
<td>3</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>1.61 x10$^3$</td>
<td>1.01</td>
<td>25.85</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>16.56 (br, m), 9.29 (br, m), 0.91 (br, m)</td>
<td>4.22 (8H, br), 2.81 (4H, br), 1.60 (4H, br)</td>
<td>4.69 x10$^6$</td>
<td>1.15</td>
<td>38.50</td>
<td>4425</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4.20 x10$^5$</td>
<td>1.10</td>
<td>9.44</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.25 x10$^3$</td>
<td>1.16</td>
<td>52.04</td>
<td>3</td>
</tr>
</tbody>
</table>

(a) Signals corresponding to n=1, n=0 (3b), or n=0 (2b) are not listed. (b) The normalized integration of peaks in the GPC chromatogram. (c) The number of repeating units is calculated from $M_w$ by GPC and the structures shown in Figure 6-6 or Figure 6-7 for polymers 6-9.

It is unlikely that steric hinderence prevented 2b-3 coupling because the reaction of 2 and 1 equivalent of PCl$_3$ formed polymer 8 in the third method (Figure 6-8c). The relatively clean $^{31}$P NMR spectrum of 8 would indicate that the polymer is structured as shown rather than having a repeating unit comprised of a 2-3 dimer. Size exclusion chromatography revealed presence of a polymer calculated to have 118 repeating units, but the major products were still low molecular weight oligomers (Table 6-1).

6.3.4.2 Phosphazocyclotriphosphazene-organic hybrid cyclo-linear polymer

The previously reported$^{7,8,30}$ and observed differences in the reactivity of terminal -N=PCl$_3$ groups and internal -N=PCl$_2$ groups allow the facile synthesis of phosphazene-organic hybrid cyclo-linear polymers from phosphazophosphazenes by the addition of a bifunctional organic linker. When 3 is treated with 1,4-diaminobutane in the presence of a proton acceptor
(Figure 6-9a), a high polymer is formed. Drop-wise addition of the diamine was used to minimize the formation of side products (Figure 6-9b). The low ratio of diamine to 3 should favor the formation of a PN-Org-PN structure rather than either of the products in Figure 6-9b. Based on the broad signals in the $^{31}$P NMR spectrum of 9, either no side product was formed as a major product or if any was formed it was removed during polymer purification. Molecular weight analysis showed that the product was tri-modal with two polymers and an oligomer (Table 6-1). If the formation of 9 is a step-growth process, by the time chain lengths reached those in Table 6-1, very little of the trimeric species should remain. One possible explanation for the quantity of material detected as trimers is the termination of growing chains as cyclic species. Another possible explanation is the termination of polymerization by incorporation of 9a into the growing chain. The termination by 9a may also explain the medium $M_w$ product.
6.4 Conclusions

Poly[[hexa-2,2,2-trifluoroethoxy phosphazo](tetra-2,2,2-trifluoroethoxy)phosphazene] (5) was synthesized by polymerization of gem-(trichlorophosphazo)tetrachlorocyclophosphazene (3), its cyclic monomer, and subsequent macromolecular substitution by 2,2,2-trifluoroethoxide. The polymer was processed by spin casting and electrospinning to give different fiber morphologies. Static WCA measurements on these films revealed that 5 is hydrophobic when spun cast (101°) and borders on super hydrophobic when electrospun (120°-155°). The
hydrophobicity of these polymer mats is a consequence of a combination of the highly fluorinated chemical environment at the films surface and the nanostructured morphologies created by electrospinning. However, when these results are compared to the hydrophobicity of poly[bis(2,2,2-trifluoroethoxy)phosphazene], there appears to be no enhancement of the hydrophobic character resulting from the higher fluorine concentration in 5. Future investigations may wish to further investigate the correlation between fluorine concentration; both in the bulk and at the surface of polyphosphazenes, and material hydrophobicity.

During the synthesis of 5, preferential macromolecular substitution of he phosphazo chlorine atoms was detected. Cyclo-linear polymers, both phosphazene-organic hybrids and purely phosphazene, were designed to exploit the unique reactivity of the phosphazo groups. The purely phosphazene cyclo-linear polymers used chemistry developed for the living cationic polymerization method to connect 2 and 3. The step-growth mechanism coupled with short reaction times and imperfect stoicheometry resulted mainly in pentamers or shorter oligomers. A second method involved the coupling of 1,4-diaminobutane with 3 to give the hybrid phosphazene-organic cyclo-linear polymer (9). This method yielded higher molecular weight products, but side reactions (9a and 9b) or cyclization of the trimer were also detected. These results show that with optimization, it may be possible to obtain high molecular weight cyclo-linear phosphazene polymers, which have proved to be elusive in earlier work.
6.5 References


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Mark David Hindenlang was born October 6, 1983 in Denville, New Jersey and was raised in Randolph, New Jersey by his parents Marilyn and David Hindenlang. He attended Gettysburg College in Gettysburg, Pennsylvania and obtained a Bachelors of Science degree in Chemistry with a minor in mathematics under the direction of Dr. Donald Jameson and Dr. William Parker in May 2005. Mark began his graduate studies at The Pennsylvania State University under the auspices of Evan Pugh Professor Harry R. Allcock in August 2005.