Spring 5-10-2019

"Click-ene" Chemistry: An Efficient Synthetic Strategy for the One-step Development of Function Monomers and Polymer

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“CLICK-ENE” CHEMISTRY: AN EFFICIENT SYNTHETIC STRATEGY FOR THE ONE-STEP DEVELOPMENT OF FUNCTIONAL MONOMERS AND POLYMERS

A thesis submitted to the Graduate School
In Partial Fulfillment of the Requirements
For the Degree of
Master of Science in Polymer Chemistry

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March 2019

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ACKNOWLEDGMENTS

I would like to express my special thanks to my advisor and mentor in my thesis Dr. Santimukul Santra, who gave me the opportunity to work in his lab. This work would not have been possible without his support and guidance.

I want to thank my all my lab members for their wonderful collaboration. They supported me greatly and were always willing to help me. I would also like to thank the chemistry department for giving me opportunity to conduct research.

Thanks to my friends and my family who were always my constant support system.

“CLICK-ENE” CHEMISTRY: AN EFFICIENT SYNTHETIC STRATEGY FOR THE ONE-STEP DEVELOPMENT OF FUNCTIONAL MONOMERS AND POLYMERS

An Abstract of the Thesis by
Ren Bean

In this study, we am going to establish a new one-step method, named as “click-ene” chemistry, using alkenes and azides. Traditionally, as discovered by Dr. K.B. Sharpless and his groups, “click” chemistry requires an alkyne and azide groups in the presence of a solvent and Cu derived catalyst. “Click-ene” chemistry provides similar orthogonality in starting materials without the requirement of potentially harmful transition metal catalyst. In this direction, the new “click-ene” chemistry will be established not only catalyst-free, but solvent-free as well. Various alkyl/aryl alkene and azide functional starting materials were selected for establishing the new “click-ene” concept. Using commercially available starting materials, small molecules were synthesized to test the viability of purposed “click-ene” chemistry. Providing a 1,2,3-triazole ring conformation “click-ene” chemistry offers: modular synthetic routes, electron rich ring configuration, hydrogen-bonding potential through nitrogen atoms, and good solubility due to a strong dipole-moment. Furthermore, a novel AB monomer was designed for the syntheses of functional “click-ene” polymers. In addition, using established “click-ene” chemistry, polymerization synthetic pathways will demonstrate the catalyst/solvent free reactions. The synthesized library of “click-ene” small molecules, functional monomers, and polymers will be characterized using various spectroscopic and chromatographic techniques.

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CHAPTER I

Introduction

Click chemistry reactions have been utilized extensively for almost two decades in the fields of small molecule and polymer science.[1] Examination of “nature’s favorite molecules” quickly reveals nature’s partiality for carbon-heteroatoms in comparison to carbon-carbon structures as Dr. K. B. Sharpless's genius states in his original publication.[1, 2] Click chemistry delivers a modular synthetic strategy allowing for more control of precisely designed molecules. Providing a new opportunity among chemists to drastically improve research specificity through the use of this highly efficient, controllable chemistry in the presence of strong transition metal catalysts.[1-3] Coming with a strict list of guidelines, click chemistry aims to provide many industries with the synthetic routes required to be as efficient as possible. Firstly, these guidelines include: small hetero atom units must reliably link together in both small- and large-scale reactions alike.[1, 2] Secondly, reactions should be highly selective resulting in high yields of the desired product without the production of any offensive side products.[1] These products must be able to be isolated with minimal effort, ideally without the use of intensive chromatographic methods. Thirdly, simple reaction conditions should be maintained resulting in water-solubilized or neat

reaction environments.[1, 2] These reactions should contain commodity starting materials once again requiring little to no effort to separate upon reaction completion.[1, 2]

By utilizing click chemistry, R. J. Thibault et al. have synthesized 1,2,3-triazole-ring containing monomers for the use of vinyl-based polymerization. Utilizing a one-pot synthesis methods containing all reactants (1-trimethylsilyl-2-vinyl acetylene, alkyl/aryl halides, Cu(I), sodium azide) in the presence of free radical initiator AIBN, R. J. Thibault was able to synthesize monomers containing additional properties not typically found in similar commodity monomers. These properties including: aromaticity, functionality, and polar bonding[3] of which can be attributed to a wide range of alkyl/aryl or mesylate starting materials.[4-6] Click reactions have also been utilized for: design of block copolymers, post-functionalization, and even polymerization [6-10]

Polycondensation reactions commonly used in the design of block copolymers can often result in polymers containing block lengths dependent on solubility and reaction conditions. The macroreagent block copolymerization approach commonly yields polymers which contain large homopolymer impurities resulting in tedious purification. In contrast, click chemistry provides the ability to independently synthesized polymers to be copolymerized providing better control over block length. Alkyl end-functionalized P3HT and azide functionalized poly(9′,9′–dioctylfluorene) (PF) were click coupled, by R. Verduzco et al., in the presence of CuI catalyst.[11] Providing a new synthetic route in which starting polymers could be previously purified before coupling resulting in better defined

copolymerized materials. Similarly to block copolymer coupling, poly(vinylacetylene) and azide functionalized dendrons provide a 1,2,3-triazole ring linked linear backbone with dendritic pendant groups, resulting in polymers containing properties such as: site-isolation in catalysis, drug delivery, and nano-scale electronics.[11] Designing improved polymers, J. M. J. Frechet et al. have shown the potential that click chemistry provides in post-modification of alkyne functionalized materials.[12, 13]

Requiring alkyne and thiol-functionalized starting materials, Thiol-yne chemistry provides the benefit of no longer using transition-metal catalysts [14], currently making thiol-based click chemistry the ideal choice for biomedical applications.[15-17] Four-, three-, and two-armed star alkyne and thiol-terminated PEG chains were utilized in thiol-yne click reactions by A. P. Dove et al. resulting in thiol alkene hydrogel products.[14, 18] These resulting hydrogels showed promising mechanical properties with the ability to be tuned according to specific applications.[14] Radical thiol-yne based polymerization has become the more popular pathway for the synthesis of materials ranging from linear polymers to block copolymers due to robust synthesis and rapid reaction rates.[14, 19, 20] Using photochemical or nucleophilic catalysts, depending on the electrophilicity of the alkene in use, thiol-yne chemistry eliminating the need to use transition-metal catalysts. [21-23] Thiodendrimers were synthesized using tris-alkene core 2,4,6-triallyloxy-1,3,5-triazine and 1-thioglycerol. Requiring catalytic amounts of photoinitiator 2,2-dimethoxy-2-phenylacetophenone. Fourth generation dendrimers were successfully synthesized using no solvents requiring 30 minute

reaction times. [24] While these traits make thiol-yne/thiol-ene chemistry promising, they also tend to be their limitations; their orthogonality can be compromised, resulting in undesirable side reactions. With respect to this issue, shelf-life/stability for many thiol-yne based formulations are drastically limited. [21] In addition, the unpleasant odor emitted from these reactants in combination with lower molecular weight polymer products could tip the scales in favor of a different synthetic route.

Project Rationale:

Click-ene chemistry further expands the click chemistry field by taking some strengths of both thiol- and carbon-based click chemistry in the effort to eliminate some of the pitfalls presented by previous methods. In click-ene chemistry, commodity alkenes and azides are reacted in catalyst-free, neat reaction conditions. This, like tradition click chemistry, provides a 1,2,3-triazole ring configuration providing the favorable properties of metal-ion coordination, large dipole-moments, acid/base solubility, and hydrogen bonding.[5] Toward this end, we have synthesized various click-ene small molecules, AB functional monomers, and polymers. This small catalog of molecules demonstrates the ease, and potential click-ene chemistry provides. While azole ring containing small molecules show the controllability of click-ene chemistry, the “click-ene” synthesized polymers represent an important step in the evolution of click-ene chemistry. The polymers were synthesized via transesterifications with monomers containing an azole ring in the backbone, as well as polymerization

via “click-ene” chemistry. This establishes the ability to design either monomers or small molecules through click-ene chemistry, in addition to bulk/melt polymerize vinyl/azide functionalized starting materials resulting in azole ring polymerized polymers with high yields, purities, and most notably solvent/catalyst free.

CHAPTER II

Literature Review

Click Chemistry

Click chemistry has became a powerful tool among chemist since its discovery by Dr. K.B. Sharpless et al. in 2001. With the inspiration of nature and the petroleum chemical industry, and all the products they provide, it is easy to see why carbonyl chemistry would be of great importance to know/understand and improve upon. With the concept of C-C bonds being “currency” simply requiring “cracking”, as Dr. Sharpless states, to reform allowing for utilization where more reactive species are required there is no misunderstanding as to why Dr. Sharplesss and his lab would set out to create a efficient modular system as they did with Click Chemistry.

Click Chemistry sets out to take the C-C bond “currency” and exchange it for new currency of which must follow a strict set of requirements. First, small hetero atom units must reliably link together in both small and large scale reactions alike. Secondly, reactions should be region-selective resulting in high yields of the desired product without the production of any offensive side products. [1, 2] These products must be able to be isolated with minimal effort ideally without the use of chromatographic methods.[1] Thirdly, simple reaction

conditions should be maintained resulting in water solubilized or neat reaction environments, These environments should contain commodity starting materials once again requiring little to no effort to separate upon reaction completion. [1] All of this was achieved by Dr. Sharpless and his team due to the use of highly reactive orthogonal starting materials leading to high thermodynamic driving forces resulting in rapidly completing “spring-loaded” reactions.[1] Cycloaddition of unsaturated species, nucleophilic substitution chemistry, carbonyl chemistry and addition to carbon-carbon multiple bonds have been listed as the most common reactions fulfilling these stringent reaction condition requirements.[1]

Thiol-yne Chemistry

Reactions between alkynes and thiol based compounds, known as thiolyne chemistry, provides advantages over similar click chemistry of being able to use photoinitiation as seen below in Figure 1

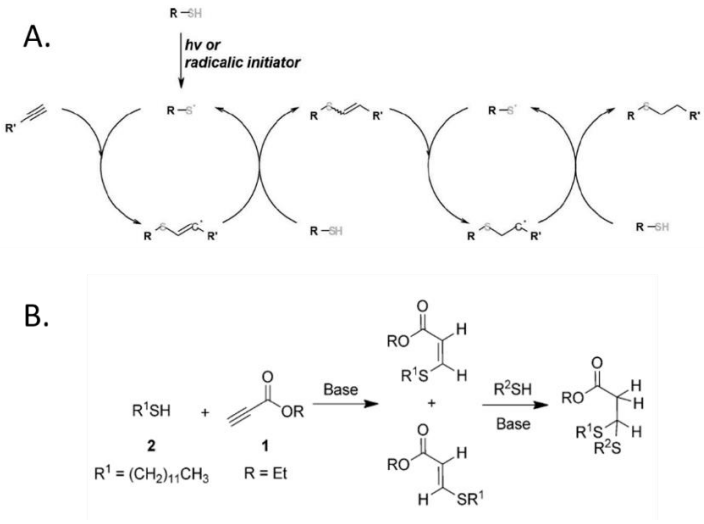


Figure 1. A) Photo-Initiated Thiol-yne reaction Mechanism [25] B) Nucleophilic Base-Catalyzed Reaction Mechanism [10]

With the recent advances in carbon based click chemistry it was only a matter of time before other types of reactive groups were introduced. Thiol-yne click reactions have proven to be a promising addition to the click chemistry family. Not unlike thiol-ene reactions the thiol-yne mechanism can be utilized both through nucleophilic and radical pathways. [8] Requiring alkyne and thiol functionalized starting materials, this time with the benefit of no longer requiring transition-metal catalyst currently makes thiol based click chemistry the ideal click chemistry choice when biomedical applications are in mind. Radical thiol-yne based polymerization has become the more popular pathway in the synthesis of materials ranging from linear polymers all the way to block copolymers due to it being transition-metal free and the ability to be photochemically induced. [9, 10] In contrast, the nucleophilic pathway has also begun to be utilized in the area of elastomers due to the efficiency and speed at which the reactions undergo, once again due to the highly reactive reactants. [9] While these traits make thiol-yne chemistry promising it also tends to be its downfall. Due to their reactivity their own orthogonality is compromised possibly resulting in undesirable side reactions. With respect to this issue shelf-life/stability for many thiol-yne based formulations are drastically limited. In addition, the odor emitted from these reactants could potentially outweigh the positives of the reactions due to typically on achieving lower molecular weight polymers.

Thiol-ene Chemistry

Similar to thiolyne chemistry, thiol-ene chemistry uses alkenes and thiols in a click reaction once again taking advantage of photoinitiation as seen below in figure 1.

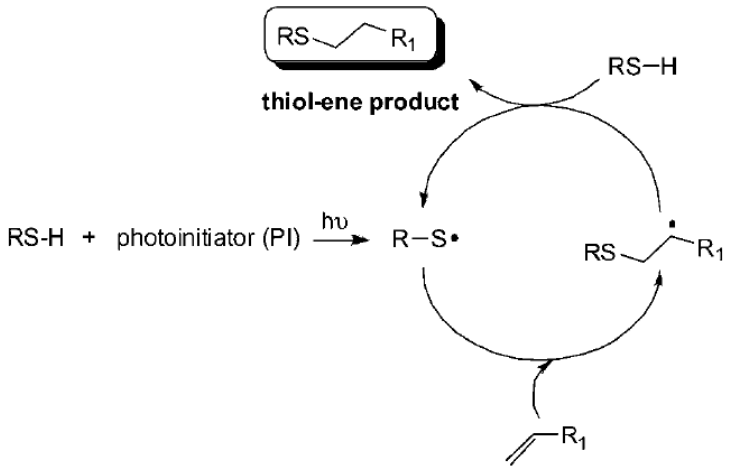


Figure 2. Photoinitiated thiol-ene mechanism [26]

Not unlike thiol-yne chemistry thiol-ene chemistry looks to expand the click chemistry family in adding the use of alkene and thiol based starting materials. Once again avoiding the difficult to remove transition-metal catalyst from the equation, thiol-ene chemistry uses photochemical or nucleophiles to catalyze the reactions depending on the electrophilicity of the alkene in use. [9, 12, 13] Once again achieving almost quantitative yields with reaction time taking seconds to minutes thiol-ene based click chemistry looks to be another good choice when transition –metal catalyst contamination is in mind. [9] [10] [25] [9-11] This being said thiol-ene click chemistry still suffers from similar issues thiol-yne chemistry

endures (odor, overly reactive species, short shelf-life, etc.) but not at the expense of a powerful tool to add to the click chemistry toolbox. [9, 10, 12, 13]

Monomer Synthesis

With click chemistry established as a quick and viable method a sudden surge in the click chemistry world appeared. Now monomers/small molecules for later use could be quickly synthesized. R.J. Thibault et al. quickly took some of the first steps in developing monomers for the use of vinyl based polymerization. Previously vinyl polymers typically had specific desired properties at the detriment of other properties that often would be desired due to lacking synthetic routes.[3] Now with the use of click chemistry this was no longer the case. Combining aromaticity functionality, and polar bonding together via click chemistry resulted in polymers containing many more desirable traits.[3]

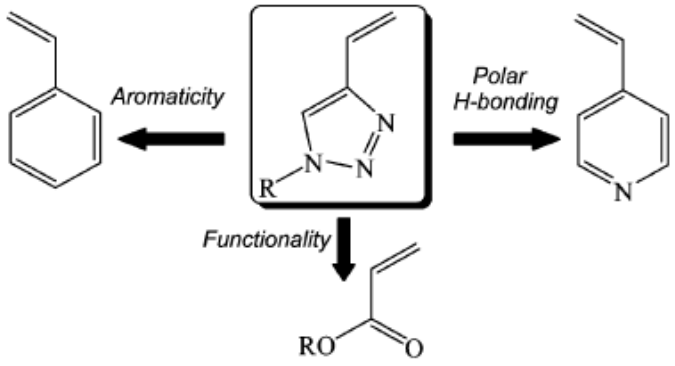


Figure 3. Structural similarities between the 4-vinyl-1,2,3-triazole monomer family and traditional vinyl systems [3]

In addition, these monomers could be made in a one pot synthesis driven by the orthogality click chemistry provides due to a wide range of alkyl/aryl or mesylates that can be utilized as reactants. [3-5]

While commonly mistaken as simply a passive linker the triazole ring posses many desirable properties further improving the traits of the small molecule/monomer and consequently the resulting polymer. [3, 4] The azole ring possesses noteworthy electron features including electron rich ring configuration capable of forming π-π interactions, metal-ion coordination and hydrogen bonding via nitrogen atoms as well as a strong dipole moment. [3, 4] This provides a plethora of possible applications as well as versatile work conditions commonly being soluble in many commodity solvents.

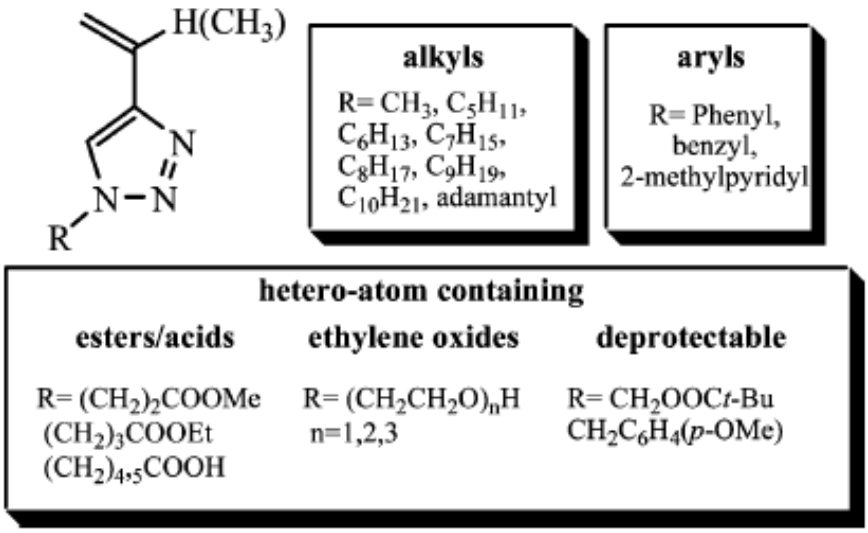


Figure 4. Examples of structural and functional diversity in 4-vinyl-1,2,3-triazole monomer library [3]

Polymer Synthesis

With polymers becoming more and more prevalent it wouldn't be unreasonable to consider this the plastics age. While less robust sounding than the Iron Age or Stone Age, plastics provide opportunity not found in any era to date. With the ability to tune the resulting material in accordance to the resulting application polymers have never been so versatile or, as a result, abundant. Coming in various viscosities, shapes and sizes there seems to be no end in sight as to what polymers can do.

The recent addition of click chemistry has drastically effected the polymer industry through monomer synthesis and much more. Finding roots in dendrimer synthesis, bio-conjugate synthesis, and post-functionalization/ surface modification of nano-structures and other useful substrates.[5] Click Chemistry is an ever evolving into an increasingly powerful tool for not only small molecule chemists but polymer chemist alike.

As previously stated the reaction between alkynes and azides are conducted, in this case, in aqueous media and catalyzed with copper (I) species generating a redox reaction of $CuSO_4$ with sodium ascorbate. [5, 6] These click reaction conditions, while standard, are ideal for dendrimers as linear polymers achieve too high molecular weights and precipitate out of solution as a result.[5] In addition to this potential issue, solubility can become a problem solved by the use of a bi-solvent heavily favoring polar organic solvents.[5] With the issue of solvent resolved AB_2 monomers were designed for the quick and easy synthesis of dendrimers using click chemistry. Unfortunately, the orthogonality that made

click chemistry so useful also limits this AB_2 system as its shelf-life is limited due to its high reactivity. The ability to self oligomerize due to the AB_2 system A_2+B_3 (**Figure 3**) systems were quickly designed once again providing new obstacles to overcome this time in the form of cross-linking or gelation concerns resulting in an insoluble network formation.[6] This issue can be easily overcome by monitoring the reaction closely and quenching just before gelation but the resulting polymer are usually only solubilize in highly polar solvents such as DMSO/DMF.[5] In this regard catalyst $Cu(PPh_3)_3Br$ was used resulting in polymers showing excellent solubility in a plethora of commodity organic solvents including THF, chloroform and dichloromethane. [5, 6]

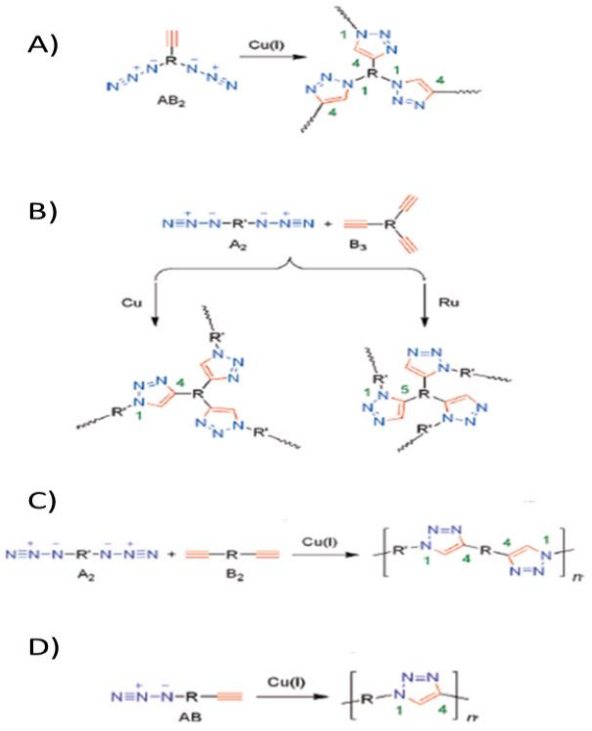


Figure 5: Examples of various Click chemistry synthetic strategies **A)** AB_2 **B)** A_2 + B_3 **C)** A_2 + B_2 **D)** AB [5]

Despite all these efforts a few drawbacks of click chemistry still remain. First, in the use of polymerization click chemistry provides lethargic reaction times occasionally taking upwards of two weeks for reaction completion. In addition to long reaction times, resulting polymer products often provide poor solubility proving difficult to deal with. These issues can both be solved with proper catalyst selection but not without new issues arising. Expensive and cytotoxic transition metal catalyst such as CuI, $Cu(PPh_3)_3Br$ and $Cp^*Ru(PPh_3)_2Cl$ prove difficult to fully remove which becomes problematic when polymers are being created with biological systems/applications are intended thus a metal-free polymerization system is highly desirable.

Post-functionalization of polymers

Click chemistry is a strong tool in post functionalization. Allowing for quick and efficient functionalization of any desired functionality with simple reaction conditions.

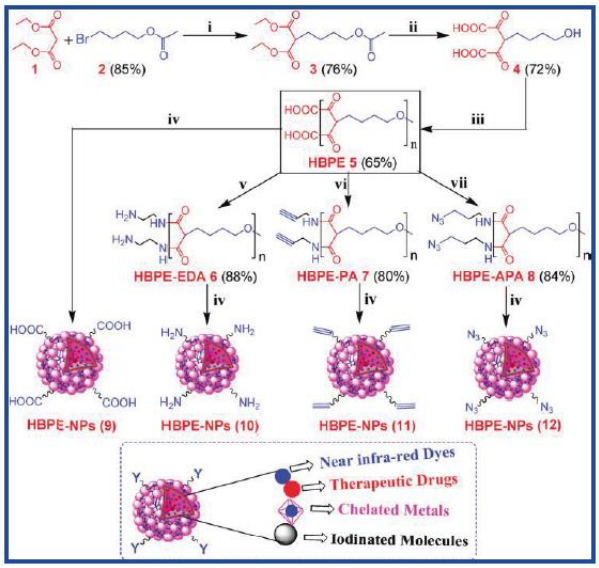


Figure 6. Click Chemistry used in the post-functionalization of hyper-branched nanoparticles [8]

With the boom of the polymers and their applications comes new applications some of which require attention even after the general product is made. A great example of this is biomedical research and the use of dendrimers, hyper-branched nanoparticles, and other similar platforms used in the targeting and delivery of various compounds resulting in great advance in imaging and treating of various diseases, commonly cancer. Post-functionalization is the modification of a material, in this case (but in no way limited to) polymeric nanoparticles, surface groups (typically carboxylic acid) to bind a ligand of other targeting molecule like folate to be attached to the surface of the nanoparticle/sub-straight. This functionalization allows for cancer cell specific targeting of the nanoparticle/dendrimer, drastically increasing the effectiveness of the nanoparticle due to the “lock and key” style mechanism provided by surface post functionalization of desired targeting molecules/ligands. With applications of this nature in mind, the same guidelines set by Dr. Sharpless must be followed in addition to other safety concerns that come into effect when dealing with biological systems. Click chemistry once again provides a promising synthetic route in which alkyne functionalized hyper-branched nanoparticles and azide-functionalized targeting molecules (or vice versa), in the presence of CuI catalyst can react in a now azole ring linked functionalized nanoparticle.[7, 8] Once again containing the properties of the nanoparticle and its cargo, the targeting abilities of the targeting molecule as well as the azole ring and the increased solubility it provides improving the effectiveness of the nanoparticle where high water solubility is required.

Click-ene Chemistry

Click-ene chemistry looks to further expand the click chemistry choices by taking some strengths of both thiol and carbon based click chemistry in the effort to compromise between some for the pitfalls present by both mechanisms. In click-ene chemistry highly strained commodity alkenes and azides are reacted with the lack of transition-metal catalyst in neat reaction conditions. This once again provides a 1,2,3-triazole ring configuration containing the positive properties of aromaticity, large dipole moments, acid/base stability, and hydrogen bonding. In addition, reactions were completed in short reaction timeframes of only 12-24 h depending on the electrophilicty of the alkene present.

CHAPTER III

METHODS AND EXPERIMENTAL SECTION

Experimental Section:

1. Materials and instrumentations. Sodium azide, DMF, allyl chloride, 4-hydroxybenzoic acid, propylene oxide, titanium(IV) isopropoxide, decene, 4-phenylbutene, 3-phenylpropylbromide, dibromohexane, DMSO, $CDCl_3$ were purchased from Acros Organic and used without further purification. Potassium carbonate (K_2CO_3), sulfuric acid, anhydrous ethanol, hexane, ethyl acetate, methylene chloride, acetonitrile were purchased from Fisher Scientific and used as received.

Infrared spectra were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer using TMS as an internal reference. Gel permeation chromatography (GPC) results were obtained using a JASCO MD 2010 Plus instrument with a PD 2020 light scattering detector. Thermal Gravimetric Analysis (TGA) were preformed on a TA instruments, TGA 550, Discovery series, sample sizes of 7-10 mg under dry nitrogen atmosphere. MALDI-TOF results were recorded on a Bruker Microflex instrument. Analytical Thin Layer Chromatography (TLC) was performed on glass plates coated with silica gel GF

254 and were visualized under iodine vapor. Flash column chromatography was carried out using neutral alumina.

2. Proof-of-concept small molecule reactions using "Click-ene" chemistry.

*2a. Synthesis of hexyl azide and 3-benzylpropyl azide (**1,2**):* The corresponding bromo-derivatives (hexyl bromide or 3-benzylpropyl bromide) (1.0 g, 0.10 mol) and sodium azide (0.50 mol) were mixed in a 50 mL round bottom flask containing 20 mL of DMF. The reaction mixture was heated at 75 ^{o}C for 24 h. The reaction mixture was washed with water and extracted using ethyl acetate. The product solution was dried over anhydrous Na_2SO_4, the resulting pure product was rotary evaporated until solvent free and stored at 4 ^{o}C for characterizations and further use.

Yield (*hexyl azide*, **1**): 0.65 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.90 (m, 3H), 1.32 (m, 2H), 1.60 (m, 2H), 3.25 (m, 2H). IR: 2958, 2931, 2861, 2109, 1739, 1685 cm^{-1}.

Yield (*3-benzylpropyl azide,* **2**): 0.66 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, J Hz): 0.90 (m, 3H), 1.32 (m, 2H), 1.60 (m, 2H), 3.25 (m, 2H). IR: 2958, 2931, 2861, 2109, 1739, 1685 cm^{-1}.

*2b. Synthesis of small molecule-based "Click-ene" products (**3**-**5**): neat a*lkene precursors (decene and 4-phenyl butene) (1.0 g, 1.0 mol) and azide derivatives (**1**-**2**, 1.0 mol) were mixed in a 25 mL round-bottom flask. The reaction mixture was heated at 80 ^{o}C and continued stirring overnight. The reaction was then

cooled to room temperature and characterized without any further purification. The yields were reported assuming reaction completion as indicated by the spectroscopic analyses.

Yield (*1-hexyl-4-octyl-4,5-dihydro-1H-1,2,3-triazole,* **3**): 1.87 g (93%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.88 (m, 3H), 1.27 (m, 2H), 2.1 (m, 1H), 2.29 (m, 1H). ^{13}C NMR (75 MHz, CDCl3, δ ppm): 14.12, 22.71, 25.84, 26.73, 28.9, 29.46, 31.6, 32.8, 54.45, 63.3, 69.82. IR: 2923.4, 2852.3, 1669, 1461.3, 1372.3, 906.73, 719.88 cm^{-1}.

Yield (*1-hexyl-4-phenylethyl-4,5-dihydro-1H-1,2,3-triazole,* **4**): 1.92 g (98%). ^{1}H NMR (300 MHz, CDCl3, δ ppm): 0.90 (m, 3H), 1.32 (m, 2H), 1.58 (m, 2H), 2.13 (m, 2H), 2.26 (m, 2H), 2.77 (m, 1H), 7.21 (m, 10H). ^{13}C NMR (75 MHz, CDCl3, δ ppm): 14.04, 21.94, 27.32, 28.84, 30.9, 31.26, 33.6, 54.5, 63.78, 70.24, 125.75, 128.2, 142.97. IR: 3188, 2980, 1557, 1589, 1516, 1443, 1370 cm^{-1}.

Yield (*4-octyl-1-(3-phenylpropyl)-4,5-dihydro-1H-1,2,3-triazole,* **5**): 2.14 g (95%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.89 (m, 3H), 1.29 (m, 2H), 1.90 (m, 1H), 2.16 (m, 1H), 2.32 (m, H), 2.70 (m, H), 7.26 (m, H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.3, 22.64, 25.7, 29.54, 30.9, 32.36, 54.1, 63.78, 70.1, 126.3, 128.9, 143.2. IR: 2923, 2855, 1719, 1455, 1265, 737 cm^{-1}.

3. Synthesis of "Click-ene"-based functional monomer (10) and polyester polymer (11).

*3a. Synthesis of ethyl 4-hydroxybenzoate (**7**).* 4-Hydroxybenzoic acid **(6)** (10 g, 0.0724 mol) and anhydrous ethanol (150 mL) were added to a 250 mL round-bottom flask. Concentrated sulfuric acid (3 mL) was added and heated to 80 ^{o}C and reflux for 6 h. The reaction mixture was then neutralized using solid $NaHCO_3$, diluted with water followed by extraction with ethyl acetate. The product was recrystallized using methanol and water solvent combination.

Yield (**7**): 10.11 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.38 (m, 3H), 4.35 (m, 2H), 6.88 (m, 1H), 7.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.64, 61.04, 114.32, 122.30, 130.9, 160.26, 167.1. IR: 3188, 2980, 1557, 1589, 1516, 1443, 1370 cm^{-1}.

*3b. Synthesis of ethyl-4-(allyloxy)benzoate (**8**).* The protected 4-hydroxybenzoic acid (**7**, 0.250 g, 0.0015 mol) and allyl chloride (0.172 g, 0.00225 mol) were added into a 50 mL round-bottom flask containing 10 mL of DMF. Oven dried K_2CO_3 (0.622g, 0.0045 mol) was added to the reaction mixture and was stirred at 80 ^{o}C for 24 h. The resulting mixture was added to water (100 mL), extracted using ethyl acetate and dried over anhydrous Na_2SO_4. The product was dried using vacuum and no further purification was required.

Yield (**8**): 0.27 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.38 (m, 3H), 4.34 (m, 2H), 4.60 (m, 1H), 5.40 (m, 2H), 6.04 (m, 1H), 6.94 (m, 1H), 7.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.47, 60.74, 70.69, 113.18, 117.95, 123.13, 130.59, 133.7, 162.1, 166.45. IR: 2983, 2905, 1709, 1505, 1248, 1158, 1100, 1015, 847, 758 cm^{-1}.

*3c. Synthesis of 1-azidopropan-2-ol (**9**).* Propylene Oxide (10 g, 0.172 mol) and sodium azide (55.97 g, 0.86 mol) were added to a 250 mL round-bottom flask containing 120 mL distilled water. The reaction was continued at 75 ^{o}C for 24 h after which the product was extracted using ethyl acetate. The product was dried using anhydrous Na_2SO_4 and rotary evaporated to obtain the pure product.
Yield (**8**): 15.49 g (89%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.19 (m, 3H), 2.86 (m, 1H), 3.22 (m, 1H), 4.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 20.28, 58.29, 66.81. IR: 3368, 2985, 2903, 2085, 1748, 1251 cm^{-1}.

*3d. Synthesis of ethyl 4-[(1-(2-hydroxypropyl)-4,5-dihydro-1H-1,2,3-triazol-4-yl) methoxy] benzoate AB monomer (**10**).* Ethyl-4-allyloxy benzoate (**8**, 0.2577 g, 0.0015 mol) and propylene oxide azide (**9**, 0.1796 g, 0.0015 mol) were added to a 5 mL round-bottom flask and heated overnight at 80 ^{o}C.
Yield (**10**): 0.42 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.22 (m, 3H), 1.36 (m, 3H), 2.02 (m, 1H), 2.39 (s, 2H), 2.87 (s, 2H), 3.28 (m, 1H), 3.81 (m, 1H), 4.12 (m, 2H), 4.32 (m, 2H), 6.91(m, 2H), 7.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.47, 21.48, 53.18, 58.8, 60.68, 62.72, 67.33, 115.22, 123.4, 130.56, 162.09, 166.35. IR: 3357, 2974, 2931, 2098, 1707, 1603, 1245, 1158, 1102, 758 cm^{-1}.

*3e. Synthesis of "Click-ene"-based polyester polymer **(11)**.* Ethyl-4-[(1-(2-hydroxypropyl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)methoxy] benzoate AB monomer

(**10**, 0.250 g, 0.00081 mol) and titanium(IV) isopropoxide (2.5 mg, $8.8x10^{-6}$ mol) were added to a 5 mL round-bottom flask and heated to 100 ^{o}C under continuous N_2 flow for 6 h. The reaction was then placed under reduced pressure (0.2 mm/Hg) for 6 h, while maintaining the temperature. The polymer was found to be soluble in DMF, DMSO or chloroform, and insoluble in water. It was purified by precipitating in water from a concentrated DMF solution. The resulting product was centrifuged and dried under vacuum to get pure polymer.

Yield (**11**): 78%. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.03 (m, 3H), 1.27 (m, 3H), 1.8 (m, 1H), 2.89 (s, 2H), 3.36 (s, 2H), 3.79 (m, 1H), 4.14 (m, 1H), 4.26 (m, 2H), 7.07 (m, 2H), 7.9(m, 2H), 7.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.47, 21.48, 53.18, 58.8, 60.68, 62.72, 67.33, 115.22, 123.4, 130.56, 162.09, 166.35. IR: 3357, 2974, 2931, 2098, 1707, 1603, 1245, 1158, 1102, 758 cm^{-1}.

4. Synthesis of aromatic "Click-ene" polymer (15).

*4a. Synthesis of 1,4-bis(allyloxy)benzene (**13**).* Hydroquinone (**12**, 2.0 g, 0.0182 mol) and allyl chloride (4.17 g, 0.0545 mol) were added to a 100 mL round-bottom flask containing DMF (25 mL). Potassium carbonate (12.55 g, 0.091 mol) was added and the reaction was refluxed at 80 ^{o}C for 12 h. The resulting reaction mixture was filtered, followed by the addition of water and extracted from ethyl acetate. The product solution was dried over anhydrous Na_2SO_4, rotary evaporated and purified using a flash column chromatography using hexane/ethyl acetate as eluent.

Yield: 2.839 g (82%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.51 (m, 2H), 5.30 (m, 2H), 5.44 (m, 2H), 6.07 (m, 2H), 6.86 (s, 2H). ^{13}C NMR (75 MHz, CDCl3, δ ppm):69.54, 114.71, 119.65, 132.44, 152.89. IR: 2929, 2856, 1666, 1507, 1385, 1258, 1090 cm^{-1}.

*4b. Synthesis of 1,6-diazidohexane (**14**).* 1,6-dibromohexane (10 g, 0.041 mol) and sodium azide (11.8 g, 0.182 mol) were placed in a 250 mL round-bottom flask containing DMF (100 mL). The reaction was heated to 75 ^{o}C for 24 h. Water was added to the reaction followed by extraction using ethyl acetate. The product solution was dried over anhydrous Na_2SO_4 and the resulting pure product was rotary evaporated and stored at 4 ^{o}C for characterizations and further use. Yield (**14**): 6.9 g (95%). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.4 (m, 8H), 1.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 26.42, 28.81, 51.30. IR: 2938, 2853, 2088, 1737, 1677, 1240, 1088, 1043 cm^{-1}.

*4c. Synthesis of Click-ene polymer **(15)**.* 1,4-bis(allyloxy)benzene (**13**, 0.3385 g, 0.0018 mol) and 1,6-diazidohexane (**14**, 0.41g, 0.0025 mol) were added to a 5 mL round-bottom flask and heated to 100 ^{o}C under N_2 for 12 h. The reaction was then placed under reduced pressure (0.2 mm/Hg) for 6 h, while maintaining the temperature. The polymer was found to be soluble in DMF and DMSO, where insoluble in acetonitrile and water. It was purified by precipitating into acetonitrile from a concentrated DMF solution. The resulting product was centrifuged and dried under vacuum to get pure polymer.

Yield (**15**): 85%. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.29 (s, 8H), 1.5 (s, 2H), 2.13 (s, 1H), 2.21 (s, 2H), 2.72(s, 2H), 3.28 (s, 2H), 3.61 (m, 1H), 5.23 (m, 2H), 5.39 (m, 1H), 5.99 (m, 2H), 6.54 (s, 2H), 6.85 (s, 2H). ^{13}C NMR (75 MHz, DMSO, δ ppm): IR: 2931, 2856, 2093, 1557, 1594, 1505, 1456, 1385, 1215 cm^{-1}.

5. Synthesis of aliphatic "Click-ene" polymer (18).

*5a. Synthesis of 2,2'-allyloxymethyl-propanoic acid (**17**).* 2,2-Bis(hydroxymethyl)propionic acid **(16**, 20 g, 0.149 moles) and KOH (66.88 g, 1.191 moles) was added to a 500 mL round-bottom flask containing toluene (150 mL) and allyl chloride (57 g, 0.744 moles). To this reaction mixture, catalytic amount of DABCO was added. Subsequently, the reaction mixture was heated to 110 ^{o}C for 48 h with continuous stirring. The product was concentrated by evaporating toluene using a rotary evaporator. The resulting mass was loaded on to a column packed with silica gel for purification using hexane and ethyl acetate as eluent (3:1).

Yield (**17**): 21.70 g (68%), ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.24 (s, 3H), 3.61 (m, 2H), 4.00 (s, 2H), 5.25 (m, 2H), 5.85 (m, 1H), 10.5 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 17.98, 48.227, 71.895, 72.459, 76.819, 77.139, 77.459, 116.94, 134.64, 180.53. FT-IR: 2920, 1709, 1458, 1350, 1250, 1097 cm^{-1}.

*5b. Synthesis of aliphatic "Click-ene" polymer (**18**). 2,2'-allyloxymethyl-propanoic acid (**17**,* 5.0 g, 0.0234 moles) and 1,6-diazidohexane (**14**, 3.93 g, 0.0234 moles) were added to a 25 mL round-bottom flask and heated to 100 ^{o}C under N_2 for 12

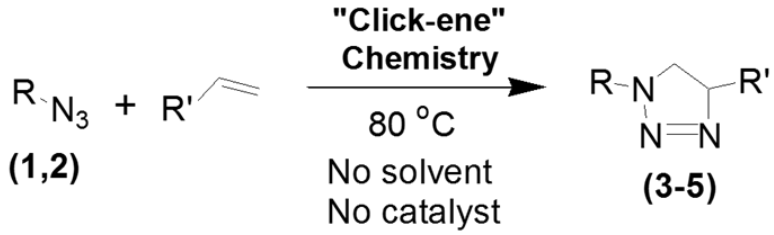
h. The reaction was then placed under reduced pressure (0.2 mm/Hg) for 3 h, while maintaining the temperature. The polymer was found to be soluble in DMF and DMSO, where insoluble in ethyl acetate and water. It was purified by precipitating in ethyl acetate from a concentrated DMF solution. The resulting product was centrifuged and dried under vacuum to get pure polymer.

Yield (**18**): 82%, ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.20 (m, 3H), 1.34 (m, 2H), 2.04 (s,), 3.54 (m, 2H), 3.96 (m, 1H), 4.13(m, 2H), 5.21(m, 2H) 5.85 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 14.32, 17.56, 18.58, 20.79, 26.42, 28.63, 48.75, 51.13, 60.17, 72.10, 116.41, 134.99, 170.96. FT-IR ($CHCl_3$): 3305, 2929, 2857, 2092, 1735 cm^{-1}

CHAPTER IV

RESULT AND DISCUSSION

Results and Discussion



Reaction #	R—N_3	R'	Product (3-5)
i)	1 (85%)		3 (93%)
ii)	1 (85%)		4 (98%)
iii)	2 (81%)		5 (95%)

Scheme 1: Proof-of-Concept, small molecule reactions for establishment of new "Click-ene" chemistry. (Note: percentages are yields)

Various triazole-containing compounds were synthesized as a proof-of-concept of proposed click-ene chemistry requiring only vinyl and azide functionality (**Scheme 1**). Using two different small molecule azides and alkenes, three 1,2,3-triazole ring containing molecules (3-5) were synthesized (reactions i-iii). This initial catalog of small molecules provided subsequent proof to design AB functional monomers. Additionally, polymer were synthesized to demonstrate the

modular synthesis capabilities of Click-ene chemistry providing further evidence of the formation of 1,2,3-triazole ring configuration construction providing multiple properties. Towards this end, we first synthesized azide derivatives (**1**,**2**) from hexyl bromide and 3-benzylpropyl bromide. The syntheses of these azides were confirmed by analyzing both IR and ^{1}H NMR spectra. As shown in **Scheme 1**, a series of small molecule reactions were carried out in effort to test proposed click-ene chemistry resulting in 1,2,3-triazole ring-based functional molecules **3**-**5**. Briefly, corresponding azides and alkenes were heated at 80 ^{0}C without using any solvent or catalyst. Examination of ^{1}H NMR spectra suggests 1,2,3-triazole ring construction via chemical shifts present at 2.21, 2.38 and 2.83 ppm (representing the carbon-carbon bonds of the azole ring) additionally, chemical shifts in the ranges of 5-6 ppm corresponding to vinyl functionality were absent upon reaction completion (**Figure 8**) indicating product synthesis. Analysis of IR resulted in a new band at 1637 cm^{-1} representative of a nitrogen-nitrogen double bond (**Figure 9**) present in triazole ring configuration click-ene chemistry provides. Additionally, the reduction of IR band present at 2100 cm^{-1}, representative of azide functionality, further proved the establishment of 1,2,3-triazole ring configuration synthesis due to starting material functionality conversion. To further test the capabilities of click-ene chemistry 1,2,3-triazole monomers and polymers were synthesized.

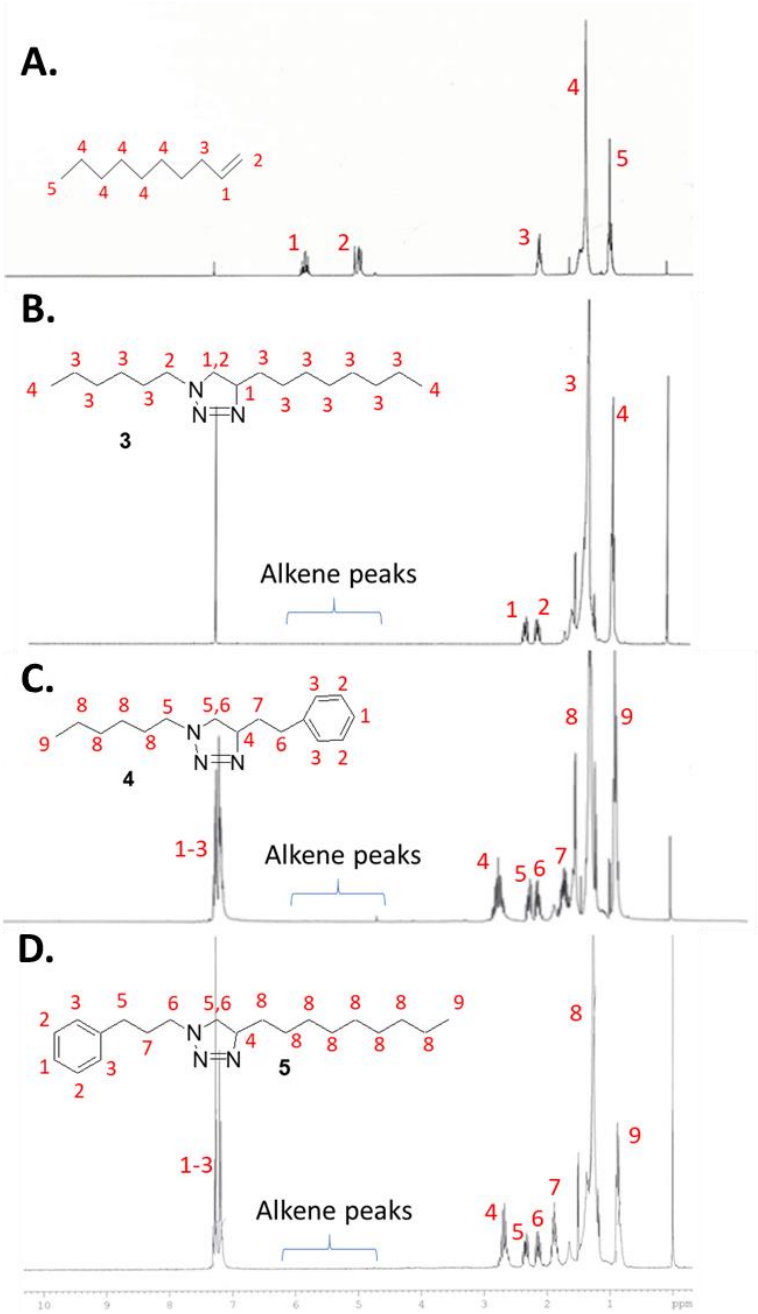


Figure 7: ^{1}H NMR spectra of **A)** hexyl azide starting material **B)** small molecule **3** **C)** small molecule **4** **D)** small molecule **5**

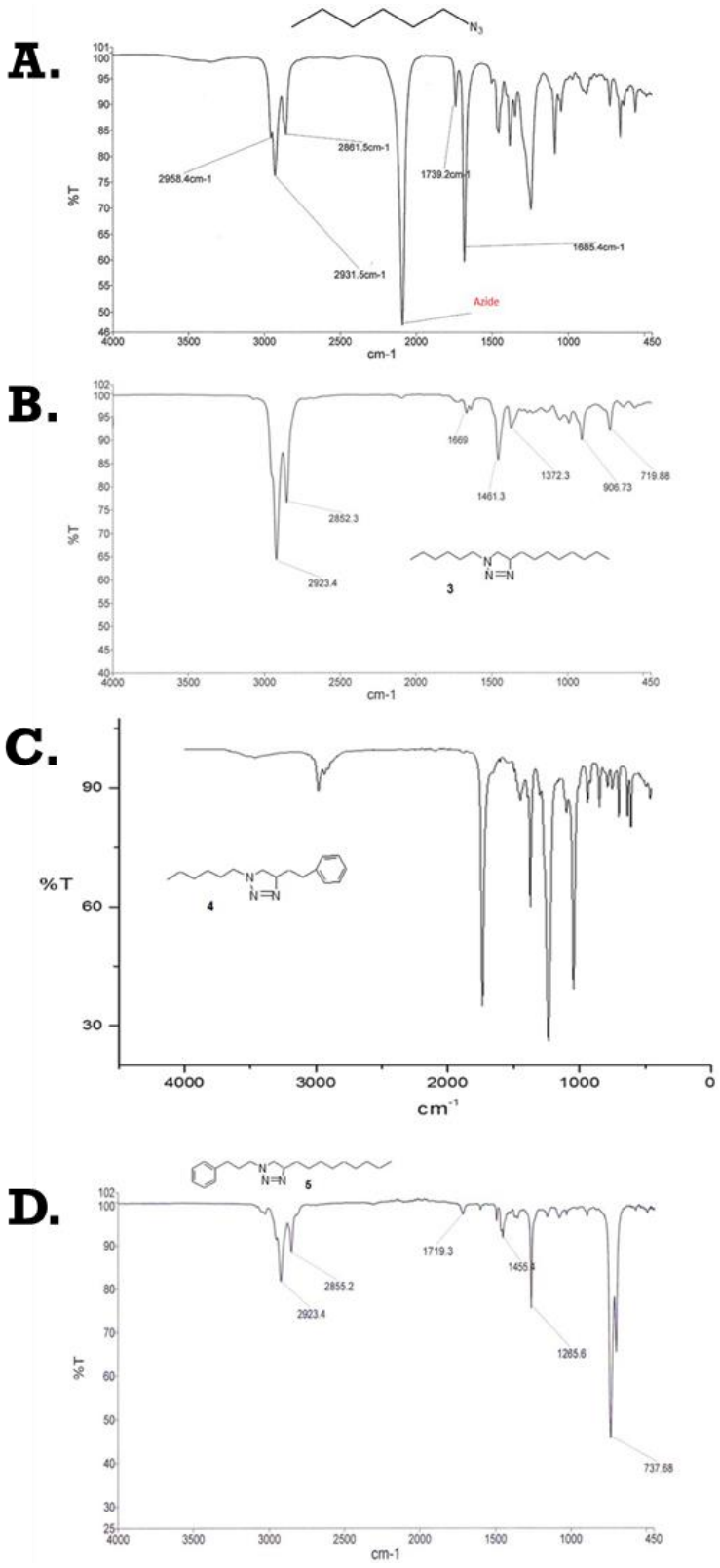
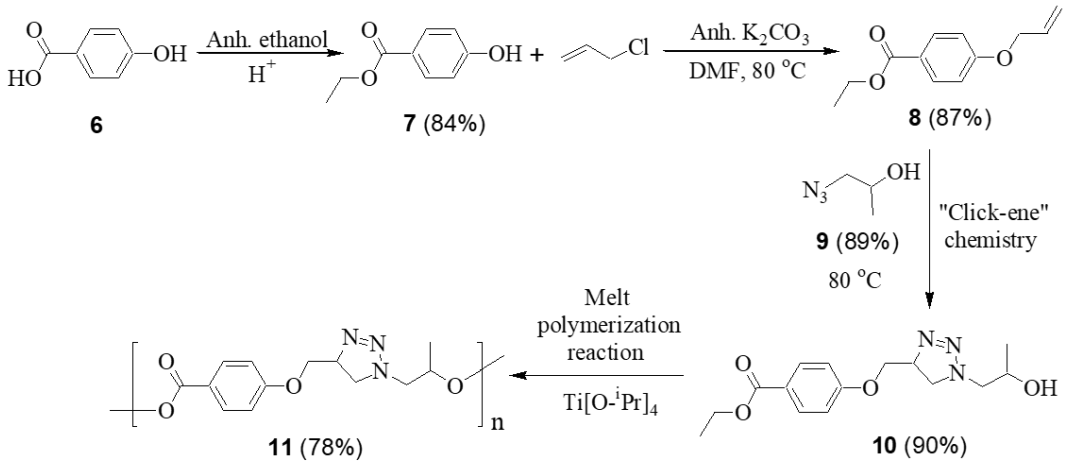


Figure 8: FT-IR spectra of **A)** hexyl azide starting material **B)** small molecule **3** **C)** small molecule **4** **D)** small molecule **5** showing azide peak disappearance

Synthesis of the Azole containing polyester polymer **(11)** was achieved by the selective protection of readily available 4-hydroxybenzoic acid **(6)** with anhydrous ethanol and catalytic amounts of sulfuric acid to yield an acid protected compound **(7)** (**Scheme 2**). Next, the protected product was purified using column chromatography, impurity spots were removed via 1:10 methanol:chloroform, efficacy was monitored using Thin-Layer Chromatograph (TLC) plates resulting in a white crystal. Product **(7)** was then reacted with allyl chloride using potassium carbonate as a base. The subsequent mixture was washed with water then extracted using ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed using vacuum and no further purification of product was required. The resulting compound **(8)** was then reacted with propylene oxide azide **(9)** Without solvent or catalyst to obtain the resulting monomer. This resulting click-ene monomer **(10)** was purified using column chromatography. After purification the monomer was polymerized via melt polymerization using catalytic amounts of titanium(IV) isopropoxide resulting in a polyester polymer **(11)**.



Scheme 2. Synthesis of "Click-ene" AB monomer (**10**) and polyester polymer (**11**)

The molecular weight of the Polymer **(11)** was determined by Size Exclusion Chromatography (SEC) giving a Mn of 29,900 (Mw = 68,770, and PDI = 2.3) Additionally, MALDI-TOF showed weights of monomer and polymer at about 307 Mw and 30,704 respectively (**figure 22**). All polymers were further characterized by ^{1}H and ^{13}C NMR and FT-IR spectroscopy (**Figure 10-12**) providing evidence of alkene/azide functionality conversion via alkene chemical shift (5-6 ppm) disappearance.The FT-IR spectrum showed transmittance peaks at 3359 cm^{-1}, 2971 cm^{-1}, 2932 cm^{-1}, 2100 cm^{-1}, 1707 cm^{-1}, and 1604 cm^{-1} once again confirming azole ring formation. Reduction in the azide peak (2100 cm-1) as well as the formation of a peak at 1604 cm^{-1} representing the nitrogen-nitrogen double bond that formed -(**Figure 12**). Thermal gravimetric analysis (TGA) showed moderate thermal stability (10% weight loss at 225ºC in air) of polymer (**11**) (**Figure 19**). As expected glass transition temperatures, provided by DSC,

aligned with those of aryl containing polyester polymers remaining just under 0 ^{0}C at -3.31 ^{0}C (**Figure 20**). [27]

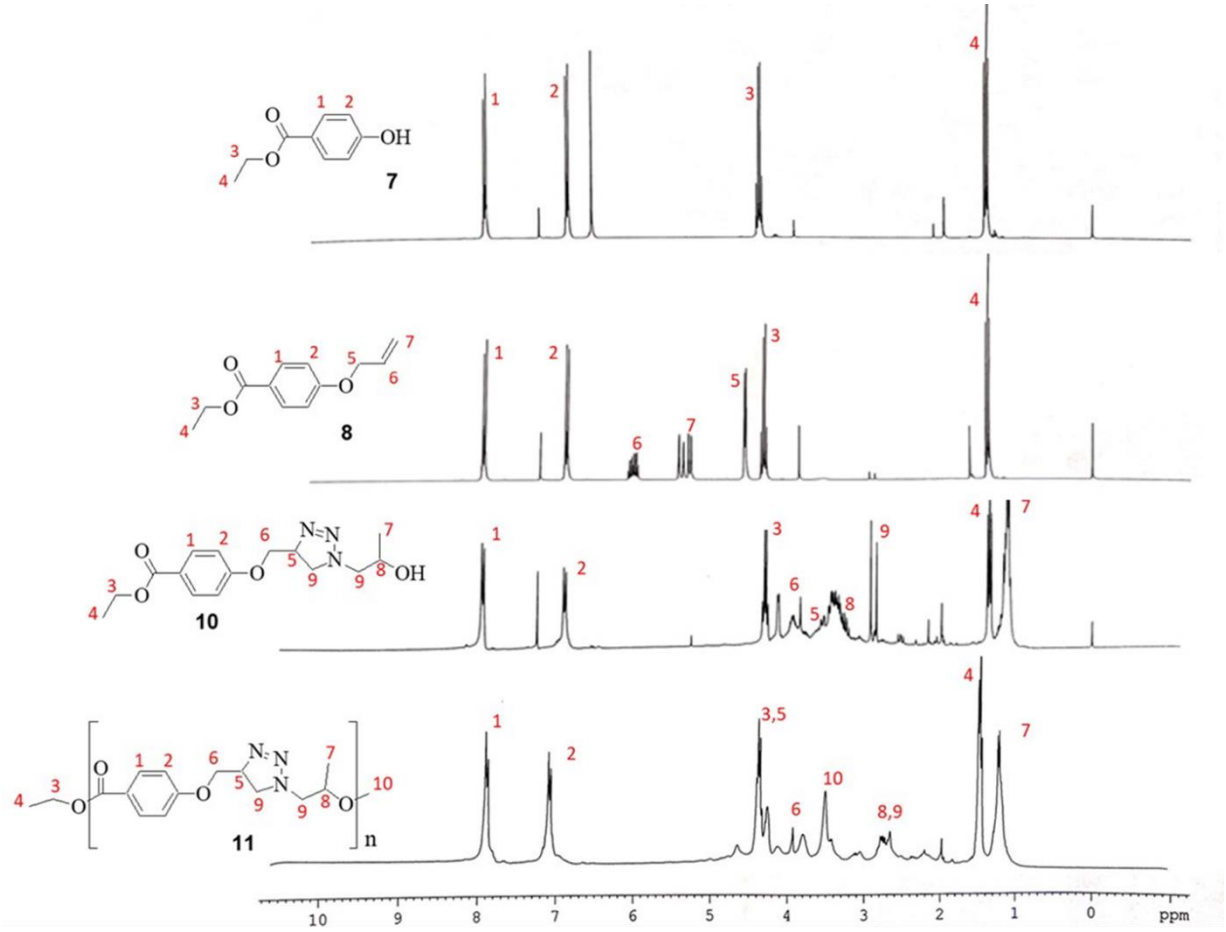


Figure 9: ^{1}H NMR spectra of “Click-ene” constructed AB monomer (**10**) and resulting polyester polymer (**11**)

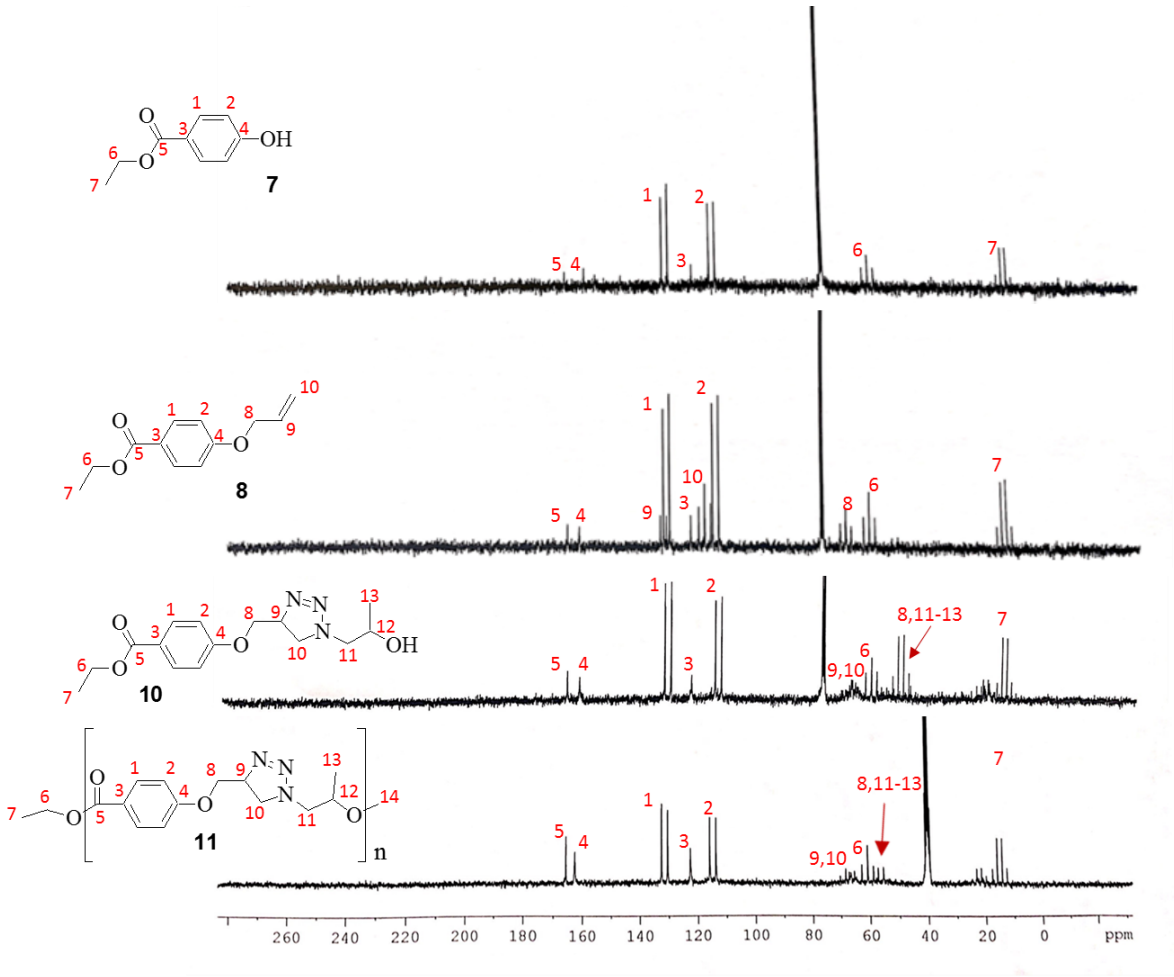


Figure 10: ^{13}C NMR spectra of “Click-ene” constructed monomer (**10**) and resulting polyester polymer (**11**)

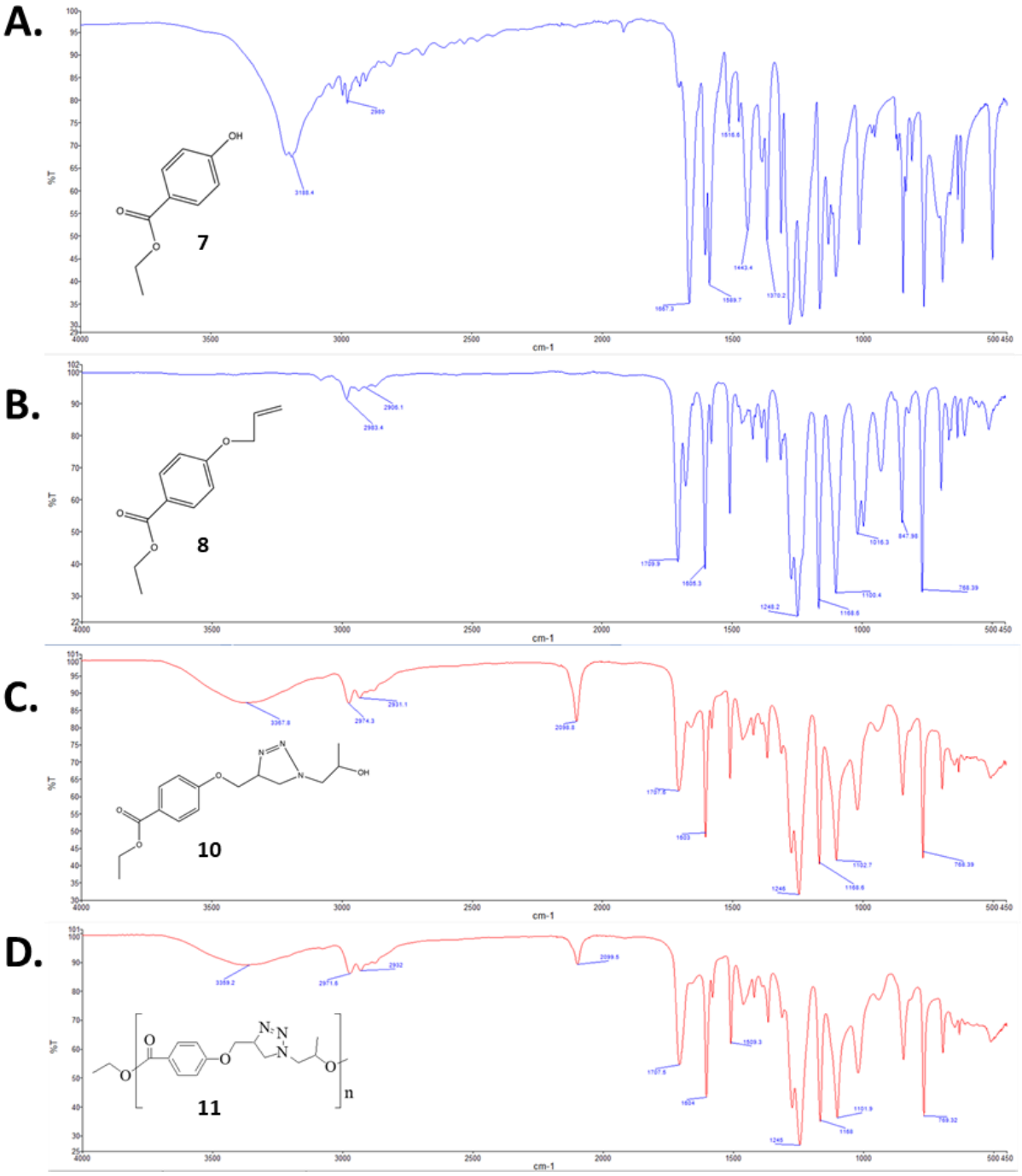
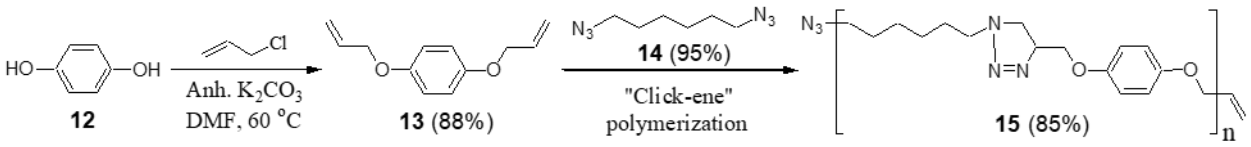


Figure 11: FT-IR spectra of **A)** Ethyl protected benzoic acid starting material **B)** subsequent vinyl functionalized starting material **7 C)** “Click-ene” constructed monomer **10 D)** resulting polymer **11**

Aryl Based Click-ene Polymerization:

With the synthesis of a click-ene based AB monomer confirmed, click-ene polymerization was tested in attempts to synthesize linear aromatic functional polymers in the absence of catalyst or solvents. The diallyl molecule **13** was synthesized by reacting hydroquinone (**12)** with allyl chloride using anhydrous potassium carbonate (**scheme 3**). The resulting diallyl (**13)** was purified using flash column chromatography. Synthesis of triazole ring containing polymers (**15)** were achieved by reacting the diallyl compound (**13)** with 1,6-diazidohexane (**14)** resulting in a diazole linked polymer which was insoluble in most solvents including: chloroform, THF, toluene. This is likely due to the long aliphatic chains resulting from the 1,6-diazidohexane (**14)**.



Scheme 3: Synthesis of aryl based “Click-ene” polymerized polymer **15**

Polymer **(15)** molecular weight was determined by Size Exclusion Chromatography (SEC) to be Mn 40,000 (Mw = 112,000 and PDI = 2.8) as well as MALDI-TOF showing weights of polymer about 41,904 (**Figure 22**). All polymers were further characterized by ^{1}H and ^{13}C NMR and FT-IR spectroscopy (**Figure 13-14**). FT-IR transmittance was tested resulting with transmittance bands providing evidence of azide functionality suppression (2093 cm^{-1}) and

nitrogen-nitrogen double bond formation (1667 cm^{-1}). Thermal gravimetric analysis (TGA) showed low thermal stability (10% weight loss at 125^{o}C in air) of the polymer (**15**). Glass transition temperatures of 5 ^{o}C found by Differential Scanning Calorimetry (DSC) provided expected values providing wide functional elastic property ranges (**Figure 20**).

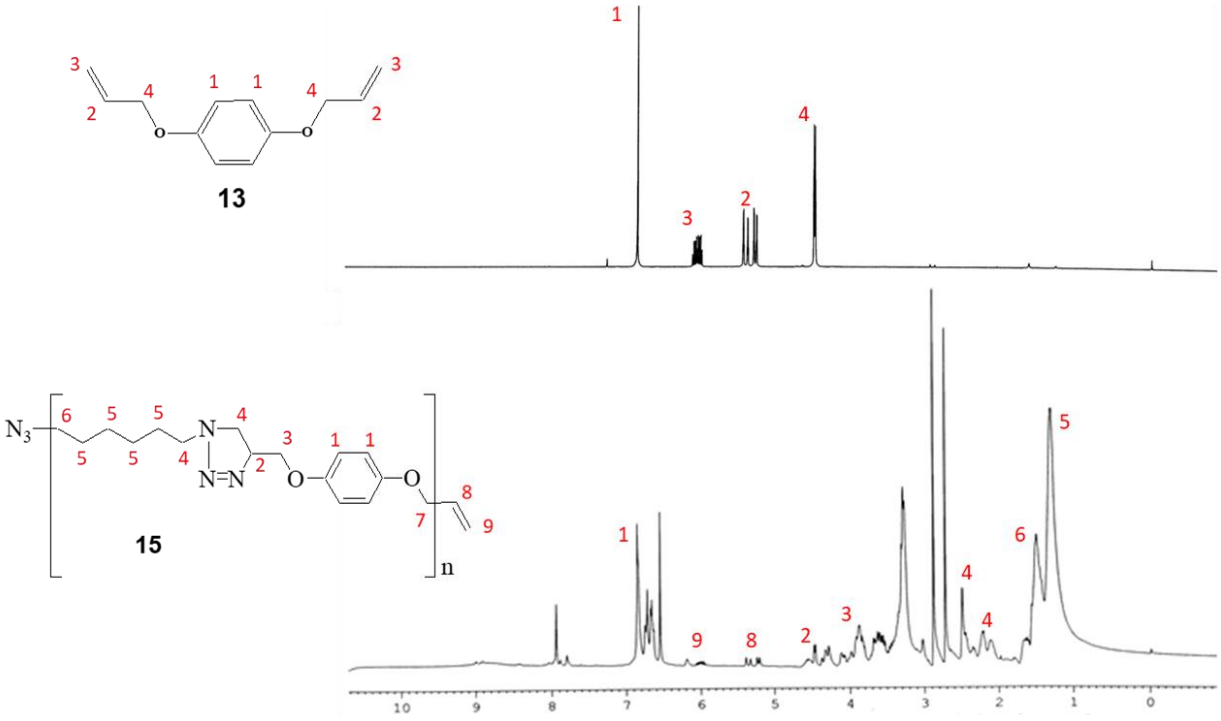


Figure 12: ^{1}H NMR spectra of aryl alkene (**13**) and resulting "Click-ene" constructed polymer (**15**)

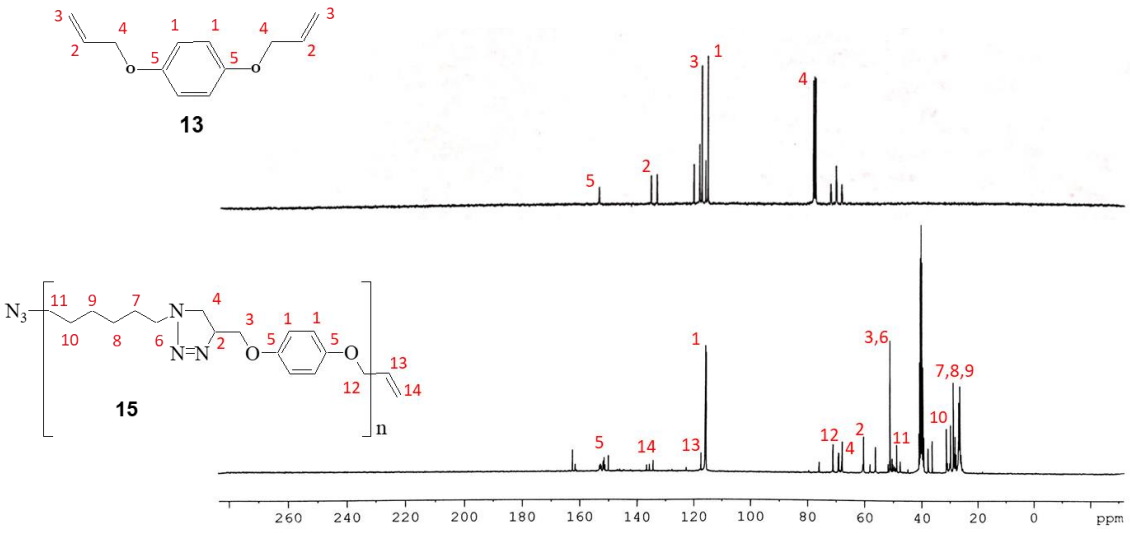


Figure 13: ^{13}C NMR spectra of aryl alkene (**13**) and resulting "Click-ene" polymerized polymer (**15**)

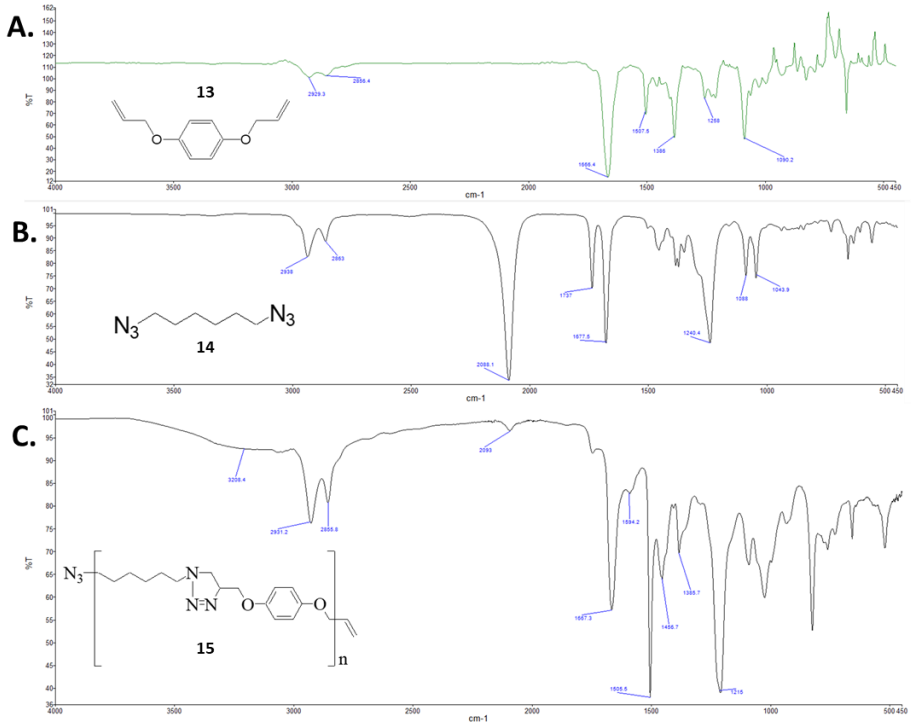
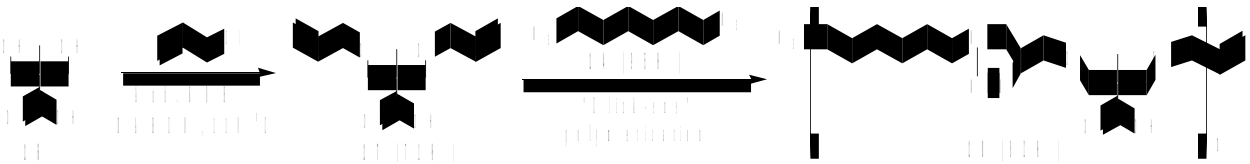


Figure 14: FT-IR spectra of **A)** aryl alkene **B)** diazide starting material **C)** resulting click-ene polymerized aryl polymer **15**

Aliphatic Based Click-ene Polymerization:

In addition to aromatic based starting materials, aliphatic compound **16** was used as a starting material in efforts to expand the range of starting material options available to click-ene chemistry synthetic reactions. Using the aliphatic starting material, diallyl molecule **17** was achieved by reacting Bis-MPA **(16)** with allyl chloride in the presence of catalytic amount of DABCO and anhydrous potassium hydroxide (**Scheme 4**). The resulting diallyl was then purified using column flash chromatography resulting in compound **(17)**. This resulting compound was then reacted with previously synthesized 1,6-diazidohexane **(14)** resulting in a diazole ring containing polymer.



Scheme 4: Synthesis of aliphatic based “Click-ene” polymerized polymer **18**

Size Exclusion Chromatography (SEC) of Polymer **(18)** resulted Mn = 44,000 (Mw = 83,600, PDI = 1.9) as well as MALDI-TOF showing polymer weights of 44,174 (**Figure 22**). All polymers were further characterized by ^{1}H and ^{13}C NMR and FT-IR spectroscopy (**Figure 15-17**) showing azole ring construction apparent by chemical shifts at 2.93 and 3.98 ppm, representative of the carbon carbon single bond formed in the azole ring, being present as well as alkene functionality conversion (5-6 ppm) and azide band reduction (2100 cm^{-1})

indication 1,2,3-triazole ring construction. Thermal gravimetric analysis (TGA) showed low thermal stability (10% weight loss at 150^{o}C in air) of the polymer (**18**). Additionally, Differential Scanning Calorimetry (DSC) provided promising glass transition (T_g) temperatures near or below zero resulting in good elastic temperatures ranges (**figure 20**).

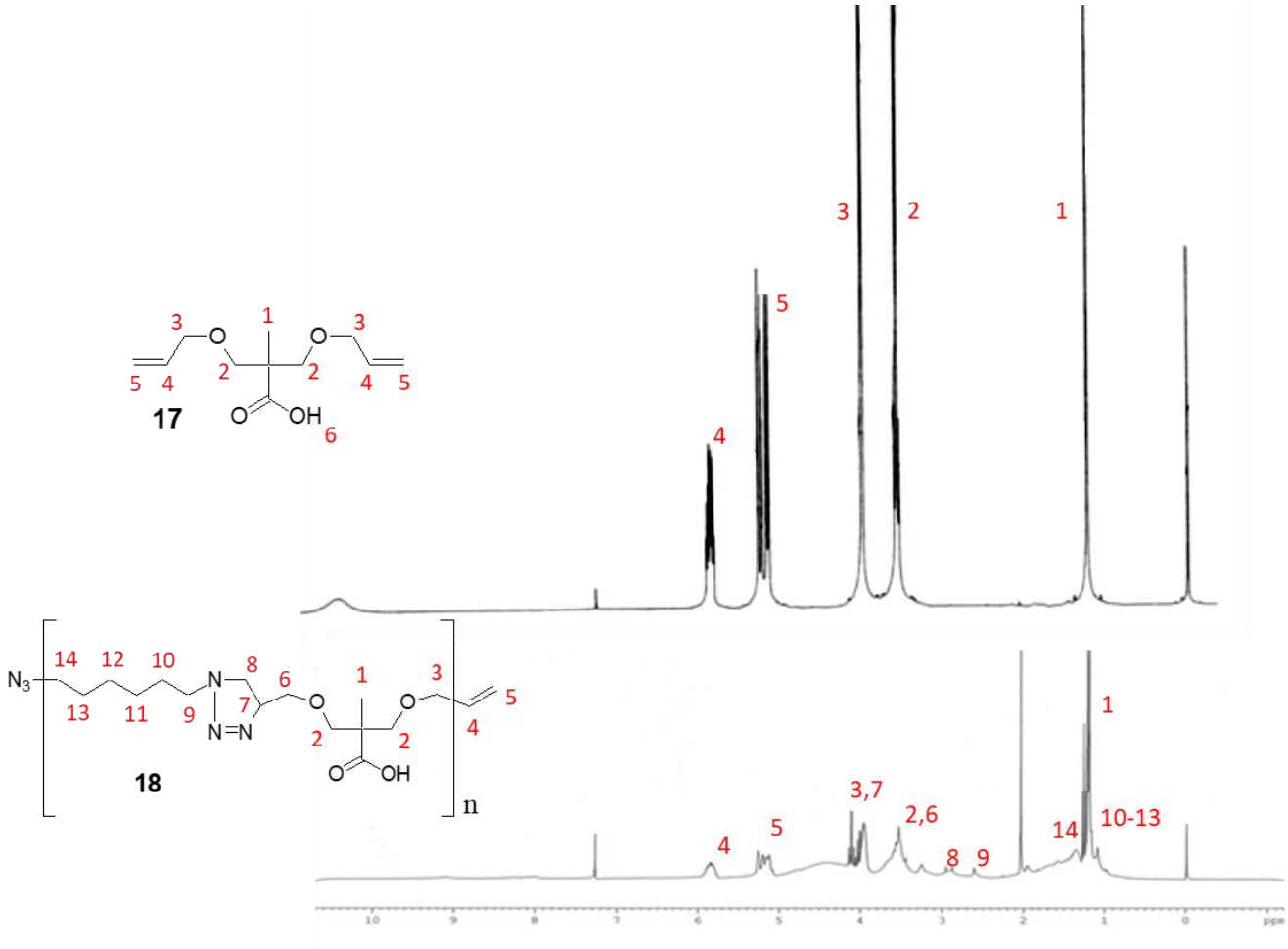


Figure 15: ^{1}H NMR spectra of aliphatic alkene (**17**) and resulting “Click-ene” polymerized aliphatic polymer (**18**)

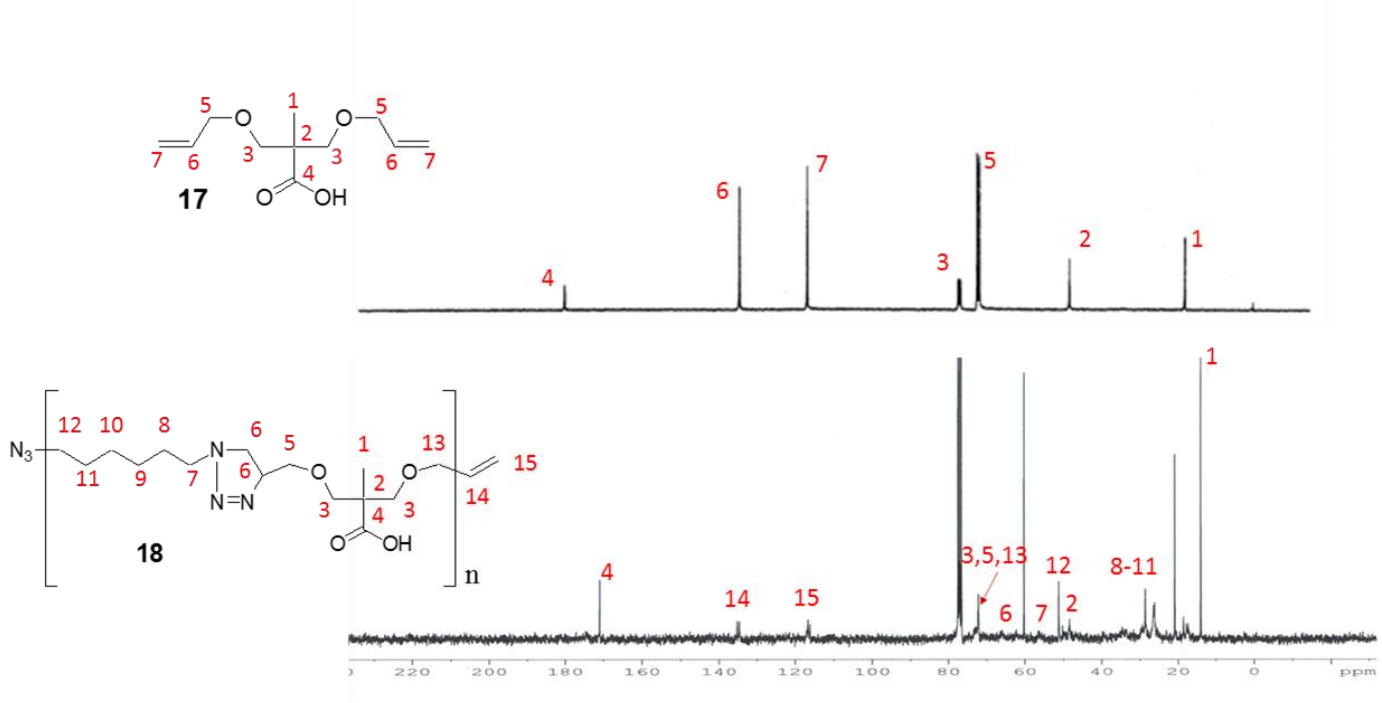


Figure 16: ^{13}C NMR spectra of akyl alkene (**17**) and resulting “Click-ene” polymerized aliphatic polymer (**18**)

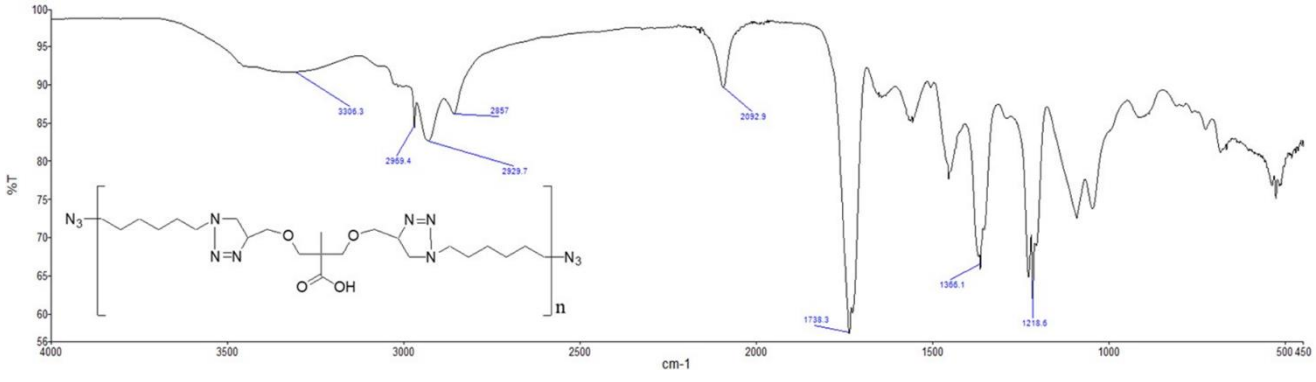


Figure 17: FT-IR spectra aliphatic “Click-ene” polymerized polymer **18**

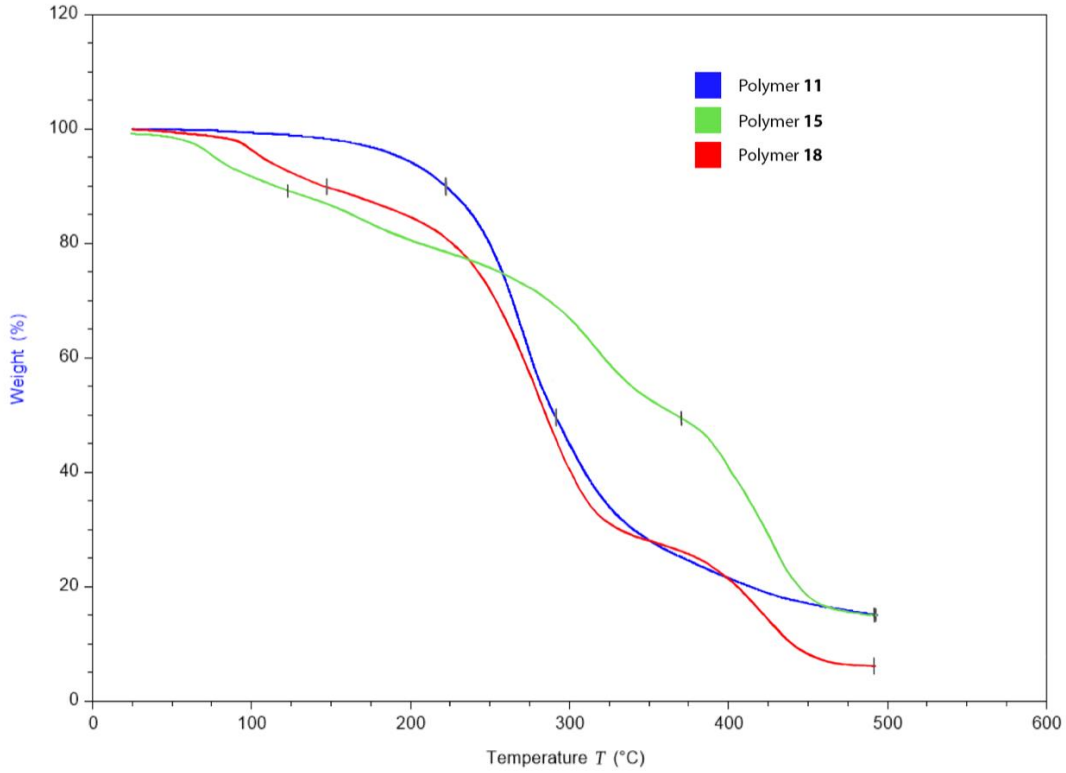


Figure 18: Thermogravimetric Analysis (**TGA**) of all “Click-ene” based polymers **11**,**15**,**18**

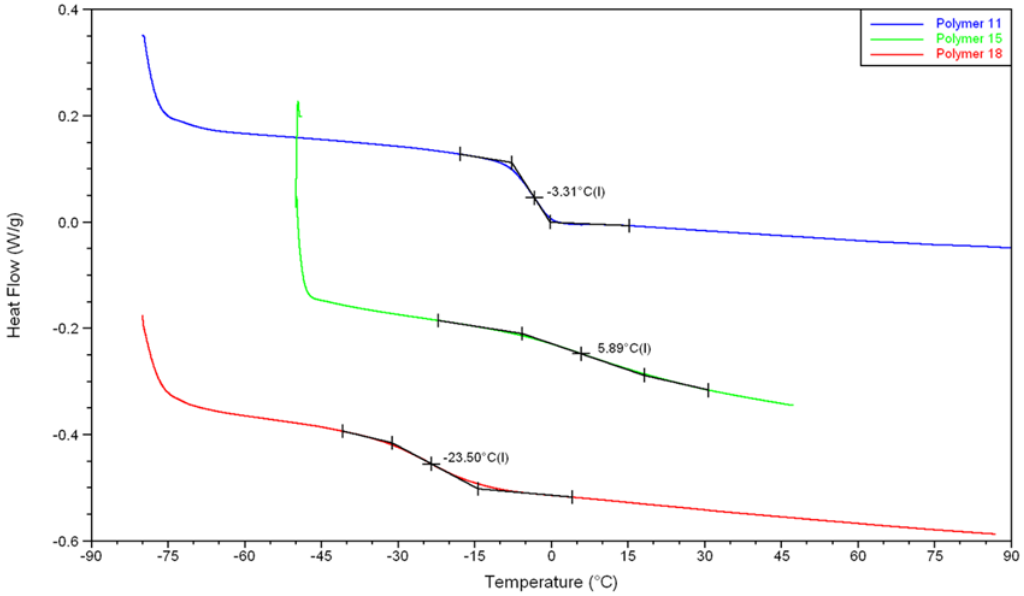


Figure 19: Differential Scanning Calorimetry (**DSC**) of “Click-ene” based polymers **11**,**15**,**18**

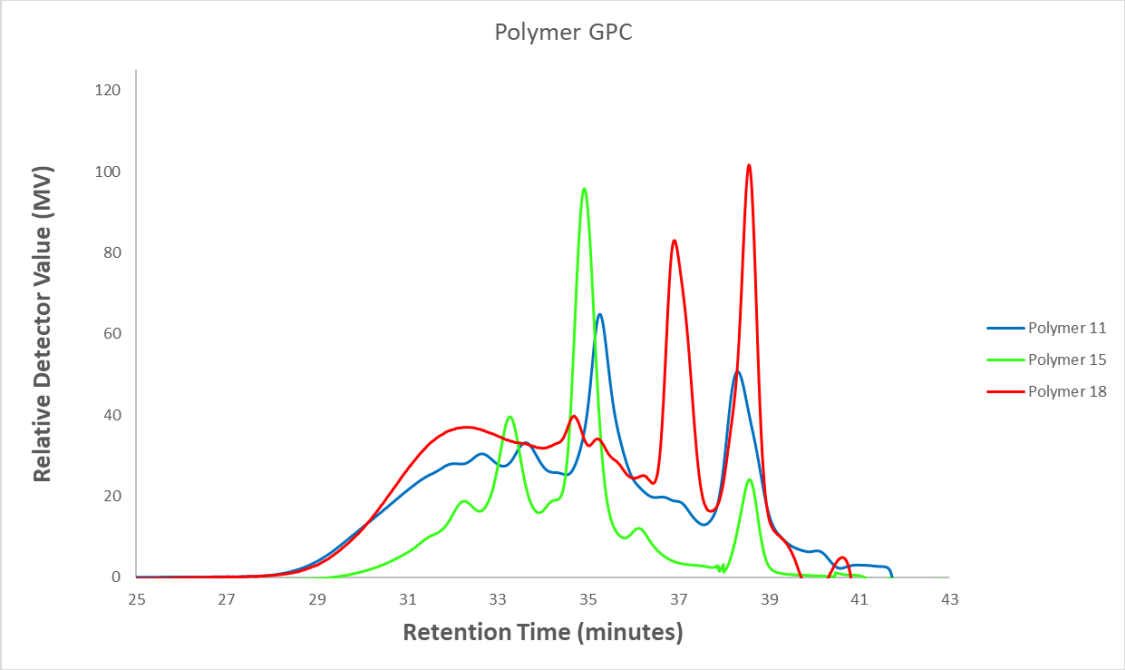


Figure 20: Gel Permiation Chromatography (**GPC**) of “Click-ene” based polymers polymers showing average molecular weight

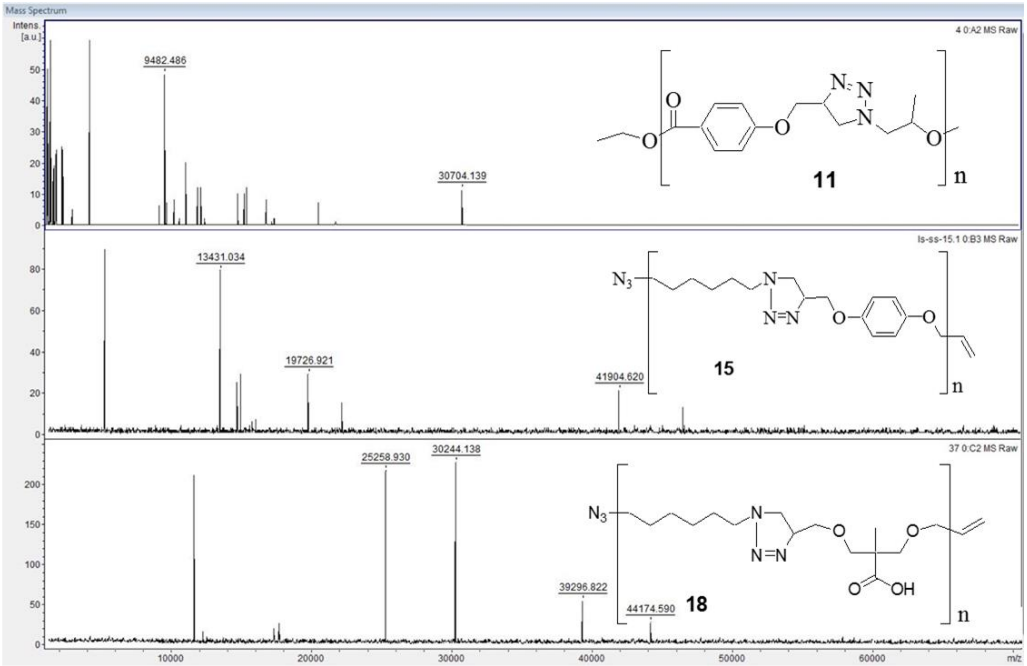


Figure 21: MALDI-TOF of “Click-ene” Polymers showing exact molecular weight

CHAPTER V

Conclusion

Conclusion:

Three 1,2,3-triazole ring containing small molecules were synthesized as proof-of-concept for click-ene reactions. Additionally, one click-ene based AB and two Click-ene polymers (aryl/aliphatic) were synthesized further supporting click-ene chemistry as a viable synthetic method. These syntheses provided solvent/transition-metal free reactions resulting monomers/polymers yields of up to 90%. Free of contamination, resulting polymers were tested via spectroscopy confirming 1,2,3-triazole ring conformation. Furthermore, the absence of both vinyl and azide functionality were consistent of click-ene reaction completion. Gel Permeation Chromatography (GPC) and MALDI-TOF showed molecular weight increases from starting materials to resulting polymers, ranging from 10,000 to 40,000 molecular weight. The resulting materials were tested using TGA and DSC. Polymers showed promising polymer characteristics with polyester polymer (11) providing similar properties to that of known polyester. As expected, click-ene based polymers provided comparable or slightly better thermogravimetric results due to heteroatom incorporation. Click-ene polymers showed glass transitions temperatures ranging from -23.5 to 5.89 ^{o}C, in relation to aromaticity.

Most importantly we have established click-ene chemistry as a viable option for both small molecule and polymer synthesis. This modified click chemistry will allow for more simplistic monomer/polymer synthesis due to the modular nature click chemistry provides.

References

References:

1. Kolb, H.C., M.G. Finn, and K.B. Sharpless, *Click Chemistry: Diverse Chemical Function from a Few Good Reactions.* Angewandte Chemie International Edition Engl, 2001. **40**(11): p. 2004-2021.
2. Iha, R.K., et al., *Applications of orthogonal "click" chemistries in the synthesis of functional soft materials.* Chemical Reviews, 2009. **109**(11): p. 5620-86.
3. Thibault, R.J., et al., *A versatile new monomer family: functionalized 4-vinyl-1,2,3-triazoles via click chemistry.* Journal of the American Chemical Society, 2006. **128**(37): p. 12084-5.
4. Nulwala, H., et al., *N-Vinyltriazoles: A New Functional Monomer Family through Click Chemistry.* Macromolecules, 2010. **43**(12): p. 5474-5477.
5. Qin, A., J.W.Y. Lam, and B.Z. Tang, *Click Polymerization: Progresses, Challenges, and Opportunities.* Macromolecules, 2010. **43**(21): p. 8693-8702.
6. Malkoch, M., et al., *Orthogonal Approaches to the Simultaneous and Cascade Functionalization of Macromolecules Using Click Chemistry.* Journal of the American Chemical Society, 2005. **127**(42): p. 14942-14949.
7. Gauthier, M., *Silicon-Containing Dendritic Polymers.* Journal of the American Chemical Society, 2009. **131**(21): p. 7477-7477.
8. Santra, S., C. Kaittanis, and J.M. Perez, *Aliphatic hyperbranched polyester: a new building block in the construction of multifunctional nanoparticles and nanocomposites.* Langmuir, 2010. **26**(8): p. 5364-73.
9. Kim, Y.H. and O.W. Webster, *Water soluble hyperbranched polyphenylene: "a unimolecular micelle?".* Journal of the American Chemical Society, 1990. **112**(11): p. 4592-4593.
10. Saha, A. and S. Ramakrishnan, *Site-Specific Functionalization of Hyperbranched Polymers Using “Click” Chemistry.* Macromolecules, 2009. **42**(12): p. 4028-4037.
11. Smith, K.A., et al., *Synthesis and Crystallinity of Conjugated Block Copolymers Prepared by Click Chemistry.* Macromolecules, 2013. **46**(7): p. 2636-2645.
12. O Liang, C., et al., *Dendronized cyclocopolymers with a radial gradient of polarity and their use to catalyze a difficult esterification*. Chemical Communications Vol. 9. 2003. 2524-5.
13. Helms, B., et al., *Dendronized Linear Polymers via “Click Chemistry”.* Journal of the American Chemical Society, 2004. **126**(46): p. 15020-15021.
14. Macdougall, L.J., V.X. Truong, and A.P. Dove, *Efficient In Situ Nucleophilic Thiol-yne Click Chemistry for the Synthesis of Strong Hydrogel Materials with Tunable Properties.* ACS Macro Letters, 2017. **6**(2): p. 93-97.

15. Langer, R. and D.A. Tirrell, *Designing materials for biology and medicine.* Nature, 2004. **428**(6982): p. 487-92.
16. Hutmacher, D.W., *Scaffolds in tissue engineering bone and cartilage.* Biomaterials, 2000. **21**(24): p. 2529-43.
17. Elsabahy, M. and K.L. Wooley, *Design of polymeric nanoparticles for biomedical delivery applications.* Chemical Society Review, 2012. **41**(7): p. 2545-61.
18. Truong, V.X., et al., *Simultaneous Orthogonal Dual-Click Approach to Tough, in-Situ-Forming Hydrogels for Cell Encapsulation.* Journal of the American Chemical Society, 2015. **137**(4): p. 1618-1622.
19. Dondoni, A., *The Emergence of Thiol–Ene Coupling as a Click Process for Materials and Bioorganic Chemistry.* Angewandte Chemie International Edition, 2008. **47**(47): p. 8995-8997.
20. Li, H., et al., *The Thiol−Isocyanate Click Reaction: Facile and Quantitative Access to ω-End-Functional Poly(N,N -diethylacrylamide) Synthesized by RAFT Radical Polymerization*. Macromolecules, Vol. 42. 2009. 6537-6542.
21. Truong, V.X. and A.P. Dove, *Organocatalytic, regioselective nucleophilic "click" addition of thiols to propiolic acid esters for polymer-polymer coupling.* Angew Chem Int Ed Engl, 2013. **52**(15): p. 4132-6.
22. Türünç, O. and M.A.R. Meier, *A novel polymerization approach via thiol-yne addition.* Journal of Polymer Science Part A: Polymer Chemistry, 2012. **50**(9): p. 1689-1695.
23. Cortez, M.A. and S.M. Grayson, *Thiol−Ene Click Functionalization and Subsequent Polymerization of 2-Oxazoline Monomers.* Macromolecules, 2010. **43**(9): p. 4081-4090.
24. Lowe, A.B., *Thiol-ene “click” reactions and recent applications in polymer and materials synthesis.* Polymer Chemistry, 2010. **1**(1): p. 17-36.
25. Liu, H., et al., *Hyperbranched polyethylenimines as versatile precursors for the preparation of different type of unimolecular micelles*. Vol. 67. 2007. 383-395.
26. Kade, M.J., D.J. Burke, and C.J. Hawker, *The power of thiol-ene chemistry.* Journal of Polymer Science Part A: Polymer Chemistry, 2010. **48**(4): p. 743-750.
27. Contreras, J., et al., *Synthesis of epsilon-caprolactone-b-L-lactide block copolymers by mean sequential polymerization, using diphenylzinc as initiator*. Vol. 71. 2014.