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Synthesis And Characterization Of Silver-Coated Polyester Dendrimers With Potential Antimicorbial Properties

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SYNTHESIS AND CHARACTERIZATION OF SILVER-COATED POLYESTER DENDRIMERS WITH POTENTIAL ANTIMICORBIAL PROPERTIES

A Thesis

by

CHE'DARRIA LACEY

Submitted to the Office of Graduate Studies of

Prairie View A&M University

In partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE

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Major Subject: Chemistry

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Approved as to style and content by:

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ABSTRACT

Synthesis and Characterization of Silver-Coated Polyester Dendrimers with Potential Antimicrobial Properties

(December 2023)

Che'Darria Lacey, B.S., Prairie View A&M University

Chair of Advisory Committee: Dr. Ananda Amarasekara

As bacterial cell lines continue to develop resistance to conventional antibiotic medications, the threat of untreatable bacterial infections continues to grow. The limited manufacture of new pharmaceuticals further exacerbates this severe health risk. This risk has facilitated numerous investigations to counter microbial species' antibiotic resistance. The use of silver, a well-known natural remedy, has grown significant attraction through its use in the nanoparticle form or even as silver ions.

This thesis project involves the synthesis of branched polymers that were suitably functionalized to enable the complexation of silver ions to develop antimicrobial materials. Polyester dendrimers were synthesized utilizing divergent dendronization. The dendrimer surface was then functionalized via photo-initiated thiol-yne click chemistry to incorporate n-acetyl cysteine, which has reported silver-chelating activity. Dendrimers are constructed in an iterative or stepwise fashion and include many branching groups – known as generations or layers – emanating from a multi-functional core. This dendrimer core was comprised of 1,1,1-tris(hydroxymethyl) ethane. The branching groups were derived from the monomer, 2,2-bis(hydroxymethyl) propionic acid, otherwise known as Bis-MPA.

These core and monomer group components are biocompatible and used extensively in polymer chemistry and material science communities for biomedical applications. Because the dendrimer increases the number of surface functional groups with each dendritic growth layer, the concentration of silver-chelating ligands also increases. Thus, this study compared the overall silver chelating affinity of polyester dendrimers due to the varying number of chelating moieties on the dendrimer surface.

Silver nitrate was added to aqueous solutions of the dendrimer chelator to induce silver complexation. After 2 hours, the complex was precipitated from acetone, and the precipitate was analyzed by SEM microscopy to observe the silver loading affinity of the polymeric system.

Index Terms----Antibiotics, antimicrobial resistance (AMR), branched polymers, chelator, n-acetyl cysteine, nanoparticles (NPs), pentanoic acid, pentynoic acid, dendrimers, polyester dendrimers, silver, silver chelation, silver nitrate, thiol-Michael addition, thiol-yne click chemistry.

DEDICATION

In loving memory of my late grandparents, Arthur McKnight, Walter and Christine Lacey, and aunt, Nedra Lacey.

I would like to dedicate this thesis to my parents, Darrell and Michelle Lacey and brother, Darrius Lacey, and the rest of my supporting family.

ACKNOWLEDGEMENTS

Special thanks to Marco Giles, Ph. D, my committee members, the faculty and staff of the Prairie View A&M Chemistry Department and the office of Graduate Studies.

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CHAPTER I

INTRODUCTION

Bacteria are single-celled microorganisms that can exist independently or dependently on other organisms. In terms of medicine, they are a primary cause of illness. There are both good and bad types of bacteria. Examples of good bacteria, which are essential to the body, include Bifidobacterium and lactic acid bacteria. Healthy bacteria, such as these, promote vitamin synthesis, digestion and absorption assistance, infection prevention, and immunity stimulation. Harmful bacteria include staphylococcus, clostridium perfringens, and E.coli (toxic strain), which are recognized as disease-causing bacteria. Staph infections, caused by the staphylococcus strain, can spread in hospitals, other healthcare facilities, and the community where people live,

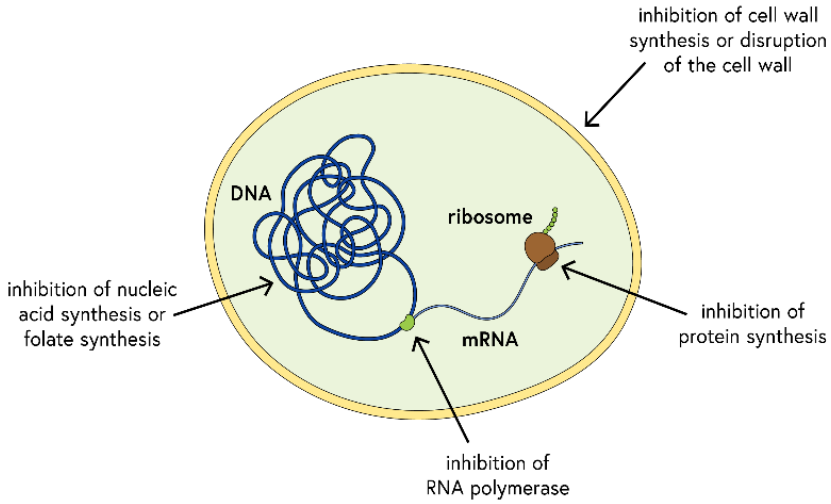


Fig. 1. Illustration of bacteria cell.

work, and attend school[1,2].

This thesis follows the style of the *Institute of Electrical and Electronics Engineers.*

Any substance that represses or kills the development and replication of bacteria or slows it down can be called an antimicrobial. Antibiotics are antimicrobials specifically targeting bacterial diseases inside or on the body[3,4]. Different antimicrobial substances work by interfering with the formation of cell walls, plasma membrane integrity, nucleic acids, ribosome function, and folate.

Antibiotics are the conventional treatment for the remediation of bacteria. However, a growing problem is that they need to be more effective due to the development of bacterial resistance. Antibiotic resistance results from genetic mutations of bacterial cells after contact with an antibiotic[5]. These adaptations then enable the bacteria to survive or 'resist' the antibiotic so that the antibiotic no longer works to kill the bacteria[5,6]. As microbes develop ways to survive and resist drugs, it becomes more difficult for researchers to combat. According to the CDC, this issue is a significant problem for public health agencies. *Antimicrobial resistance* is a global public health risk attributed to millions of infections and deaths annually in developing and developed countries[3–5,7–12]. Each year, more than 2.8 million illnesses in the US are due to resistance to antibiotics. If antibiotics become ineffective, there will be no way to treat infections or prevent these public health issues.

There has been a decline in drug development for years[3–5]. Unfortunately, the lack of updated medications contributes to the limited availability of adequate care for the public. Nonconventional methods are unlikely to substitute or replace antibiotic use fully but could provide new treatment options through combined use with antibiotics[13].

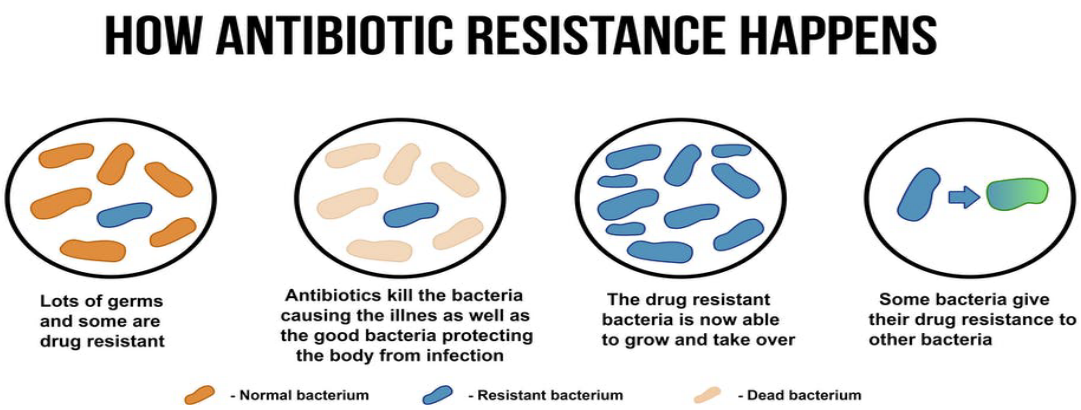


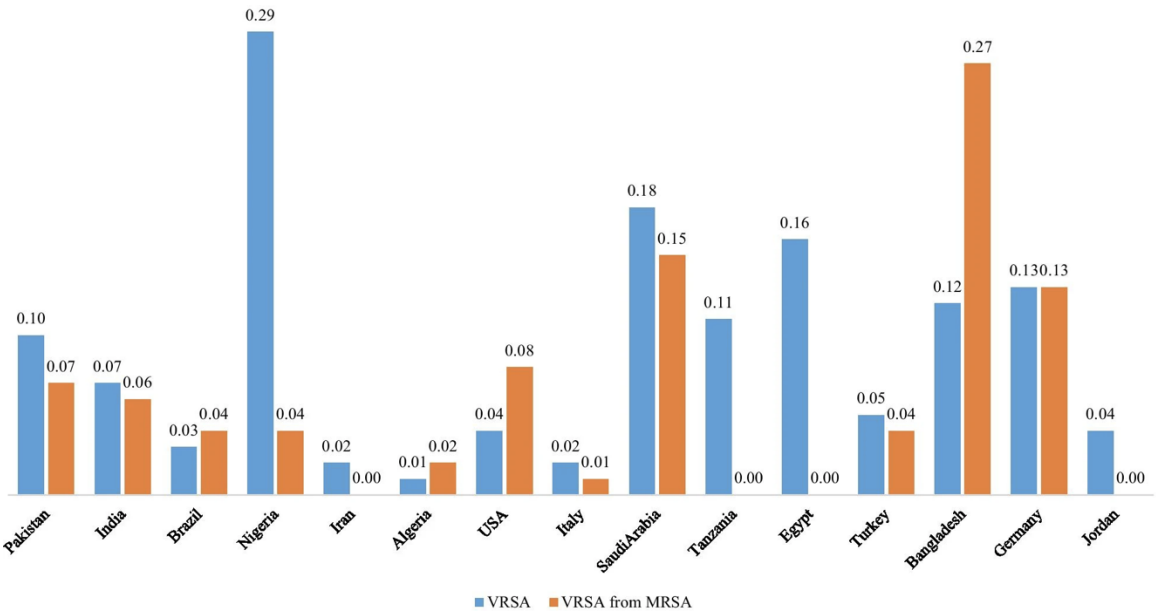
Fig. 2. Illustration describing the evolution of antibiotic-resistant bacteria.

Antimicrobial resistance (AMR) is the ability of a microorganism like bacteria, viruses, and some parasites, to limit or prevent the effectiveness of antimicrobials, such as antibiotics, antivirals, and antimalarials, from working. Human overuse and misuse of antibiotics have also resulted in the rise of pathogenic and non-pathogenic bacteria resistant to the drugs on the market[14, 15]. Methicillin-resistant Staphylococcus aureus (MRSA) is a cause of staph infection that is difficult to treat because of resistance to the antibiotic Methicillin. Vancomycin-resistant Staphylococcus aureus (VRSA) is a strain of Staphylococcus aureus resistant to the antibiotic called vancomycin [16]. *Staphylococcus aureus* is a prominent human nosocomial pathogen that leads to infections of the skin and soft tissues as well as fatal systemic illnesses. Because of the diminished effectiveness of antibiotics against bacterial strains, the remediation of infections has become increasingly difficult. Treatment can be very aggressive when patients contract an infection from a highly resistant bacterial strain. Patients experience treatment that can be highly painful, often resulting in loss of tissue, limbs, or even death. Alternatively, researchers have sought to use compounds and additives that facilitate attack by targeting the bacteria cell

differently than antibiotics. This includes using nanotechnology to evade existing mechanisms and developing quick, highly accurate, inexpensive techniques for drug-resistant organism genome sequencing to enable targeted treatment. Due to the advent and spread of MRSA and VRSA, the public health crisis continues to be difficult on a global scale. Table 1 shows the prevalence of VRSA in different countries, such as S. aureus and VRSA in MRSA. 11,074 S. aureus isolates from Asia had a prevalence of VRSA of 5% (95% CI 3-8), compared to 1% (95% CI 0-5) in Europe, 456 S. aureus isolates from America, 4% (95% CI 2-7), 171 isolates from South America, and 16 (95% CI 3-35) in Africa. Oceania has not reported any cases of VRSA. The most common VRSA prevalence was 29% (95% CI 24-35) in Nigeria and 18% (95% CI 12-26) in Saudi Arabia.[17]

TABLE 1

Illustration of the prevalence of VRSA and VRSA in MRSA in various continents



Another well-known solution to the drug-resistant bacteria problem is colloidal silver. Historically, it is a well-documented antimicrobial that the metal has been shown to kill bacteria, fungi, and certain viruses. The antibacterial effect of colloidal silver is attributed to the method of interaction between the positively charged silver ions and the bacteria's cell wall, and bacteria cells have shown no resistance to the metal (see Fig. 3). The advantageous impact of the silver ion has contributed to several approaches to administering the metal safely to control bacteria growth and infections.

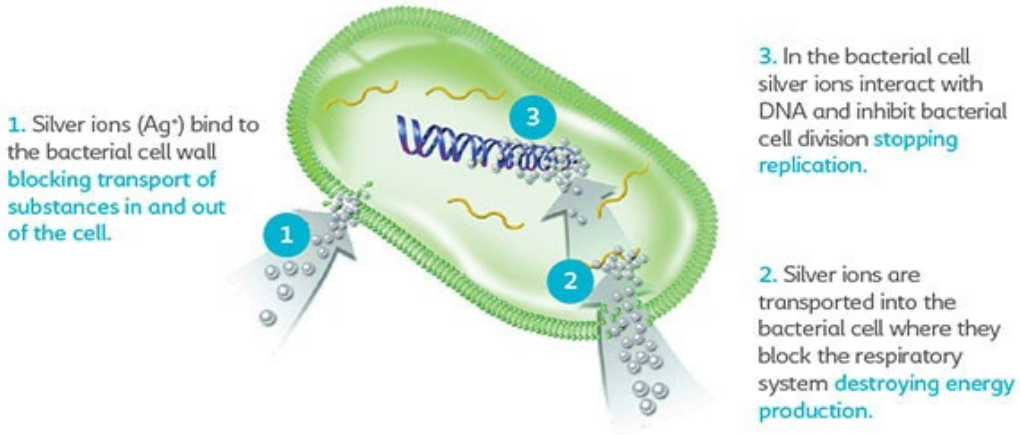


Fig. 3. Illustration describing the antimicrobial behavior of silver ions.

The term "nanotechnology" describes the manipulation of matter on a nanoscale. Nanomaterials include polymeric materials assembled to adopt a spherical shape and possess sizes on the nanometer scale. When used against susceptible and multi-drug resistant bacterial strains, nanoparticles (NPs) are equally efficient as nano bactericides and nanocarriers. They can be tuned or designed to have antimicrobial and antibacterial properties or as drug delivery systems for antimicrobial drugs. These materials' small size and high surface area-to-volume ratio make them very valuable for antibacterial activity[14]. Because of their controlled size, NPs can easily interact with bacteria and pass through the cell membranes of their hosts and the bacterial envelopes. The study of and

utilization of nanoparticles as drug delivery agents to maximize absorption and the proper selectivity and biodistribution is known as NP-pharmacokinetics[18]. Nanoparticle design is broadly defined, including various polymers and metallic and lipid-based compositions. The incorporation of ligands, pH-sensitive linkages, and even size are parameters that invoke the selectivity of these delivery systems.

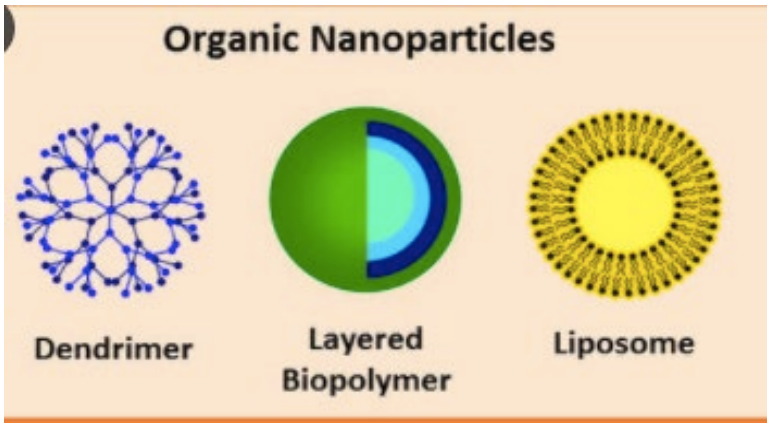


Fig. 4. Illustration describing different organic nanoparticles.

There have been several approaches with using silver as an antimicrobial, such as using nanocomposites and silver complexes based on polyamidoamine dendrimers. Polymer-metal nanocomposite materials enable a combined approach to nanoparticle pharmacokinetics. Investigators synthesize polymer NPs, which can bind to metal ions like copper, gold, iron, or silver to aid in effective antibacterial activity. The polymer architecture can significantly impact the dynamics of the NP delivery agent. Factors such as size, solubility, morphology, and surface valency are important to ensure sufficient

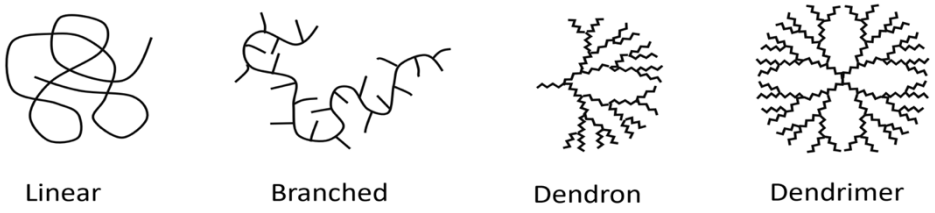


Fig. 5 Illustration of different types of polymers.

uptake of metal ion complexation. Thus, numerous polymer types have been investigated, including linear homopolymers, linear block copolymers, and branched polymers like star polymers, hyperbranched polymers, and dendrimers.

Linear polymers represent a class of macromolecules derived from the repetitive addition of monomer repeating groups, all constructed on a single strand as illustrated in Fig. 5. The reactive end-group functionalities that ensure the growth of linear polymers are limited to including only the head and tail sections of the chain. Depending on the nature of the repeating unit, branching groups can be incorporated from the interior segments via post-polymerization functionalization unless the repeating unit bears some benign branch prior to polymer chain growth.

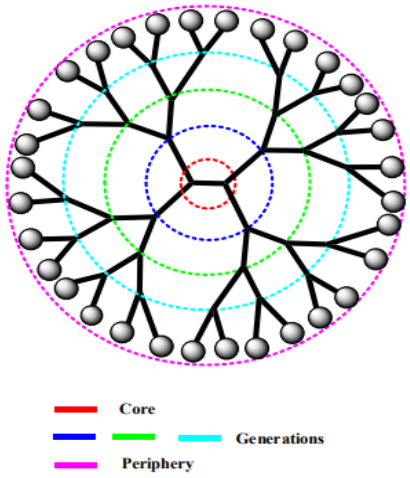


Fig. 6. Illustration of parts of dendrimers.

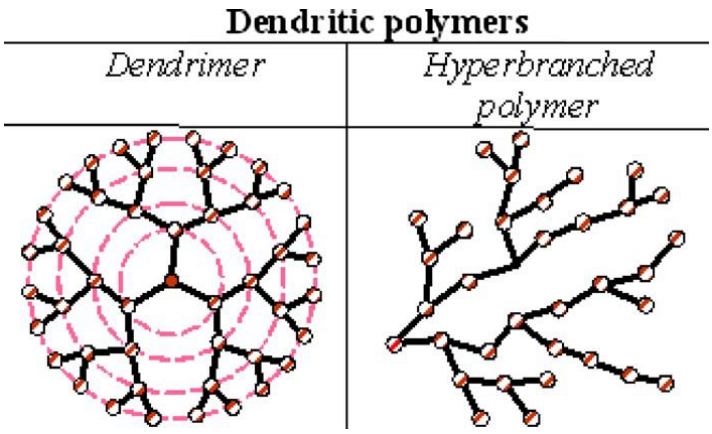


Fig. 7. Illustration of branched polymers, including dendrimers and hyperbranched polymers.

Branched polymers are synthesized in a contrasting fashion to linear polymers. Whereas linear polymers are produced by complementary reactions between monomers or initiators with one to two reactive end-groups, branched polymers involve monomers serving as or reacting with other monomers or initiators with more than two terminal

reactive groups simultaneously or sequentially. Hyperbranched polymers (HBPs) are highly branched 3D macromolecules prepared through a single-step process (Figure 6)[19–35]. Though this particular class of branched polymer displays high degrees of branching, they lack uniformity. Overall, the HBP architecture varies in the degree of branching. They are beneficial for large-scale polymer synthesis, but control is limited. One benefit of hyperbranched polymers is that they are affordable synthetic routes. Dendrimers are highly branched and monodispersed macromolecules with structural uniformity as shown in Figs. 6 and 7[19–28,31,33,34,36–38]. They are synthesized in a multi-step fashion and comprise three distinct regions: a) a multifunctional core (or nucleus), which emanates outwards towards b) a densely branched corona, which is eventually terminated by c) a multifunctional periphery. Iterative coupling steps yield successive polymeric layers, known as generations. The focal points of each dendritic wedge create "void spaces" that enable the encapsulation of small guests within the dendrimer architecture. Upon sufficient activation, the surface of the dendrimer bears peripheral active sites, which allow further tunability or modification because of the attachment of additional surface functionalities. They attain globular, spherical architecture at high generational growth, and their surface functionality can control their physical, chemical, and mechanical properties.

There are two synthetic approaches for dendrimers: 1) divergent synthesis, which involves growth from the core outwards towards the dendrimer surface, and 2) convergent synthesis, which involves growth from the surface inwards towards the core. Specifically, the monomer continuously reacts with the dendrimer core/surface in divergent synthesis to build outwards. Convergent synthesis requires the monomer to generate a "dendritic wedge," which will bear an unreactive or protected focal point. Eventually, the protecting group is removed from the fully synthesized dendritic wedge to allow complete conjugation with the multifunctional core of the eventual dendrimer.

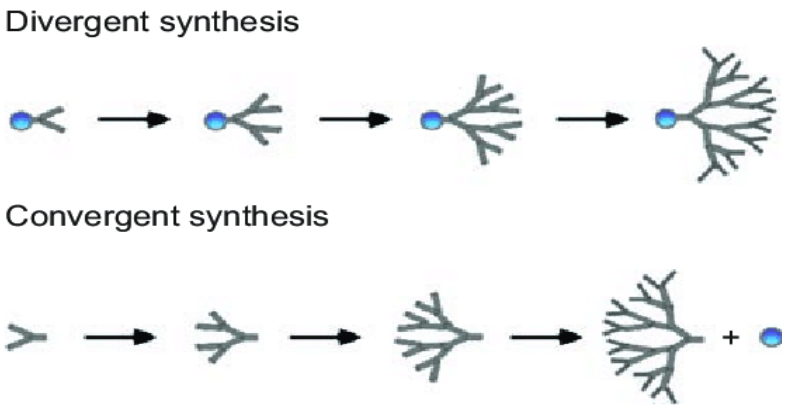


Fig. 8. Illustration of divergent and convergent synthesis.

Due to their pristine structural control and chemical versatility, dendrimers are considered perfect "nano-objects" and are valid for drug delivery and antimicrobial applications. Dendrimers have drawn significant interest for nanomedicine because their multi-branched nanoarchitecture equips them with multiple active sites for potentially loading

antibiotics and interacting with bacteria. Researchers declared that functionalized dendrimers demonstrated higher antibacterial activity than plain antibiotics.

Several dendrimers have been used as drug delivery systems for natural products such polylysine (PLL)[39], polyamidoamine (PAMAM)[40–43], polypropylene (PPI)[40,44], and

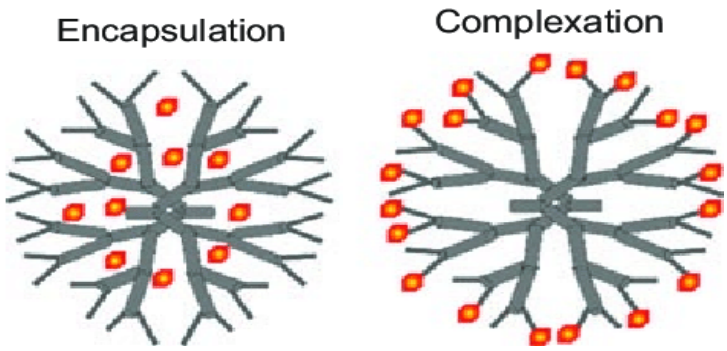


Fig. 9. Illustration of encapsulation and complexation.

polyglycerol[45,46]. These dendrimers can be deployed for targeting drugs through various techniques, including [32,45–48]subcutaneous, intravenous, oral, intraperitoneal injection and ocular delivery. The therapeutic value of using natural materials as medicine to treat various diseases is well-known. However, limited solubility and low bioavailability of most natural compounds present serious problems. Several pharmacological nanocarriers have been created to address these problems. Dendrimers are a great example because of their superior features, including a regulated molecular structure, a limited polydispersity index, and various functional groups. Dendrimers have distinguished themselves among these techniques as vectors for natural products. Dendrimers have been vastly investigated as drug carriers for various pharmaceuticals, including antitubercular, antiviral, antimalarial, antiprotozoal, and anticancer medications.

Although there are numerous types of dendrimers crafted with several core molecules, branching groups, and surface functionalities, the poly(propyleneimine) and

poly(amidoamine) (PAMAM) dendrimers have been the most extensively studied dendrimers concerning drug delivery applications. Although these dendrimers can be used as drug carriers, there are serious health hazards associated with PAMAM dendrimers in biomedical applications. The dendrimers can be toxic to the body because of the amines in the structure. They are great in vitro cell studies but toxic when used in living systems in vivo. Biocompatible dendrimers have been created and manufactured to lessen this toxicity, and surface engineering has been employed to alter the dendrimers' peripheral sites positively.

CHAPTER II

LITERATURE REVIEW

2.1 Silver Complexes Formed with Thioether-Containing Amino Acids

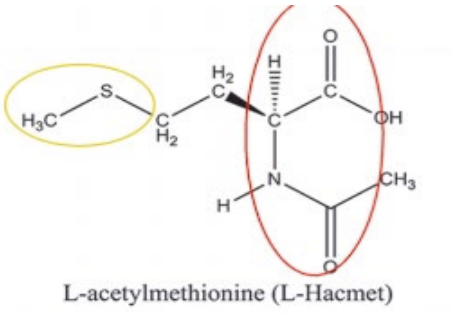


Fig. 10. N-acetylmethionine (L-Hacmet), highlighting the thioether functionality responsible for metal chelation.

-Acetyl Methionine has been identified as highly effective for forming water-soluble, light-stable, antimicrobial complexes. Soft ligands, such as phosphines, boost the silver(I) complexes' light stability, but they reduce their antimicrobial activity when added to a solution containing Ag-O binding complexes. Characterizing silver(I) thiolate complexes is challenging, especially for those with aliphatic thiolate ligands because of their oligomeric nature. Although they demonstrate a smaller range of antimicrobial activity against Gram-negative bacteria, they are more light-stable. Kasuga et al. describe the synthesis of silver(I) complexes derived from N-acetylmethionine, methionine, N-acetylcysteine, and S-methyl cysteine[49]. N-acetylmethionine was considered to be a promising candidate for creating a water-soluble, light-stable, and potent antibacterial silver(I) complex because it possesses both the O-C-N-C-COO- moiety and the soft S-donor atoms of the thioether groups in the backbone; both of which form water-soluble silver(I) complexes. The interactions between the silver(I) ion and the thioethers are less

compared to that of silver (I) (thiolate) bonding silver(I) complexes; group substitution converts the zwitterionic nature of the methionine to acid and also allows the ligands to form interunit hydrogen bonds.

Based on all compounds, silver chelation was investigated because of the presence of the thiol or thioether functional group. The thioether is a soft base with a complimentary attraction to silver due to the metal's soft acid nature. The complex above enabled the formation of the silver complex, the soft sulfur, and the silver. The thioether and a partial −OOC-C-C-C=O group, including the acetyl group of acmet−, achieve a good balance between stability and antimicrobial activities in silver complexes. In

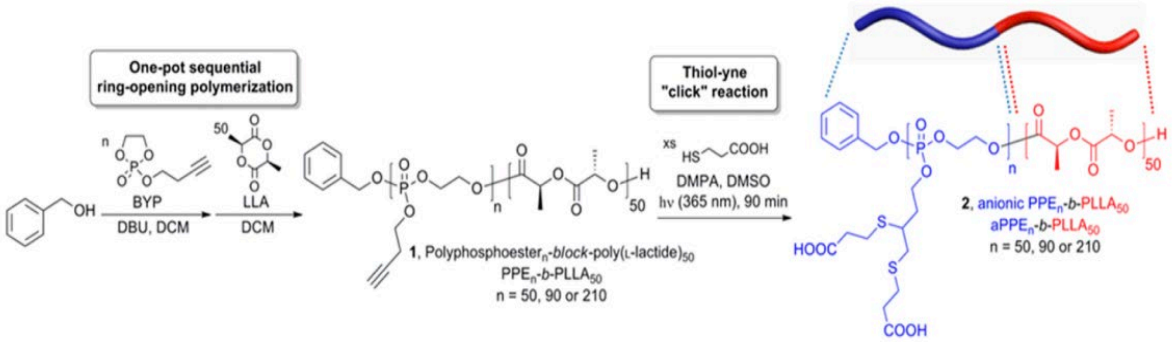
Fig. 11. Crystal structure of silver Hacmet composite network.

addition to the N-acetylmethionine, the other thioether-based ligands, methionine, and S-methyl cysteine, were similarly evaluated.

Silver acetyl methioninates yielded remarkably effective antimicrobial activities against two Gram-negative bacteria as shown in Figure 11. The antimicrobial efficacy of these two silver(I) N-acetyl methioninates was comparable to that of water-soluble Ag-O bonding complexes against both yeasts (Candida albicans and Saccharomyces cerevisiae) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa). They also

reported that the N-acetylmethionates were significantly stable in light, were highly influential for silver chelation, and had the best antimicrobial activity.

2.2 Antimicrobial Activity of Silver-Loaded Degradable Polymeric Nanoparticles (dNPs)



Scheme 1. Synthesis of thioether-containing phosphoester-lactide block copolymer.

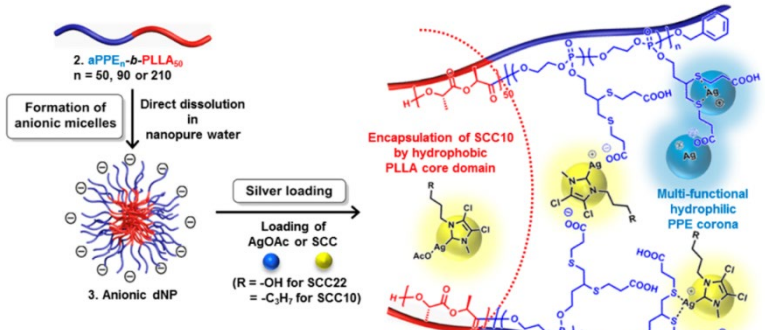


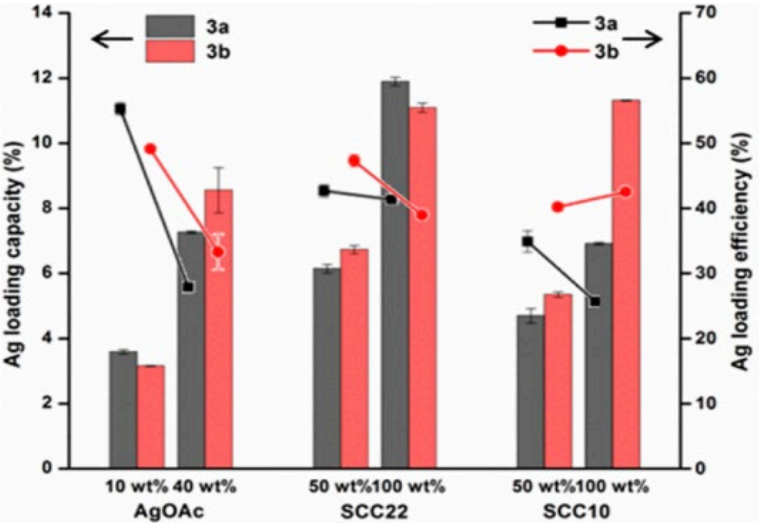
Fig. 12. Illustration of silver loading of dNPs.

Lim et al. synthesized degradable polymeric nanoparticles (dNPs) prepared from block polymers composed of phosphoester and l-lactide repeat units as the hydrophilic and hydrophobic segments. Prior to the self-assembly of the dNPs, the block polymers were outfitted with thioether groups via thiol-yne click chemistry between pendant alkyne groups of the polymer and thiopropionic acid. This functionalization step incorporated the metal binding sites onto the water-soluble region of the block polymer. Ultimately, the functionalization resulted in the chelating ligand situated on the nanoparticle's surface

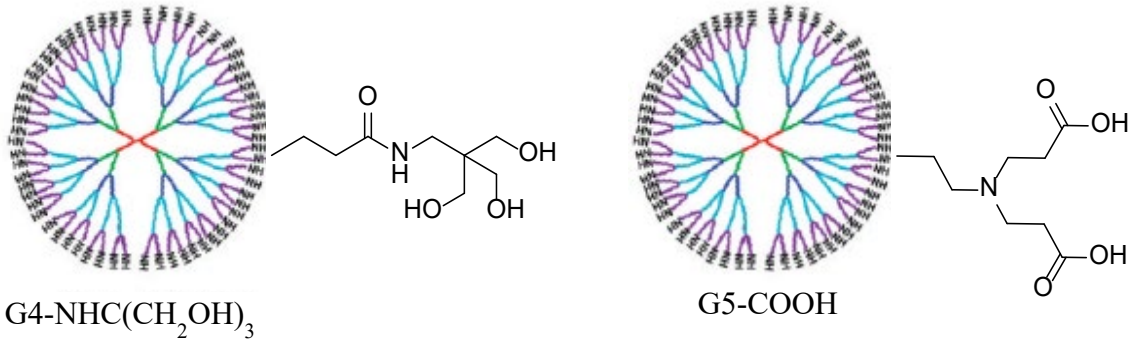
after dNP self-assembly. The dNPs were effective in silver loading when mixed with solutions of silver acetate, silver carbene complex 10, and silver carbene complex 22. Furthermore, the degradable dNPs displayed fast silver release and effectively killed multiple strains of S. Aureus (see Table 2). The loading ratio between the chelator and metal was the most significant factor in overall antibacterial behavior.

TABLE 2

Silver loading capacities based on chelator and silver source



2.3 Silver Complexation and Antibacterial Behavior of Poly(amidoamine) (PAMAM) Dendrimers



G4-NHC(CH_2OH)$_3$ G5-COOH

Fig. 13. Illustration of Fourth [G4-(OH)n] and fifth [G5-(COOH)n] generation dendrimers have Hydroxyl-terminated surface and carboxylic acid surfaces.

A study executed by Balogh et al. included the use of dendrimers as the ligand platform for silver nanocomposite materials. Poly(amidoamine) PAMAM dendrimers are highly branched and mono-disperse macromolecules with an array of interior amide and tertiary amine groups as well as terminal primary amines. The amine composition of PAMAM dendrimers renders them suitable for utilization as water-soluble nanocarriers.

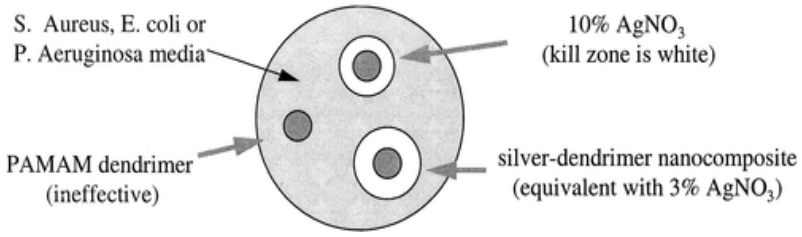


Fig.14. Illustration of PAMAM dendrimer, silver nitrate, and silver-dendrimer effeteness against fighting bacteria.

The divergent approach was used to synthesize these nanocarriers, which were produced with an ethylenediamine (EDA) core and tris(2-hydroxymethyl)-aminomethane (TRIS) termini up to the fifth generation and an aliphatic OH-surface. Aqueous solutions of the dendrimers were added to the specified amount of silver acetate powder to create silver-containing PAMAM complexes. The antibacterial activity of dendrimer-silver compounds was evaluated for diffusion. Even in sulfate or chloride ions, PAMAM silver salts and nanocomposites exhibited strong antibacterial activity without losing their solubility or potency. Silver remained macroscopically coupled to the dendrimer as ions, stable metallic silver clusters, or silver compounds. The immobilized silver can be delivered in solution thanks to the solubility nature of the dendrimer host. Silver remained coupled to the dendrimer as ions, stable metallic silver clusters, or silver compounds. The trapped silver in the agar medium can be delivered by diffusion since the dendrimer host is soluble. Due to the relatively large surface area of the silver

clusters, they continue to be active. Both silver complexes of poly(amidoamine) (PAMAM) dendrimers and other silver-PAMAM dendrimer nanocomposite solutions have been tested in vitro against Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli bacteria as shown in Fig. 14. Compared to silver nitrate, the dendrimer composite material effectively remediates bacteria. Even in the presence of sulfate or chloride ions, PAMAM silver salts and nanocomposites exhibited strong antibacterial activity without losing their solubility or potency.

CHAPTER III

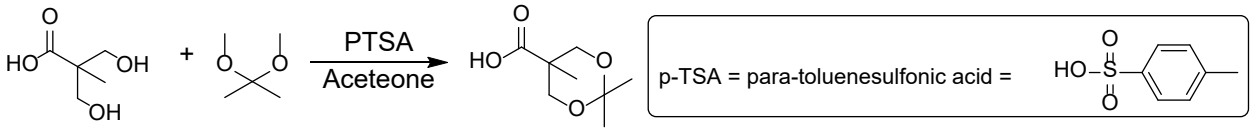
METHODOLOGY

Broadly, multiple classes of macromolecules have been recognized as highly effective alternative sources for drug delivery and other biomedical applications. As many researchers have demonstrated, suitably functionalized carriers generate versatile and potent weapons to combat antimicrobial resistance when combined with highly active antimicrobial/antibacterial agents. Previous studies have shown that nanocomposite materials bearing soft base ligands of amines, carboxylates, thiols, and thioethers are highly effective for silver chelation and subsequent antimicrobial activity. One of the most important structural aspects of nanomaterial design was the degree of branching. This thesis project used silver-appended polyester dendrimers to treat AMR effectively. We have methodically considered the structural and chemical makeup of the eventual metal transporting system with significant consideration for biocompatibility, biodegradability, and access to silver binding sites (valency). Although dendrimers require a more tedious synthetic approach, the platform was selected because of the reported purity and monodispersity of the eventual carrier materials. The multivalent dendrimer surface ensures that the vehicle has a high surface area of binding sites. Considering that these molecules will be evaluated for biomedical studies, the chemical composition of the polyester dendrimer lacks the peripheral toxicity associated with PAMAM dendrimer systems[50,51]. Additionally, polyesters are known to exhibit biocompatibility and biodegradability[35,52–56]. Finally, the dendrimer surface is outfitted with amino acids as metal-chelating moieties, ensuring sufficient metal complexation and contributing to the biocompatibility of the system. We hypothesized that polyester

dendrimers bearing the requisite soft base ligands on the surface would display sufficient silver chelating behavior to render them effective antimicrobial nanocomposite materials. Herein is described the synthesis, characterization, and silver chelating activity of amino acid-functionalized polyester dendrimers.

3.1 Monomer Synthesis

3.1.2 Preparation of Acetonide protection of Bis-MPA

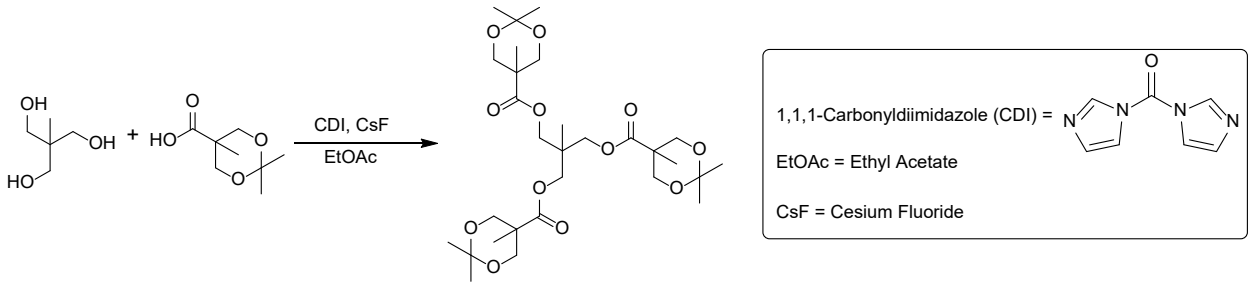


Scheme 2. Acetonide protection of Bis-MPA monomer.

2,2'-Bis(hydroxymethyl)propionic aid, or Bis-MPA (10.00 g, 74.6 mmol), was added to a round bottom flask charged with 100 mL of acetone, followed by 2,2-dimethoxypropane (8.15 g, 78.3 mmol) and the reaction immediately became a suspension. p-Toluenesulfonic acid (PTSA) (0.709 g, 3.73 mmol) was added to the reaction. The suspension began to go into solution within minutes, and a notable temperature decrease was observed. The reaction was stirred vigorously for 24 hours at room temperature. Triethylamine (0.377 g, 3.73 mmol; 0.520 mL) was added to quench the reaction, then acetone was evaporated via rotovap. The crude product was then diluted with dichloromethane (DCM), transferred to a separatory funnel, and washed three times with 150 mL of deionized water. The organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and then dried under vacuum to yield a white, crystalline product (7.788 g, 60%).

3.2. Dendrimer Synthesis

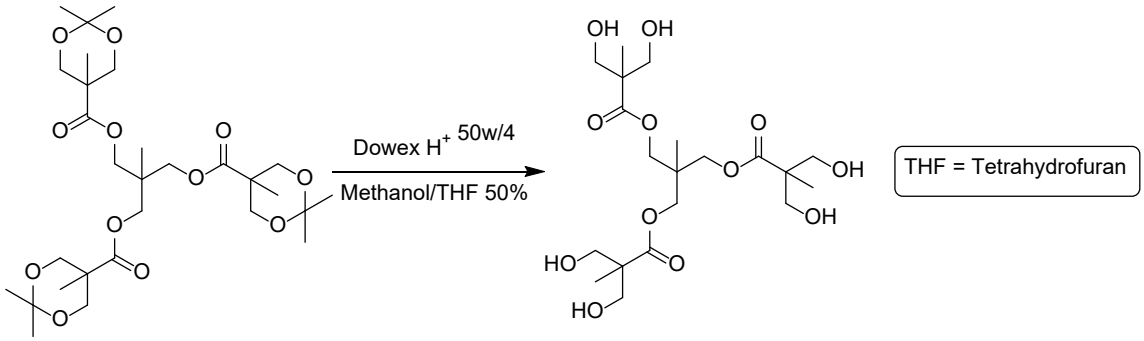
3.2.1 Preparation of G1-Acetal Protected, Polyester Dendrimer G1-(Ac)$_3$



Scheme 3. Synthesis of G-1 Bis-MPA polyester dendrimer.

Carbonyldiimidazole (6.07 g, 37.43 mmol) (1.5 eq. per OH group) was added to ethyl acetate to make a suspension. Acetonide Bis-MPA (6.52 g, 37.45 mmol) (1.5 eq. per OH group) was added to the heated suspension, and the reaction was stirred for 30 minutes. Cesium fluoride (0.76 g, 0.49 mmol) (0.2 eq per OH group) and 1,1,1-tris(hydroxymethyl)ethane (1.00 g, 8.32 mmol) was added, and the reaction continued to stir for an additional hour. After confirmation of completion via MALDI-TOF, water was added to the reaction. The mixture was then transferred to a separatory funnel with DCM and washed three times with water, sodium bicarbonate, and sodium bisulfate. The organic layer was dried over sodium sulfate, filtered, and concentrated under a vacuum. To further purify, the product was flushed over a silica gel column with DCM as the eluent (2.0745 g, 43.4%).

3.2.2 Synthesis of G1- Deprotected Polyester Dendrimer, G1-[(OH)$_2$]$_3$

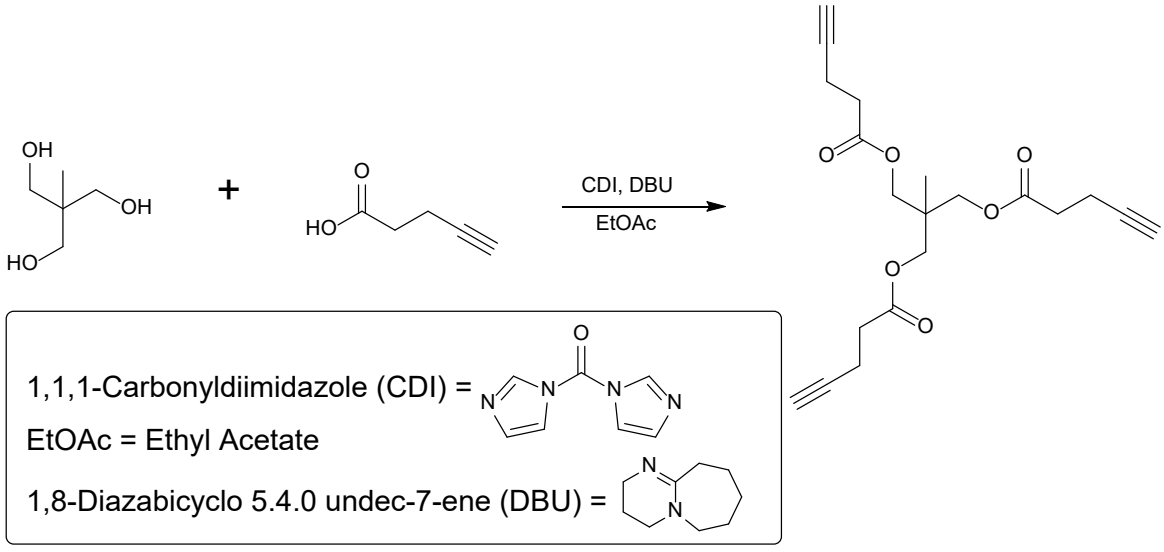


Scheme 4. Deprotection of G-1 dendrimer.

Dowex® H^+ (10 mass %) proton exchange resin was cleaned in methanol, filtered, dried, and added to a 1:1 methanol/tetrahydrofuran solution, followed by the G1-(Ac)3 dendrimer. The reaction was heated to 50 degrees and stirred vigorously for two hours. The reaction was then filtered, the solvent was evaporated, and then dried on a vacuum to yield a colorless viscous liquid (quantitative).

3.3 Surface Functionalization

3.3.1 Preparation of G0-(Alkyne)$_3$

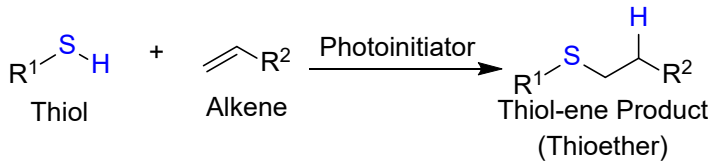


Scheme 5. Synthesis of tris(pentynoate).

Carbonyldiimidazole, or CDI (0.911 g, 5.62 mmol) (1.5 eq. per OH group), was added to 50 mL ethyl acetate, and the suspension was heated to 50 degrees C. 4-pentynoic acid (0.551 g, 5.62 mmol) (1.5 eq. per OH group) was added to the heated suspension, and the reaction was stirred for 30 minutes. DBU, or 1,8-diazabicyclo [5.4.0] undec-7-ene (0.116 g, 0.749 mmol) (0.2 eq per OH group) and 1,1,1-tris(hydroxymethyl)ethane (0.150 g, 1.25 mmol) was added, and the reaction continued to stir for an additional hour. After confirmation of completion via MALDI-TOF, water was added to the reaction. The mixture was then transferred to a separatory funnel with DCM and washed three times with water, sodium bicarbonate, and sodium bisulfate. The organic layer was dried over sodium sulfate, filtered, and concentrated under a vacuum. To further purify, the product was flushed over a silica gel column with DCM as the eluent (0.445 g, 99.0%).

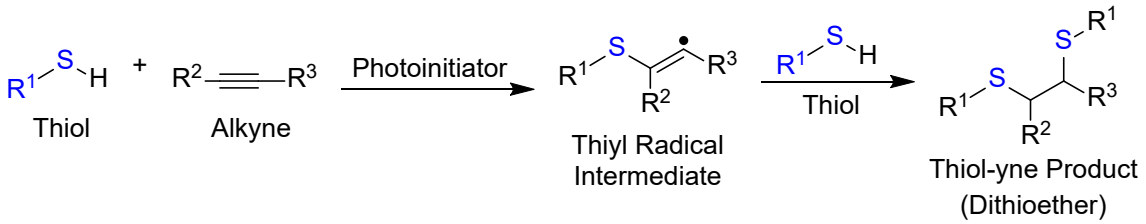
3.4 Thiol-Michael Addition Reactions

A carbanion, or any other suitable nucleophile, was added to an unsaturated carbonyl molecule with a functional group that was electron-withdrawing in nature to produce the Michael reaction, a nucleophilic addition reaction. Click reactions are a valuable technique for giving compounds specialized features, such as boosting their water solubility and enabling the chelation of metals.



Scheme 6. Thiol-ene click addition reaction.

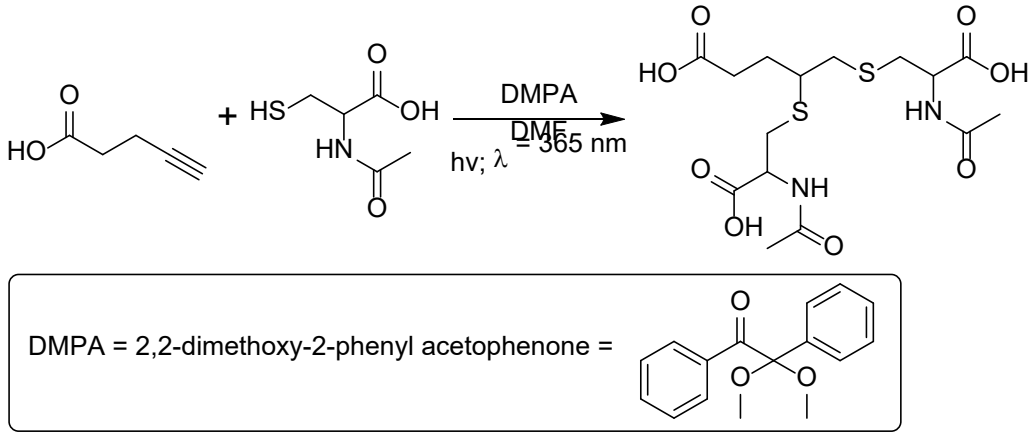
The thiol-ene reaction, or thiol-ene coupling (TEC), is considered a "click" reaction. It is a thiol and alkene reaction to form a thioether. Characteristics of click reactions include high yields, lack of side products, compatibility with aqueous conditions, and orthogonality to many other synthetic reactions.



Scheme 7. Thiol-yne click addition reaction.

A well-known synthetic technique for adding sulfur-containing compounds with various functional groups to a monomer or polymer is called thiol-yne click chemistry. The thiol-yne reactions involve the coupling between two thiols and an alkyne to form a vicinal dithioether[19,21,24,25,27,30,31,34,36,57–59].

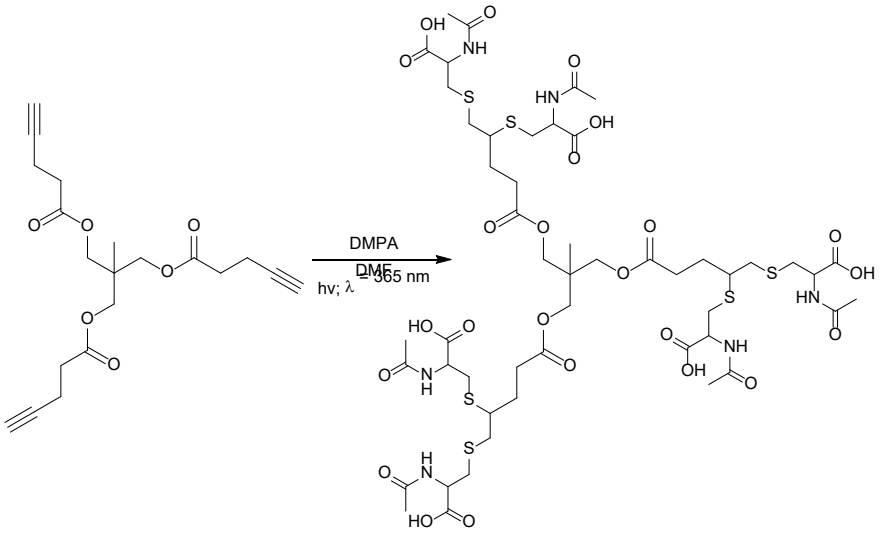
3.4.1 Synthesis of 4,5-bis(N-Acetyl cysteinyl) Pentanoic acid, $(SR)_2$ – Single Arm Chelator



Scheme 8. Thiol-yne click reaction to produce single arm chelator.

N-acetylcysteine (0.832 g, 0.510 mmol; 2 eq. per alkyne) was dissolved in dimethylformamide (DMF), followed by the addition of 4-pentynoic acid (0.25 g, 2.55 mmol; 1 eq.). The photo-initiator, 2,2-dimethoxy phenyl acetophenone, or DMPA (0.065 g, 0.255 mmol; 0.2 eq. per alkyne), was then added, and the reaction deoxygenated by bubbling in nitrogen gas for 20 minutes. The reaction was then placed inside a UV chamber and irradiated at 365nm while stirred vigorously for 30 minutes. Afterward, the crude product was precipitated from ethyl acetate before separation via centrifuge. The pure product was then dried on a vacuum pump and isolated as a yellowish foam (0.822 g; 76% yield).

3.4.2 Synthesis of Hexa-[4,5-bis(N-Acetyl cysteinyl) Pentanoic acid]-Functionalized G-0 Dendrimer, G0-[$(SR)_2]_3$– Three-Arm Chelator



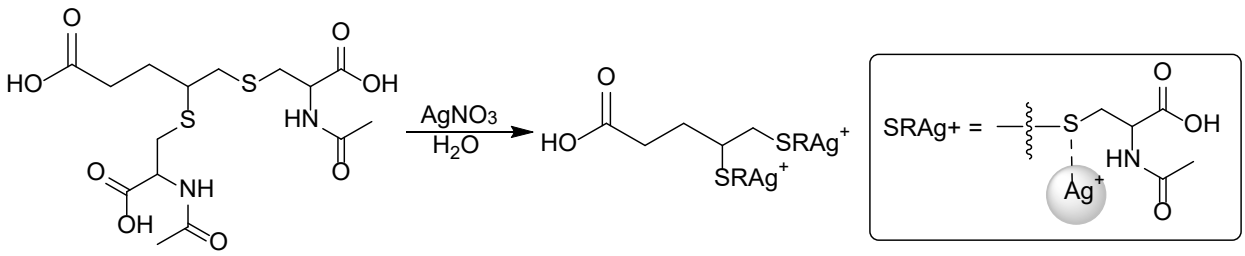
Scheme 9. Thiol-yne click reaction to generate three-arm chelator.

N-acetylcysteine (2.0102 g, 12.32 mmol; 2.2 eq. per alkyne) was dissolved in 6 mL dimethylformamide (DMF), followed by the addition of 4-pentynoic acid (0.25 g, 2.55 mmol; 1 eq.). The photo-initiator, 2,2-dimethoxy phenyl acetophenone, or DMPA (0.065

g, 0.25 mmol; 0.2 eq. per alkyne), was then added, and the reaction deoxygenated by bubbling in nitrogen gas for 20 minutes. The reaction was then placed inside a UV chamber and irradiated at 365nm while stirred vigorously for 90 minutes. Afterward, the crude product was precipitated from ethyl acetate before separation via centrifuge. The pure product was then dried on a vacuum pump and isolated as a yellowish foam (quantitative).

3.5 Silver loading

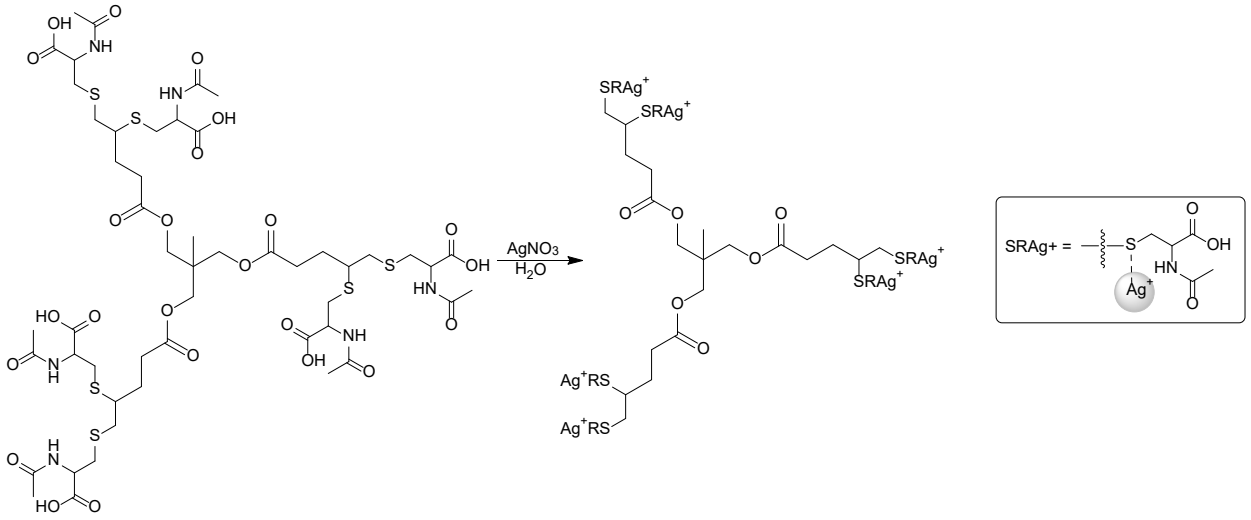
3.5.1 Chelation of Silver with Single-Arm Chelator, $(SRAg^+)_2$



Scheme 10. Silver loading with single-arm chelator.

Silver nitrate (0.1039 g, 0.449 mmol) was dissolved in a round bottom flask in deionized water. The chelator (0.050 g, 0.037 mmol) was dissolved in water in a separate round bottom flask. The aqueous chelator solution was added to the silver nitrate and stirred overnight while covered in aluminum foil to block light. The complex was precipitated from acetone and isolated by centrifugation at 6000 rpm for 15 minutes. The silver complex was dried by a vacuum pump and recovered as a white solid.

3.5.2 Chelation of Silver with Three-Arm Chelator, G0-[(SRAg$^+$)$_2$]$_3$



Scheme 11. Thiol-yne click reaction to generate three-arm chelator.

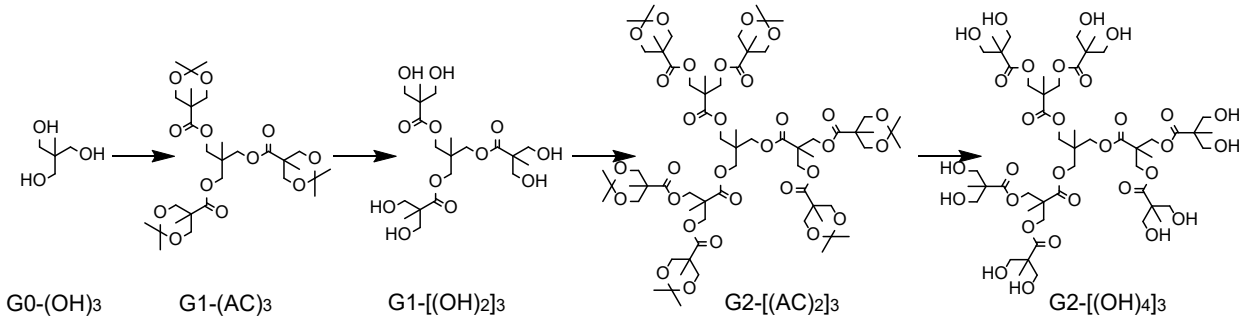
Silver nitrate (0.38 g, 2.24 mmol) was dissolved in a round bottom flask in deionized water. The chelator (0.10 g, 0.075 mmol) was dissolved in water in a separate round bottom flask. The aqueous chelator solution was added to the silver nitrate and stirred overnight while covered in aluminum foil to block light. The complex was precipitated from acetone and isolated by centrifugation at 6000 rpm for 15 minutes. The silver complex was dried by a vacuum pump and recovered as a white solid.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Polyester Dendrimer Synthesis

The synthesis of the monomer, dendrimers, surface modification, and silver chelation was observed with multiple analytical techniques. Specifically, the synthetic steps that involved modification of the dendrimer architecture were supplemented with high-resolution mass spectrometry through matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). Pencil lead (2HB grade) was selected as the matrix for each sample, which was accomplished by directly drawing onto the surface of the sample wells of the MALDI sample plate. Sodium trifluoroacetate and potassium trifluoroacetate were the two cationization agents (4 mg/mL). The



Scheme 12. Polyester Dendrimer Synthesis.

Fig. 15 shows the MALDI-TOF MS characterization of the dendrimer at each growth step. The first peak at 611.334 represents the mass of the G1-(Ac)3 product. The second peak at 491.201 represents the mass of the G1-[(OH)2]3 product. The last peak at 1443.845 represents the mass of the G2-[(OH)4]3 product. The miscellaneous smaller peaks are noise from the matrix.

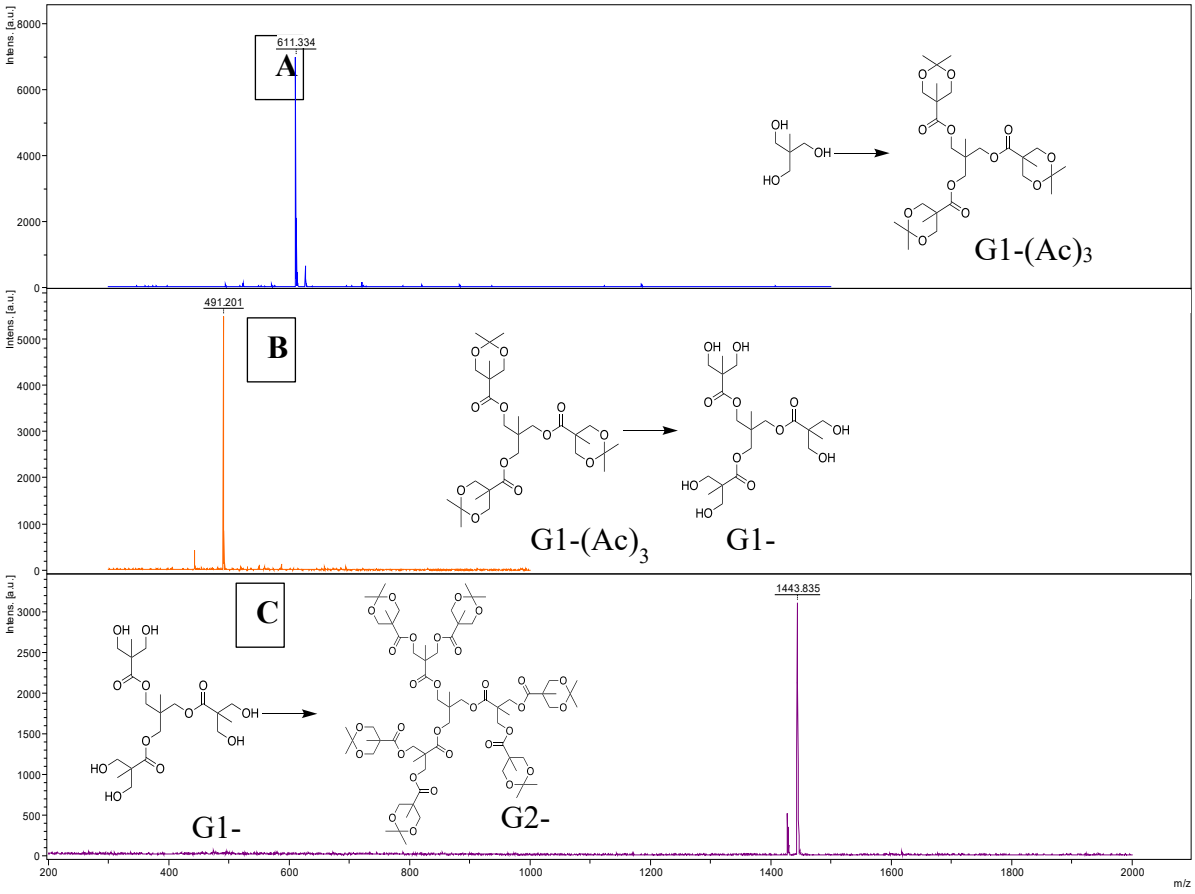
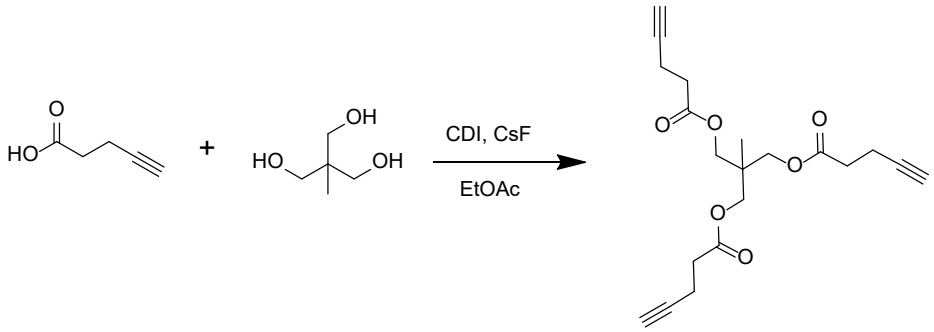


Fig. 15. MALDI-TOF spectrum of polyester dendrimer synthesis up to second generation: a) G-1 Acetonide; b) G1-OH; c) G2-Acetonide.

4.2. G0-(Alkyne)$_3$ Synthesis

1,1'-Carbonyldiimidazole was added to ethyl acetate to make a suspension.4-pentynoic acid was added to the heated suspension. Cesium Fluoride (CsF) was added and stirred vigorously. Tris(hydroxymethyl)ethane – or hydroxy-terminated dendrimer – was added, and the reaction stirred. After confirmation of completion via MALDI-TOF, water was added to the reaction. The mixture was then transferred to a separatory funnel with DCM and washed three times with water, sodium bicarbonate, and sodium bisulfate. The organic layer was dried over sodium sulfate, filtered, and concentrated under a

vacuum. To further purify, the product was flushed over a silica gel column with DCM as the eluent.



Scheme 13. G0-(Alkyne)$_3$ Synthesis.

Fig. 16 shows the MALDI-TOF MS of the reactants and the product. The peak at 119.236 represents the mass of the 4-pentynoic acid. The second peak at 383.139 represents the pentanoic acid with the attached functionalized surface groups.

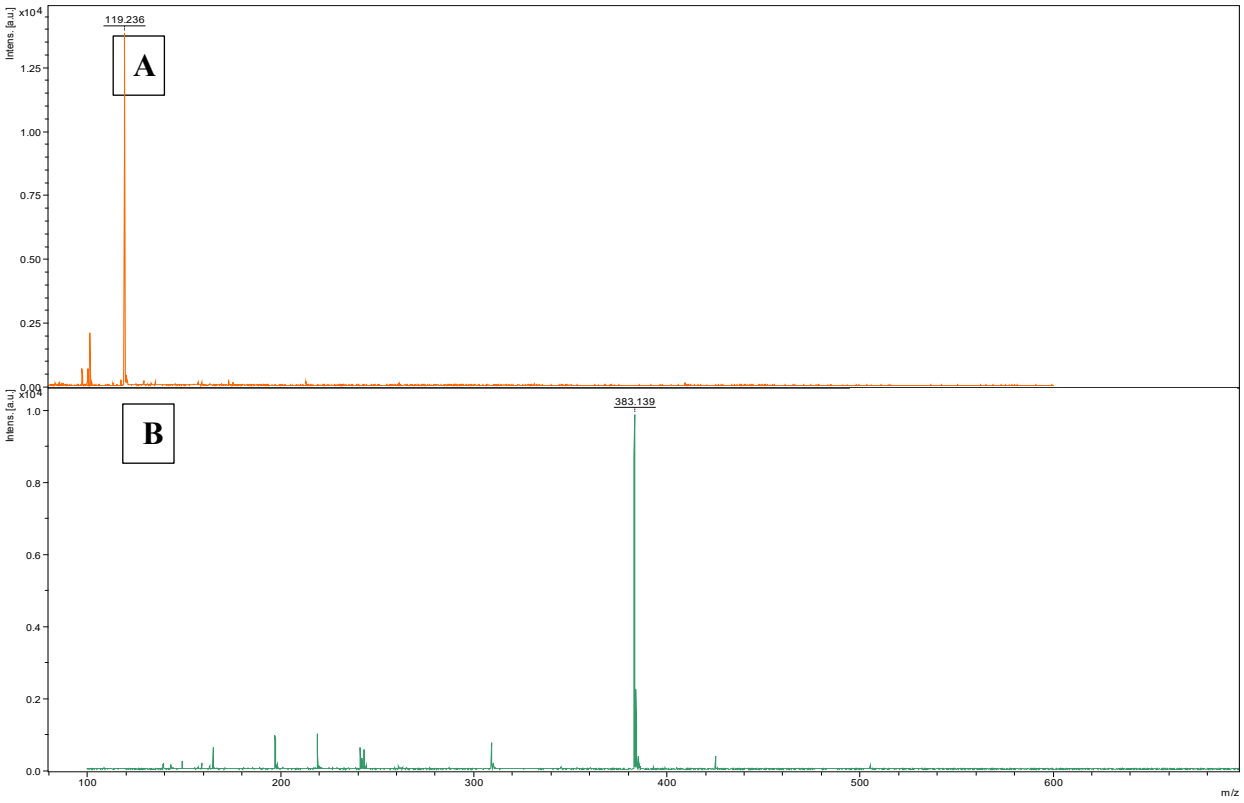
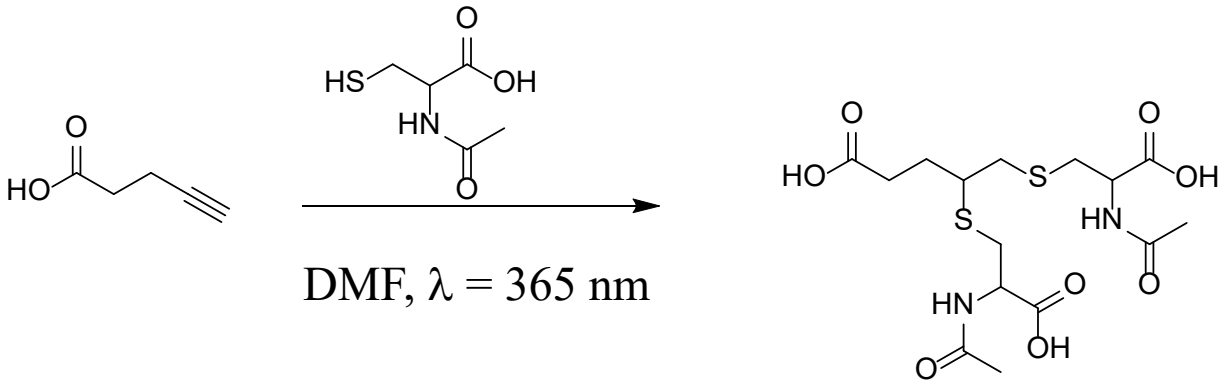


Fig. 16. MALDI-TOF MS of 4-pentynoic acid (top) and G0-(Alkyne)$_3$ (bottom).

4.3 G0 Surface Modification via Thiol-yne Click Chemistry

Scheme 14 highlights the synthesis of NAC-conjugated pentanoic acid by dissolving N-acetylcysteine in dimethylformamide (DMF) and adding 4-pentynoic acid. The photo-initiator, 2,2-dimethoxy phenyl acetophenone, or DMPA, was added, and the reaction was deoxygenated by bubbling in nitrogen gas for 20 minutes. The reaction was then placed inside a UV chamber and irradiated at 365nm while stirred vigorously for 90 minutes. Afterward, the crude product was precipitated from ethyl acetate before separation via centrifuge. The pure product was then dried on a vacuum pump and isolated as a yellowish foam.



Scheme 14. G0 Surface Modification via Thiol-yne Click Chemistry.

Fig. 17 shows the MALDI-TOF MS of the of the reactants and the functionalized surface groups. The peak at 463.172 represents the mass of the 4-pentynoicacid with the cysteine attached at the surface.

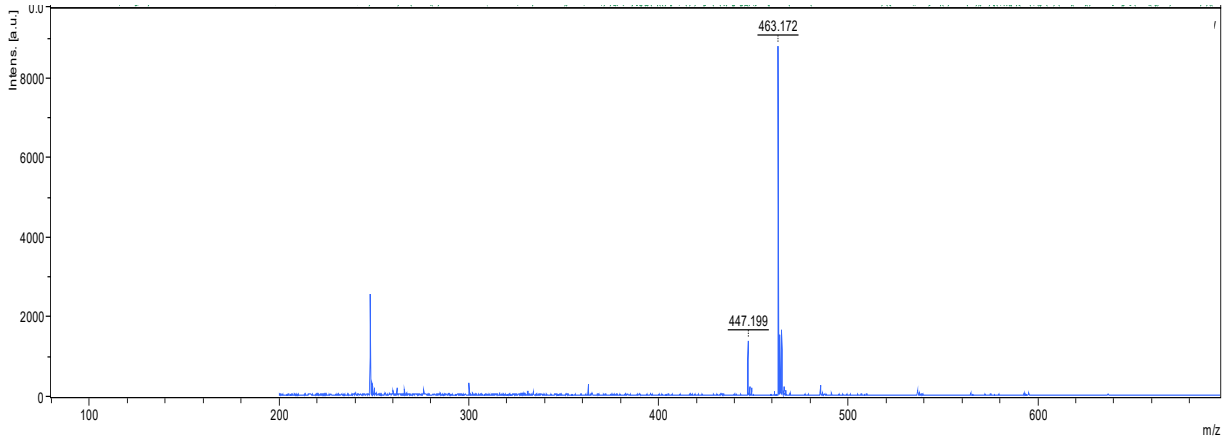


Fig. 17. MALDI-TOF MS of G0 Surface Modification via Thiol-yne Click Chemistry.

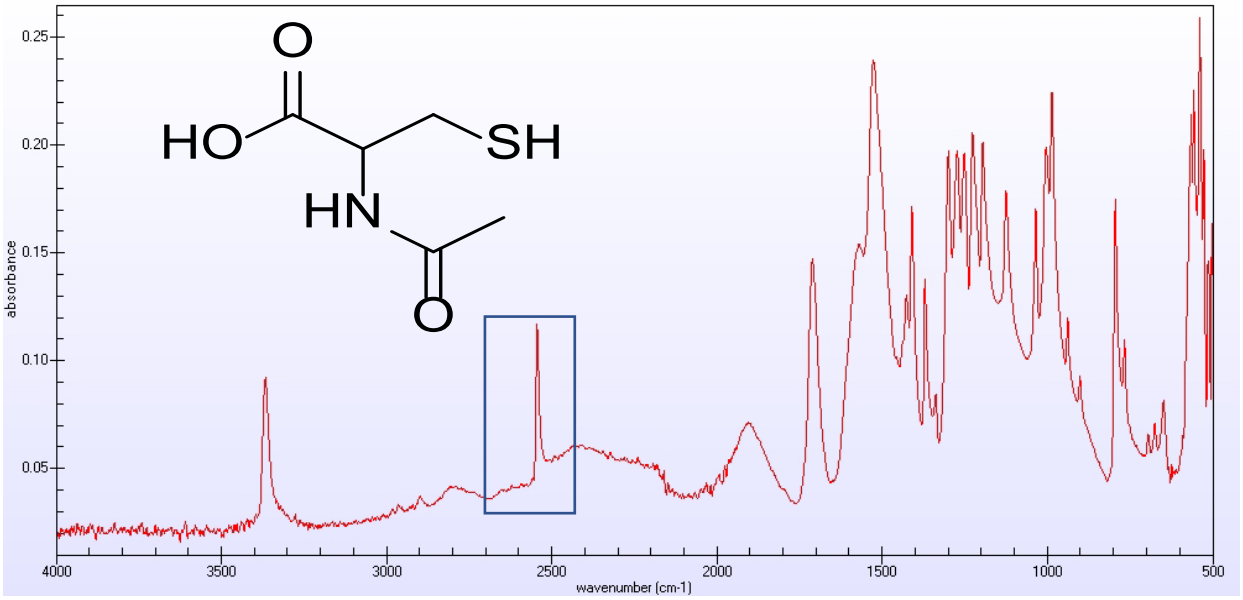


Fig. 18. IR spectrum of N-acetylcysteine.

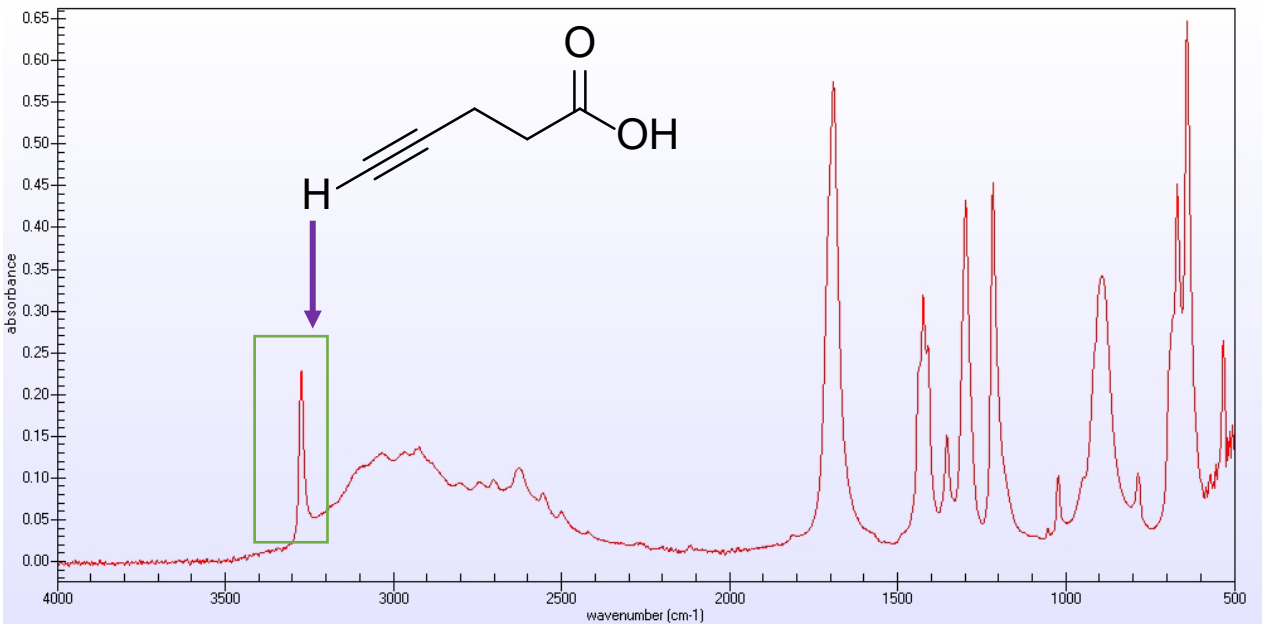


Fig. 19. IR of 4-pentynoic acid.

There is a C≡C-H stretch at 3250 cm^{-1} which indicates that the alkyne is present (Fig. 19).

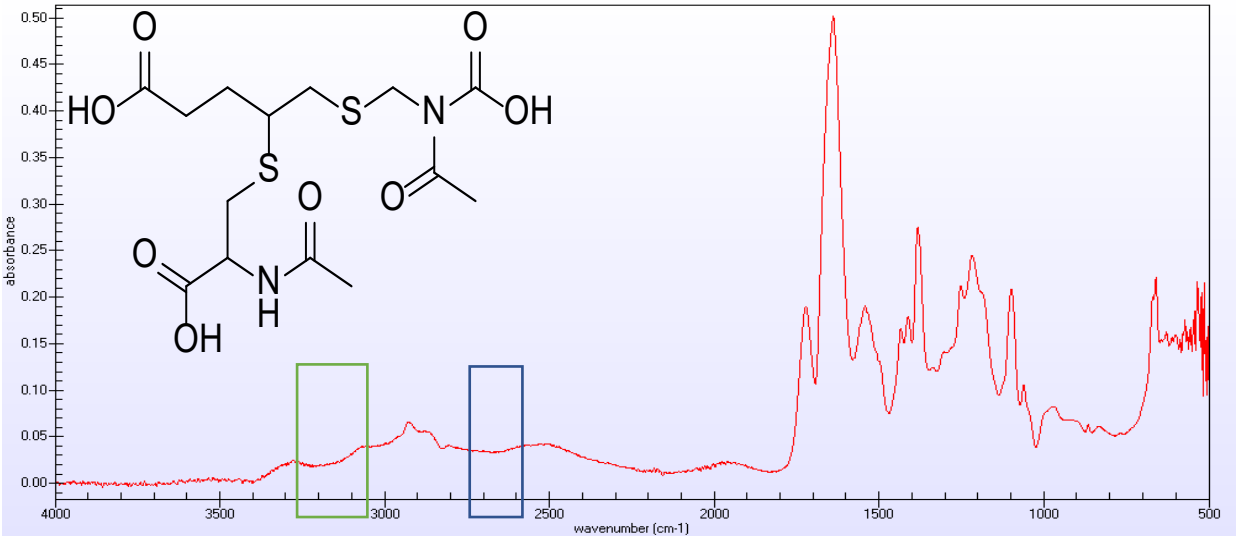
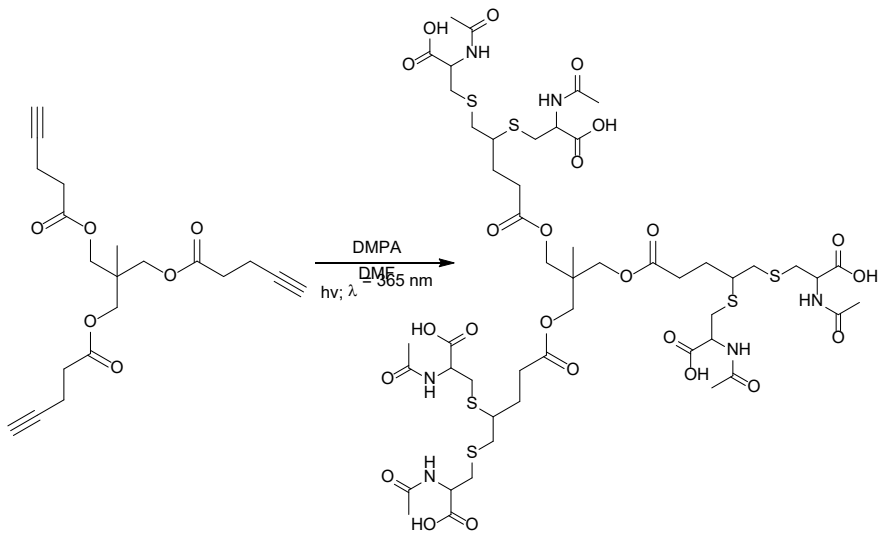


Fig. 20. IR of G0 Surface Modification via Thiol-yne Click Chemistry.

There is loss of SH stretch at 2500 cm^{-1} which indicates that the thiol is gone, and the cysteine is attached. There is also loss of C≡C-H stretch at 3250 cm^{-1} which indicates that the alkyne C-H bond has been lost (Fig. 20).

4.4 G0 Alkyne Click Rxn.

This synthesis (Scheme 9) yielded a 6-arm metal chelator was synthesized by mixing N-acetylcysteine, 4-pentynoic acid, 2,2-dimethoxy phenyl acetophenone (DMPA) in a small volume of DMF. The photocatalyzed reaction was initiated inside a photo crosslinker, and irradiated for 90 minutes under a 365 nm uv light. MALDI-TOF was used for characterization.



Scheme 9. Thiol-yne click reaction to generate three-arm chelator.

The Fig. below shows the MALDI-TOF spectra of the of the reactants and the functionalized surface groups. The peak at 463.172 represents the mass of the G0-(Alkyne)$_3$. The peak at 1361.518 m/z represents the mass of the chelator with six cysteine units attached to the surface plus a sodium ion.

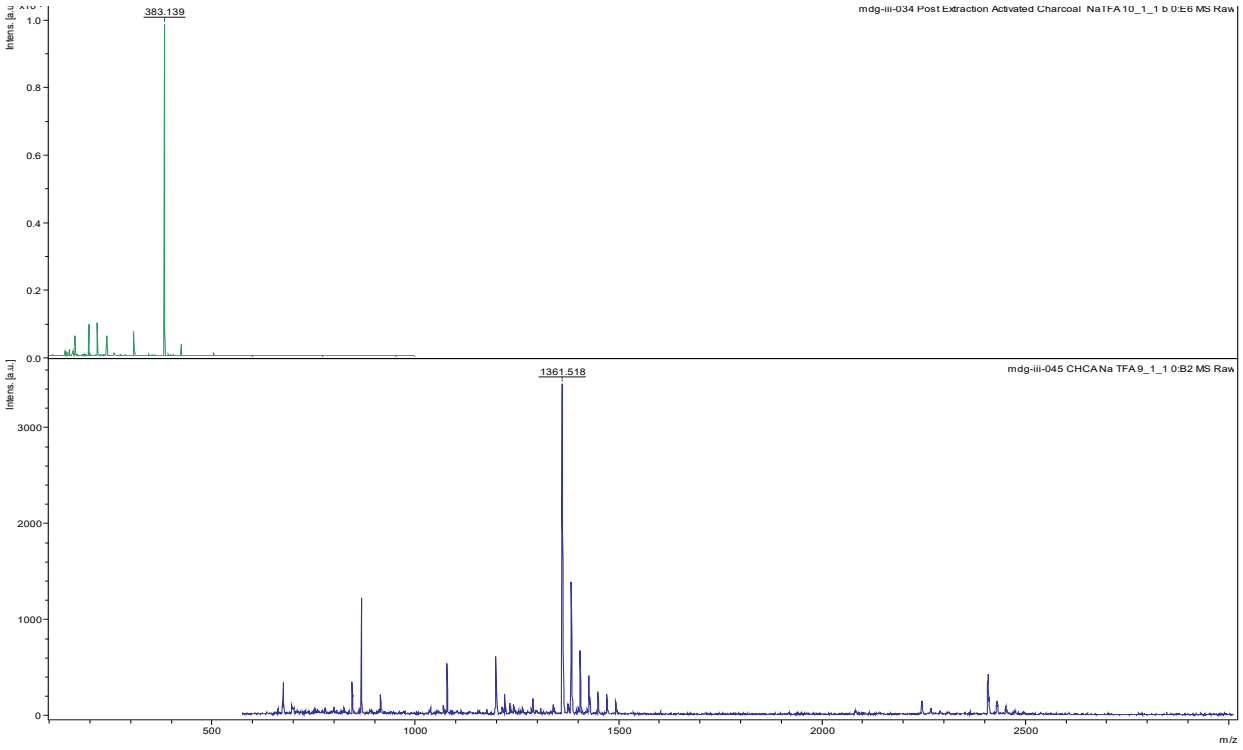
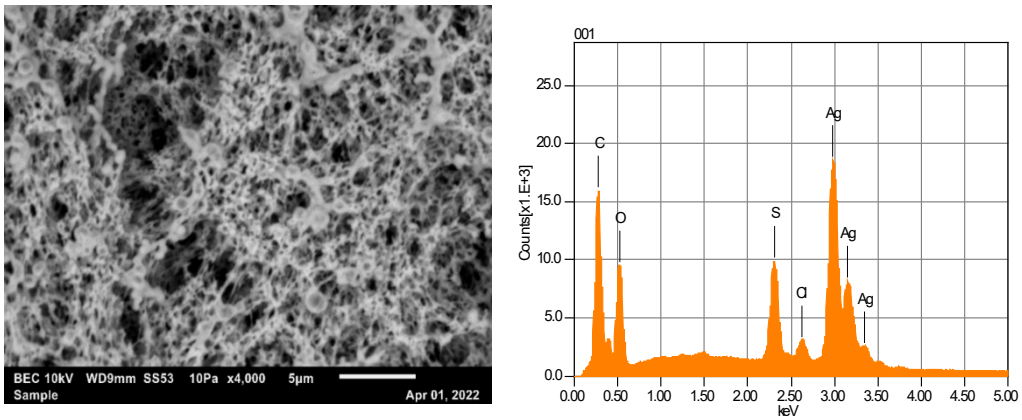


Fig. 21. MALDI-TOF spectra of tris(pentynoate) (top), and three-arm chelator (bottom).

4.5 Silver Chelation Studies

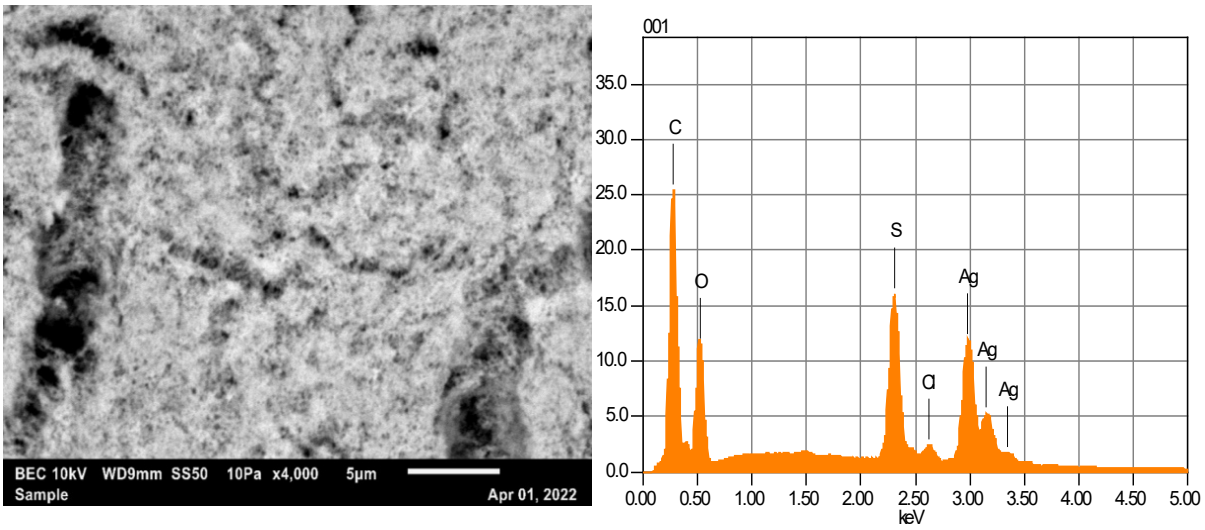
The metal chelation affinities of the NAC-conjugated ligands were tested by mixing aqueous or organic solutions of the chelator and metal species with each other to induce complexation. We evaluated solution mixtures with M/C ratios of 1/3 and 1/6, using deionized water or methanol.



Chemical formula	mass%	Atom%	Sigma	Net	K ratio	Line
C	17.19	47.25	0.01	332875	0.0801099	K
O	11.85	24.45	0.02	205037	0.1451386	K
S	7.93	8.16	0.02	354182	0.3501863	K
Cl	1.34	1.25	0.02	53699	0.0649064	K
Ag	61.69	18.88	0.12	1193068	2.1468377	L
Total	100.00	100.00				

Fig. 22. SEM Analysis of G0 $(HNAc)_3$ + Ag^+; Chelator to Ag ratio = 1:3 (in water).

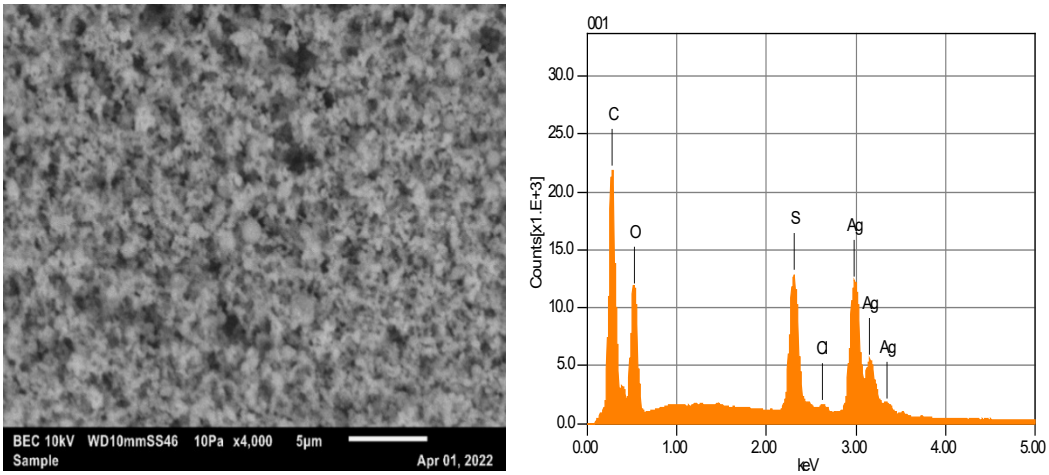
This reaction was a 1:3 ratio in water. The mass percentage of 18.88% show that silver was chelated. This chelated the most abundant amount of silver.



Chemical formula	mass%	Atom%	Sigma	Net	K ratio	Line
C	34.17	63.37	0.01	566301	0.1362863	K
O	13.70	19.07	0.02	258564	0.1830282	K
S	13.01	9.04	0.02	614069	0.6071423	K
Cl	1.04	0.65	0.02	42586	0.0514744	K
Ag	38.09	7.87	0.09	762837	1.3726692	L
Total	100.00	100.00				

Fig. 23. SEM Analysis of G0 $(HNAc)_3$ + Ag^+ Chelator to Ag ratio = 1:3 Metal (in methanol).

This reaction was a 1:3 ratio in methanol. The mass percentage of 7.87% shows that silver was chelated. Although this is the same ratio as the one above, it chelated less silver.



Chemical formula	mass%	Atom%	Sigma	Net	K ratio	Line
C	29.43	58.76	0.01	477813	0.1149906	K
O	15.16	22.72	0.03	256929	0.1818708	K
S	11.58	8.66	0.02	488403	0.4828937	K
Cl*	0.26	0.18	0.01	9644	0.0116571	K
Ag	43.57	9.69	0.10	785518	1.4134817	L
Total	100.00	100.00				

Fig.24. SEM Analysis of G0 $(HNAc)_3$ + Ag^+ Chelator to Ag ratio = 1:6 Metal (in methanol).

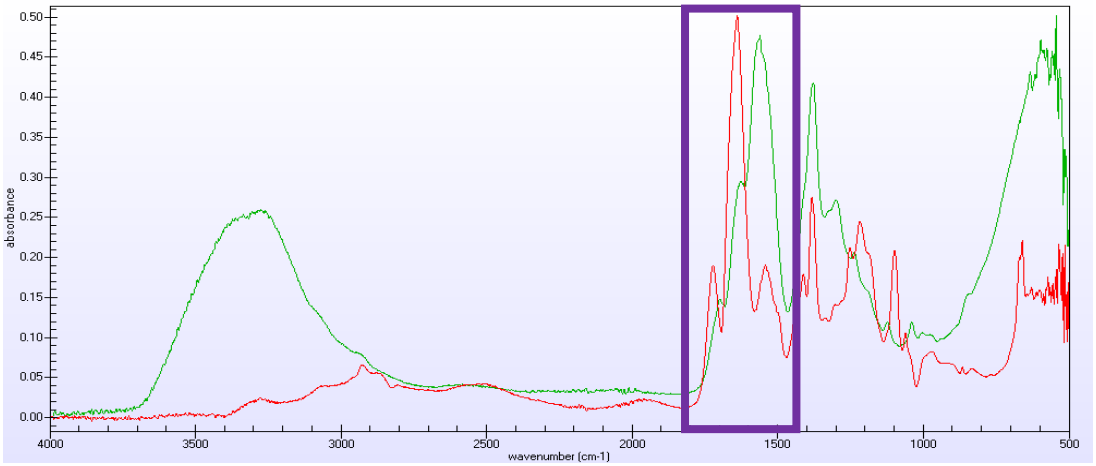


Fig. 25. FTIR spectrum of pentynoic acid naked chelator and pentynoic acid silver chelation.

This reaction was a 1:6 ratio in methanol. The mass percentage of 9.69% shows that silver was chelated. It does have more silver than the 1:3 in methanol, but still less than the 1:3 in water. It can be concluded that water is better for chelating silver than methanol. The red represents the pentynoic acid naked chelator (PANC), and the green represents the PANC silver chelation. There is a Shift of C=O stretch.

CHAPTER V

CONCLUSION AND FUTURE STUDIES

5.1 Conclusion

This thesis described the production of synthetic materials to address antibiotic-resistant bacteria. We selected the natural metal silver because of the reported inability of bacteria cell lines to develop resistance to the metal. Based on Bis-MPA, the synthetic targets intended to sequester and eventually transport silver ions were constructed with a biocompatible and biodegradable polyester dendrimer system. Following the previously investigated synthetic protocol, we successfully synthesized the dendrimers for the second generation. The dendrimers were eventually outfitted with the natural amino acid N-acetylcysteine through thiol-yne click addition, enabling the branched polymers to bind silver ions in an aqueous solution and methanol sufficiently. With the suitably functionalized chelator species, we compared the silver loading efficiency based on solvent dependence and metal/chelator loading ratios.

However, the tests in methanol increased silver loading when the metal/thioether ratio was doubled. Sample analysis of these tests using Scanning Electron Microscopy / Energy-dispersive X-ray Spectroscopy (SEM/EDS) revealed that the polyester dendrimer displayed greater silver binding behavior in water. Elemental mapping achieved with this analytical approach highlighted sample silver compositions between 18 and 62 mass percent. Thus, these results supported the original hypothesis that the thioether-decorated dendrimer system would effectively complex silver ions in aqueous media.

5.2 Future Studies

The optimization of this polyester dendrimer chelator system is still underway. A full battery of tests will be executed to determine the more significant impact of binding sites on the dendrimer surface by comparing second, third, and likely fourth generation dendrimers under identical conditions. The system's stability, following silver sequestration, is of great significance due to the nature of the light-sensitive metal. Light exposure of the complexes will be evaluated. Finally, actual bacteria cell studies are necessary to determine the true effectiveness of the dendrimer-metal complex.

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EXPERIENCE

- Company: FlowChem
  Position: Senior Quality Lab Technician, May 2019 - Present
  Job: -Analyze and Perform Various Test on Intermediate - Samples and Finished Goods
  -Test Samples via H NMR, C NMR, IR Spectrometry, BARTEC, Karl Fischer, Particle Size Analyzer, Density Meter, Rheometer, etc.

- Company: Prairie View A&M Chemistry Department
  Position: Graduate Assistant, August 2017-May 2019
  Job: -Conducted Research / Analysis on major subject matter to impact world-wide innovation
  -Taught Laboratory Classes and Graded Assignments
  -Set-Up / Breakdown Laboratory
  -Chemistry Tutor

- Company: Prairie View A&M Biology Department
  Position: Lab Assistant, October 2016-May 2017
  Job: -Administered Exams and Conducted Department Tours
  -Assisted with Laboratory Classes and Graded Assignments
  -Set-Up / Breakdown Laboratory