PHOTO-INDUCED COPPER(I) CATALYZED AZIDE-ALKYNE CYCLOADDITION POLYMERIZATION: FUNDAMENTALS

AND APPLICATIONS

by

Bassil M. El-Zaatari

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemical Engineering

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ABSTRACT

The copper(I) catalyzed azide—alkyne cycloaddition (CuAAC) reaction is one of the most utilized click chemistries and has applications that include organic synthesis, bioconjugation, surface modifications, medicinal chemistry and polymer materials. Typical of all 'click' reactions, the CuAAC chemistry is characterized by high yields and selectivity, limited by-products, and proceeds under mild ambient conditions. Recently, significant advances have been made to afford spatiotemporal control to the CuAAC reaction by introducing an in situ photoinitiator with a light source, creating new avenues in materials research including CuAAC shape memory polymers and wrinkles. Moreover, the triazoles formed from CuAAC reactions are rigid and able to undergo hydrogen bonding as well as π - π interactions, allowing for enhanced material performance and desirable mechanical properties.

One potential avenue of photo-CuAAC chemistry is dental materials as a replacement for the currently used methacrylate free radical polymerization system. Despite being widely used in dental composites, current free radical polymerization chemistries that are utilized in these composites suffer from low final methacrylate conversions (only 55-70%), leading to undesired side reactions, mechanical wear and degradation, and promotion of bacterial growth, all of which shorten the overall lifetime of dental materials. The suitability of the photo-induced CuAAC reaction in dental composites is demonstrated where the composites show similar mechanical properties to that of the methacrylate system. Moreover, the new polymerization schemes developed are completely compatible with dental lamps where the reaction can be initiated under blue (470 nm) light. These polymerization are furthermore rapid and can proceed to near full conversion in less than 10 minutes.

Despite the broad impact of the photo-CuAAC reaction, very little work had been done to understand the underlying kinetic limitations of this reaction. Through Fourier Transform Infrared Spectroscopy (FTIR) investigations of different parameters, namely copper(II) concentrations, photoinitiator concentrations, and incident intensity, an optimized kinetic profile of the reaction in both a solvent-based and network forming polymer system has been determined. The results in the solvent-based system show near first-order kinetics on copper and photoinitiator concentrations up to a threshold value in which the kinetics switch to zeroth-order. This kinetic shift shows that the photo-CuAAC reaction is not susceptible from side reactions such as copper disproportionation, copper(I) reduction, and radical termination at the early stages of the reaction. The overall reaction rate and conversion is highly dependent on the initial concentrations of photoinitiator and copper(II) as well as their relative ratios. Furthermore, the performance of the copper(II) catalytic source through synthesizing various copper(II) amine-based ligands (PMDETA, TMEDA, HMTETA, Me₆TREN, BPY, DPA) with different counter anions (Cl, Br, TFSI, OTf, OAc) have been assessed. Their impact on the kinetics of a photo-CuAAC network-forming system has also been evaluated. The polymerization rate can be manipulated by changing the counter anion of the copper(II) source. Namely, samples using a copper(II) bromide ligand shows the Through these results, a better fundamental greatest rate of polymerization. understanding of the photo-CuAAC kinetic behavior is provided and, importantly, the applicability of this reaction in polymer systems is expanded.

Using the blue light photoinitiating system, the photo-CuAAC polymerization can be used as a polymer ionic liquid (PIL). Through effective ionization of a difunctional alkyne, the incorporation of charged moieties in a photo-CuAAC network was achieved. Full conversion of these monomers occurred within 30 minutes under mild irradiation conditions. Through a facile exchange of hydrophobic anions for hydroxide, hydroxide conductive polymer networks (>19 mS/cm) are yielded illuminating their potential as membranes in alkaline fuel cell applications. Photo-CuAAC characteristics of this polymerization, such as spatiotemporal control were retained where the network can be easily photopatterned. Furthermore, this reaction has shown potential in other applications such as vitrimers and in copper-metal organic polyhedra.

Chapter 1

INTRODUCTION

1.1 Defining Click Reactions

In 2001, Sharpless et al. defined click reactions as a subset of organic chemical reactions that have a specific set of desirable properties¹. Click reactions are favorable energetically, proceed under mild conditions, are highly selective, are high yielding with a wide scope of starting materials, and produce a product that is easily extracted and isolated². Some examples of click reactions are the thiol-ene, thiol-yne³, Diels-Alder^{4,5}, copper(I)-catalyzed azide-alkyne cycloadditions (CuAAC)^{6,7}, and sulfide-fluoride exchange reactions⁸. The main advantage of using click reactions in materials synthesis is the ability to react multiple functional groups selectively to produce a well-defined functional product, as illustrated in Figure 1.1



Figure 1.1 Illustration of 'click' reaction strategy to selectively functionalize a material with multiple functional groups. In this example, three reactions are shown: the azide—alkyne cycloaddition reaction between an azide and an alkyne yields a triazole; the thiol-ene reaction between a thiol and an 'ene' yields a thioether; and the reaction between a sulfur (VI) fluoride and a nucleophile produces a sulfone product.

1.2 Copper(I) Catalyzed Azide Alkyne Cycloadditions

1.2.1 Impact of CuAAC chemistries

The azide—alkyne cycloaddition reaction is a 1,3-dipolar cycloaddition that occurs between an azide and alkyne. Prior to the development of the copper(I) catalyzed version of the reaction in 2002, this reaction would take place under high temperatures (>100°C) and long reaction timescales,⁹ with little control over 1,4 or 1,5 di-substituted triazole products. The triazole, however, is desirable because of its rigid linkages, lack of side reactions, and protection against hydrolytic cleavage and oxidation or reduction^{2,10}. Specifically, 1,2,3-triazole adducts are advantageous in the drug and medicinal chemistry fields due to this inherent stability and rigidity, as well as their hydrogen bonding features, and pharmacokinetic safety¹¹. Due to the unstable, and

potentially explosive nature of the azide group, however, thermally initiated azide alkyne conjugations are often avoided commercially or on a large scale.

The copper(I) catalyzed azide—alkyne cycloaddition (CuAAC) reaction (Figure 1.2) provides a facile synthetic route for the production of 1,4 disubstituted 1,2,3-triazole products. The reaction has been used in a range of fields, such as material science and polymers^{12–18}, protein chemistry^{19–21}, bioconjugation reactions^{22–25}, drug discovery^{26–29}, and ligation reactions.^{30–32}. In the CuAAC reaction, the copper(I) is typically introduced in one of two methods. The first is via *in situ* copper(II) to copper(I) reduction. This reduction takes places in the presence of a reducing agent, such as sodium ascorbate³³. The second is through addition of a copper(I) salt such as copper iodide or copper(I) triflate, in the presence of an amine base^{34–36}. The kinetics of the copper-catalyzed azide-alkyne addition are up to seven orders of magnitude faster than without the catalyst (i.e., the Huisgen cycloaddition reaction)⁶. While copper(I) is the most common route to catalyze the azide—alkyne cycloaddition, the azide—alkyne cycloaddition has been observed to be catalyzed in the presence of copper(0) (copper metal)^{37–40} as well as copper nanoparticles^{41,42}.



Figure 1.2 Schematic of the copper(I) catalyzed azide cycloaddition reaction.

1.2.2 Ligands in CuAAC reactions

The use of ligated copper species in CuAAC reactions provides kinetic stability to the reaction and is hence advantageous for its various applications. The most popular and successful copper ligands used in CuAAC chemistries are multidentate N-donor chelators⁴³. Amine based-ligands prevent copper(I) oxidation, reducing detrimentalf oxygen by-products. They moreover stabilize the copper(I) species and disfavor copper disproportionation into copper(II) and copper(0) which could retard the kinetics of the CuAAC reaction. Tris(heterocycle)methyl amine ligands, specifically, have shown to provide an accelerating effect on the kinetics of CuAAC reactions⁴⁴. Sharpless et al. were the first to use copper ligands with the CuAAC reaction and used tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA)⁴⁴. The tris(heterocycle)methyl amine ligands include tris-(hydroxypropyl-triazolylmethyl) amine (THPTA), {3-[4-({bis}[(1-tert-butyltriazolyl)methyl]-amino}methyl)-triazolyl]propyl}trimethylammonium

(TABTA), 2-[4-{(bis[(1-tertbutyltriazolyl)methyl]amino)methyl}-triazolyl]ethyl hydrogen sulfate (BTTES), and 2-[4-{(bis[(1-tert-butyltriazolyl)methyl]amino)methyl}-triazolyl]acetic acid (BTTAA) (structures shown in Figure 1.3), and have been used in biological applications and protein labeling^{25,45–49}. Other types of tris(heteroarylmethyl)amine such ligands include derivatives tris(2as benzimidazolylmethyl)amine [(BimH)₃], which exhibit kinetics than traditional TBTA⁵⁰. The structures of these ligands are shown in Figure 1.3. Beyond these traditional ligands, Finn and Díez-González explored a library of ligands capable of catalyzing the CuAAC reaction in the presence of copper(I) which include 2,2'bipyridine and 1,10-phenanthroline derivatives⁵¹ and phosphine functional groups^{52–54}.



Figure 1.3 Commonly used tertiary amine ligands in CuAAC reactions.

When copper(I) salts are used directly in CuAAC reactions, the need to stabilize the copper(I) state and protect it from oxidation or disproportionation is especially significant. An excess amount of base, typically an amine, is hence used to both facilitate deprotonation of the alkyne and stabilization of the copper(I) oxidation state³⁶. Examples of amines used with copper(I) salts are shown in Figure 1.4.



Figure 1.4 Popular bases used in CuAAC chemistries include triethylamine (TEA), N,N-Diisopropylethylamine, and N,N,N',N'',N''-Pentamethyldiethylenetriamine (PMDETA)

1.2.3 Mechanistic considerations in CuAAC reactions

The mechanism of the CuAAC reaction has been studied in detail for the past 15 years. While there is wide controversy over the exact mechanism of the reaction, kinetic studies have shown that the reaction typically exhibits second power scaling of copper at catalytic concentrations^{36,49,55}. This observation led to the hypothesis that a dinuclear copper intermediate is formed, which has subsequently been supported by DFT calculations,⁵⁶ direct experimental evidence,⁵⁷ and even isolation of bis(copper) intermediates⁵⁸. The mechanism of the CuAAC reaction, as it is understood today, is shown in Figure 1.5 (adapted from reference 58). Briefly, copper(I) is generated (1) which then ligates to the alkyne (2), allowing for the alkyne to reaction with the copper(I), forming a copper(I)-acetylide complex (3). An azide moiety then undergoes nucleophilic attack of the acetylide complex, producing the dinuclear copper(I) azide/alkyne intermediate (4), which undergoes dissociation of one of copper species to form a copper-bound cycloaddition product (5). With copper regeneration, the triazole product is formed (6), and the cycle is completed.



Figure 1.5 CuAAC mechanistic cycle showing the binuclear copper intermediate adapted from reference [58].

1.3 Photochemical Reactions

There are several advantages to using light (ultraviolet, visible or infrared) to trigger a chemical reaction, such as spatiotemporal control (control over where and when the reaction takes place). These advantages owe largely to the large amount of energy transferred to a molecule through photon absorption, which subsequently activates a chemical reaction. One can calculate the energy of a photon using

$$E_{photon} = \frac{hc}{\lambda}$$

where E_{photon} is the single photon energy, *h* is Plank's constant, c is the speed of light, and λ is the wavelength of light. Thus, it can be shown that a 365 nm photon (commonly used UV wavelength) is ~130 times greater than the thermal energy available (kT) to start a reaction at room temperature⁵⁹. Owing to the required high energy of photoinitiation, photoactive molecules are typically stable at room temperature in the absence of an external light source. Hence, spatial and temporal control is afforded to a reaction by simply shining light at a specific location or specific time, respectively.

A simple mechanistic picture of a photoinitiation is illustrated in Figure 1.6 in which an absorbed photon promotes an electron from the ground state (S_0) to an excited singlet state (i.e., S_1). The photon will undergo intersystem crossing from its singlet state (S_1) to a triplet state (T_1). The triplet state can then undergo a photochemical transition via intersystem crossing, or a photophysical transition via phosphorescence back to the ground state (S_0). Alternatively, in the absence of a photochemical process, the excited singlet state (S_1) of the chromophore deactivates back to the ground state by fluorescence emission or internal heat dissipation. Internal conversion could also occur during this process and is defined as the radiationless transition between energy states of similar spins (e.g., from T_1 to T_2). There are three main types of photochemical process, bond

forming reactions (namely, cycloadditions), and bond breaking reactions (namely, radical formations).



Figure 1.6 Jablonski diagram. In the presence of a photochemical reaction, an excited singlet state (S_1) goes to a triplet state (T_1) via intersystem crossing. This transition allows it to undergo one of several photochemical reactions.

1.3.1 Isomerization

Chromophore isomerization under incident light is a powerful tool for synthesis, and modification in polymer science. These moieties can be incorporated both chemically within the polymer backbone or side chains or physically dissolved into a polymer framework⁵⁹. Of these chromophores, azobenzene and its derivatives have been popular for use in polymeric materials. Under UV-light the azobenzene molecules azobenzene can undergo isomerization, via the N=N double bond, from the trans to the cis confirmation within picoseconds; moreover, this isomerization can be reversed

under a longer wavelength, typically blue light^{60,61}. The photo-induced isomerization of azobenzene is shown in Figure 1.7. The use of azobenzene and its derivatives in polymer science includes liquid crystalline elastomeric materials^{62–66}, polymer modification and architecture^{67–69}, uperconversion nanoparticles^{70–72}, and metal organic frameworks and polyhedra^{73–77}.



Figure 1.7 Azobenzene photochemical isomerization. Under UV-irradiation (hv₁), the trans conformation of azobenzene can be switched to the cis conformation. Under visible light (hv₂), typically between 400-500 nm, the cis conformation can be switched to back to the trans-isomer.

1.3.2 [2+2] Cycloaddition reactions

While many cycloaddition reactions exist, some [2+2] and [4+4] cycloadditions can be photoinduced. Of these cycloaddition reactions, [2 + 2] cycloadditions are the more common. These reactions give rise to the formation of a new molecule from the addition of two unsaturated molecules (typically alkenes). Recent applications of this reaction include solid state polymerizations^{78–80}, metal organic frameworks,⁸¹ and healing⁸².
1.3.3 Radical forming reactions

Photoinduced polymerization reactions are widespread in several industrial applications such as adhesives, dental materials, and 3D printing. The ability to rapidly and spatially transform a liquid resin or soft film into a solid with specific properties is desirable as a provides a short and simple method of reaction while enabling control over the specific process. These radical initiated photo-induced polymerizations involve the use of a photoinitiator to produce radicals under incident light. It is common, however, to add a co-initiator, a photosensitizing agent, or a radical scavenger with the photoinitiator⁸³. The initiation rate (R_i) of a photoinitiator is

$$R_i = 2f\varphi I_0 \varepsilon d \ln(10)[I],$$

where *f* is the radical efficiency, φ is the quantum yield, ε is the molar absorptivity, *d* is the sample thickness, I_0 is the incident light intensity, and [*I*] is the concentration of the photoinitiator. The above equation is only valid if the film is optically thin. This is because light intensity (*I*) is governed by the Beer-Lambert law,

$$I = I_0 \, 10^{\varepsilon d[I]}.$$

In other words, the light will exponentially attenuate throughout the thickness of the sample, which inherently limits the application of photoinitiated radical-induced polymerizations to optically thin films.

1.3.4 Photoinitiator types

It is critical to select a suitable photoinitiator based on the application. Some considerations include solvent or resin solubility, effect on the mechanical properties of the polymer, and reactivity. There are three main types of photoinitiating systems: one-component (Norrish Type I), di-component (Norrish Type II), and iniferters.

1.3.4.1 One component photoinitiators

One component of photoinitiators also known as Norrish Type(I) photointiators include the direct homolysis of a bond (typically a ketone or aldehyde C-CO bond) under light and the formation of two radicals. An example of a Type(I) photoinitiating system is the photocleavage of 2,2-dimethoxy-2-phenylacetophenone (DMPA), as shown in Figure 1.8. DMPA belongs to a class of photoinitiators known as benzoin ethers, which have been widely used in polymer synthesis^{84–87}.



Figure 1.8 DMPA photoinitiation produces two radical species.

Outside of benzoin ethers, benzoyl phosphine oxides such as phenylbis(2,4,6trimethylbenzoyl)phosphine oxide (BAPO), 2,4,6-trimethyl and benzoyldiphenylphosphine oxide (TPO) have been studied and utilized for 12

photopolymerizations, namely for their ability to absorb in the visible light range^{88–90}. Lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP), which also belongs to this group of photoinitiators, is widely utilized in biomaterial and hydrogel applications due to its excellent solubility in water^{91–95}. Other classes of Type(I) photoinitiators include: benzoyl oxime esters such as 2-propanedione-2(ethyoxycarbonyl) oxime (PDO), sulfoxides, sulfonyl ketones, and thiobenzoates. The structures of these photoinitiators is shown in Figure 1.9.



Figure 1.9 Commonly used photoinitiators for polymerizations. Cleavable bonds are shown in blue.

1.3.4.2 Two component photoinitiators

These types of uncleavable photoinitiators work in their triplet state and undergo electron transfer in the presence of a co-initiator, such as a tertiary amine. Examples are

mainly benzophenones, thioxanthones and camphorquinones as shown in Figure 1.10. These photoinitiators are used in multiple free-radical polymerizations and in industrial applications, such as adhesives and dental materials^{96–101}.



Figure 1.10 Common Norrish Type(II) (two-component) photoinitiators.

1.3.4.3 Iniferters

Iniferters are molecular units that serve as *ini*tiators, trans*fer* agents, and *ter*minators¹⁰². They are gaining popularity for use in responsive polymers^{103–105}. In brief, a polymer network is formed using labile bonds. Under specific triggers, such as heat, force or light, these labile bonds can break into radicals which can then initiate another polymerization or functionalization. These radicals allow for control over polymer architecture where it can be engineered towards specific applications. Recent examples of using iniferters include dynamic materials¹⁰⁶ and self-healing materials^{107–109}.

1.4 Photo-induced 'Click' Polymerizations

Due to the high efficiency and orthogonality of 'click' reactions, their use in the functionalization of monomers in the preparation of macromolecules has gained increasing popularity over the past decade^{4,6,19,25,72–77}. The marriage of these two fields has allowed for the preparation of complex architectures, well-defined structures and efficient post-modification of materials that was previously unattainable. The combination of photochemistry and 'click' reactions is thus ideal. On the one hand, the nature of 'click' reactions provides a robust and rapid approach to polymer synthesis. On the other hand, the ability to afford the reaction with spatiotemporal control provides added simplicity and command over the synthetic process.

1.4.1 Photo-induced CuAAC reactions and polymerizations

Despite the numerous applications of the CuAAC reaction, it initially lacked the temporal control characteristic of other photo-enabled click reactions, such as the thiolene^{117–119}, thiol-yne⁸², and the photocaged-base-thiol-Michael addition¹²¹. Hence there were several efforts to photo-trigger the CuAAC reaction via reducing a copper(II) species to catalytic copper(I) utilizing photochemical scheme. In 2006, Ritter and König were able to reduce copper(II) using a riboflavin based photoinitiating scheme¹²². The photoreduction of copper(II) to copper(I) in the CuAAC system was then continued by Yagci in aqueous conditions¹²³. The photo-CuAAC reaction was later extended to polymerizations by the Bowman group in 2011¹²⁴. In this realization, the Bowman group photoinitiated the reaction using UV-light in the presence of a photoinitiator and copper(II); the copper(II) was reduced to catalytic copper(I) by the resulting photoinitiator radicals (see Figure 1.11). This simple initiation scheme allowed the applicability of the CuAAC reaction in photopatterning and photolithographic applications. An alternative approach to photoinitiating the azide—alkyne reaction was demonstrated by Popik et al. Cyclopropenone structures were used, which form cyclooctynes under UV-light¹²⁵. The cyclooctynes then undergo strain promoted [3+2] azide-alkyne cycloaddition (SPAAC) in the presence of azides and absence of a copper source.



Figure 1.11 Photochemical CuAAC scheme: A photoinitiator (PI) dissociates into photoinitiator radicals (PI•) in the presence of a light source. Some or all of these radicals can then reduce copper(II) to copper(I). Once copper(I) is present in the system, it can catalyze the reaction between the azide and the alkyne, forming the triazole linkage.

After the seminal work by the Bowman group¹²⁴, there have been numerous applications of photo-CuAAC reaction and polymerization. This chemistry has been used in the synthesis of copolymers and in living radical polymerizations^{126–130}, polymer wrinkles¹¹⁸, and biomaterials^{131–134}. One of the most powerful applications of this chemistry in polymer science, however, is a bulk step-growth photopolymerization of multifunctional azides and

alkynes first shown by Gong et al. in 2013. The resulting polymer films were highly crosslinked, homogenous and showed high glass transition temperature due to the rigid nature of the subsequent triazole linkages formed¹³⁵. This bulk photopolymerization has been used in applications such as shape memory materials^{136,137} and interpenetrating networks.¹³⁸

1.4.2 Photo-CuAAC applications in dental materials

Tooth decay is the most prevalent chronic disease in the United States where over one hundred million dental restorations are performed annually¹³⁹. These dental procedures typically utilize photopolymerizable composites based on dimethacrylate specifically 2,2-bis[4-(2-hydroxy-3chemistries, methacryloyloxypropoxy) phenyl]propane (BisGMA) and triethylene glycol dimethacrylate (TEGDMA). Treatment utilizing this chemistry was first developed in the 1950s and has remained in use despite key limitations. Specifically, the system suffers from low final double bond conversions (only up to 55 - 75%) and undesired side reactions that can lead to mechanical wear, and degradation, which has been shown to promote bacterial growth^{140–142}. These inherent shortcomings of the dimethacrylate system shorten the half lifetime of these composite materials to a mere 7.8 years¹⁴³. Thus, to enhance the durability and longevity of dental composite materials, new chemistries are being investigated and implemented. The photo-induced CuAAC reaction is a promising alternative to the dimethacrylate system owing to its high conversions, efficiency, and selectivity.

A dental composite is comprised of two main components: an organic (resin) phase and an inorganic (filler) phase (Figure 1.12). The organic phase typically consists of dimethacrylate monomers, photoinitiators, radical inhibitors, as well as pigments to help match the white color. Currently, BisGMA and TEGDMA are the most extensively used. The inorganic filler includes glassy and silica particles or ionomers which provide the necessary mechanical properties (i.e., hardness or stiffness) and constitutes 70-80% of the dental composite¹⁴⁴. Typically, a coupling agent such as a thin film of silica with methacrylated end groups is added to enhance the bonding between the filler particles and the polymer resin that surrounds it.



Figure 1.12 Schematic of a dental composite showing the filler and resin components. The resin is mainly made up of Bis-GMA and TEGDMA dimethacrylate monomers.

Given the inherent limitations of the dimethacrylate-based dental composites, and owing to the stable and durable nature of triazoles formed from photo-CuAAC polymerizations, a CuAAC dental composite is hypothesized to exhibit increased performance over current systems. CuAAC monomers need not contain hydrolyzable ester groups, which will reduce composite degradation. In addition, the high conversion and step-growth mechanism of the CuAAC reaction may lead to fewer unreacted monomers. Lastly, the photo-CuAAC polymerization reaction continues in the dark, even after light is no longer irradiated onto the sample, allowing shorter irradiation times¹²⁴.

1.5 Objectives

The photo-CuAAC polymerization has potential for use in various material and polymer science applications. Inspired by the highly selective, rapid, and high yielding nature of the photo-CuAAC polymerization, the goal of the thesis was to study the suitability of this reaction for use in dental materials. In order to assess the chemistry's suitability as a dental resin, a fundamental understanding of the reaction kinetics both in solvent and in bulk polymerizations, was required. This understanding was necessary to optimize the reaction kinetics, since dimethacrylate polymerizations in dental materials reach their optimal conversion in 40 to 60 seconds, whereas the initially reported bulk photo-CuAAC polymerization was over 100 times slower¹³⁵. In addition, exploring different methods of photo-polymerizing the CuAAC reaction using various photoinitiating schemes and types was of interest, mainly because dental lamps operate in the blue light (470 nm) region.

The aims of the thesis are as follow:

<u>Aim 1:</u> To develop an understanding of the reaction kinetics of photopolymerizable CuAAC reactions as well as explore how different parameters, such as copper(II) sources, affect the polymerization kinetics. To understand the capability of CuAAC to replace current methacrylate chemistries, the reaction times of the CuAAC system should be similar to or better than those of the methacrylate based composites. (Chapters 2 and 4)

<u>Aim 2:</u> To develop new photoinitiating schemes for CuAAC reactions that can polymerize and operate under blue light. (Chapter 3)

<u>Aim 3:</u> To expand the applicability of photo-CuAAC polymerizations in different materials science and polymer fields. Achieving this aim includes novel azide and alkyne monomer synthesis and characterization, which can be tuned for these specific applications. (Chapters 5 and 6).

Chapter 2

KINETIC TRENDS IN THE PHOTO-CUAAC REACTION

This chapter contains results that were published in Physical Chemistry Chemical Physics in 2016¹⁴⁵.

2.1 Introduction

Click chemistry refers to a set of high yielding and selective reactions with limited or easily removable byproducts which proceed under simple reaction conditions.¹ In addition to the ease and versatility associated with these reactions, a few click reactions are initiated by light, affording spatiotemporal control of product formation. One of the most widely used click reactions is the copper(I) catalyzed azide– alkyne cycloaddition (CuAAC) reaction^{6,7} In the CuAAC reaction, the copper(I) catalyst is typically introduced by the in situ reduction of copper(II) into copper(I)³³ or by the direct addition of copper(I) salt in the presence of a base which immediately triggers the azide–alkyne cycloaddition reaction Despite its utility in applications requiring bio-orthogonal reactions², the CuAAC reaction had previously lacked the temporal control characteristic of other photo-enabled click reactions, such as the thiol-ene¹¹⁷ and thiol-yne^{112,120} radical mediated reactions as well as the photocaged-base-thiol-Michael addition¹²¹.

In the last decade, there have been considerable efforts to trigger the CuAAC reaction using light. One of the most straightforward routes is to simply reduce the copper catalyst from copper(II) to copper(I) using a photochemical scheme. Ritter and König were the first to reduce copper(II) using a photosensitizing system¹²², which was later extended to non-aqueous conditions by Tasdelen and Yagci¹²³. The photo-CuAAC

reaction was further demonstrated in systems capable of undergoing a light-initiated CuAAC polymerization by Adzima et al¹²⁴. thereby enabling photolithography and photo-functionalization¹³⁵.

Despite the impact of the photo-CuAAC reaction in bioconjugation and more broadly in materials systems, the kinetic behavior and the limitations of this reaction are still relatively unexplored. Mainly, understanding how and why the copper catalyst, photoinitiator, and light intensity affect its rate in monofunctional, solvent-based systems as well as network forming systems is critical for practical applications of this reaction. In the work presented here, the reaction conditions that affect photo-CuAAC kinetics and examine its limitations are investigated. The key variables associated with the photo-CuAAC reaction and provide insight in controlling the reaction rate and extent are identified. Moreover, these results are applicable in both solvent based model systems and polymer network-forming reactions, thus demonstrating their broad applicability. Importantly, the reaction kinetics show distinct and unique behavior as compare to the traditional, non-photo CuAAC reaction. Overall, both the quantitative and qualitative trends contained herein will inform users of the photo-activated CuAAC reaction of suitable reaction conditions for applications in both solution-based systems and polymer networks.

2.2 Experimental Procedures

2.2.1 Materials

The following chemical compounds were used without further purification: 1dodecyne (Sigma Aldrich), methyl 2-azidoacetate (Sigma Aldrich), copper sulphate pentahydrate (Sigma Aldrich), bis(2,4,6-trimethylbenzyoyl)-phenylphosphineoxide (Irgacure 819) (Ciba), N,N-dimethylforamamide (Fisher Scientific), N,N,N',N',N''-pentamethyldiethylenetriamine (Sigma Aldrich), copper chloride (Sigma Aldrich).

2.2.2 Synthesis Procedures

Bis(6-azidohexyl)(1,3-phenylenebis(propane-2,2-diyl))dicarbamate (monomer 1; Figure 2.2) was synthesized using a 2-step synthesis¹⁴⁶.



(1) To an argon purged round bottom flask: was charged with 1,3-Bis(2isocyanato-2-propanyl)benzene (10.0 g; 0.041 mol), and dibutyltin dilaurate (a few drops) were added to 50 mL of THF. The reaction mixture was then placed in an ice bath where 2 equivalents of 6-chloro-1-hexanol (11.5 g; 0.084 mols) was added dropwise. After addition, the reaction flask was cooled to room temperature and left to react overnight. Then, excess THF (100 mL) was added and the mixture was flowed through a silica plug. The product was dried under high pressure to yield to a translucent oil.

(2) The product from (1) (10.0 g; 0.021 mol) was dissolved in 150 mL ofDMF. Sodium azide (5.5 g; 0.084 mol) was added in aliquots to the reaction mixture.The flask was then heated to 80°C under reflux for 24 hours. The product was

extracted with ethyl acetate (3 × 200 mL) and washed with water (3 × 200 mL) to remove any remaining DMF. Column chromatography (1:1 Ethyl acetate:Hexanes) was used for further purification to yield a clear viscous oil (8.8 g; 78% yield). ¹H NMR (400MHz, CDCl₃) δ 7.42 (1H, s), 7.28 (2H, s), 5.06 (2H, s), 3.97(4H, t), 3.26 (4H, t), 1.25-1.80 (28H, m).

1-(Prop-2-ynyloxy)-2,2-bis(prop-2-ynyloxymethyl)butane¹³⁵ (monomer 2; Figure 2.2): Trimethylolpropane (7.50g, 0.056 mols) was added to a solution of KOH (26.00g, 0.46 mols) in 100 mL of DMSO. The reaction mixture was then cooled down to 0°C using an ice bath for 30 minutes. Propargyl bromide (80% in toluene; 22.0g, 0.15 mols) was filtered from MgO and added dropwise to the slurry. The reaction was then allowed to equilibrate to room temperature and reacted for an additional 48 hours. The resulting mixture was added to 1000 mL of water and extracted with a 50:50 vol% mixture of ethyl acetate and diethyl ether (3 × 500 mL). The organic layer was then washed with brine (4 × 500 mL) and dried over MgSO₄. The mixture was concentrated under reduced pressure and separated using column chromatography. ¹H NMR (400 MHz, CDCl₃): δ 4.12 (d, 6H), 3.41 (s, 6H), 2.40 (t, 3H), 1.42 (q, 2H), 0.88 (t, 3H).

All ¹H NMR spectra are shown in Appendix A.

2.2.2 Monitoring reaction kinetics

A Nicolet Nexus 670 Series Fourier Transform Infrared (FTIR) spectrometer was used in conjunction with a SL-2 sealed liquid cell equipped with calcium fluoride windows (International Crystal Laboratories). Solutions containing the reactants, 1dodecyne and methyl 2-azidoacetate, the copper catalyst (CuSO₄•5H₂O), and Irgacure-819 were prepared in DMF and stirred for at least 30 minutes. The reaction system is depicted in Figure 2.1. Typical reaction systems contained 110 mM of 1-dodecyne and methyl 2-azidoacetate and 10 mM of copper(II) and photoinitiator. Aliquots of the reaction system were injected in the liquid cell which was then mounted on the FTIR. After 30 seconds the liquid cell was irradiated using an OmniCure Series 2000 lamp, that was filtered using a 405 nm band pass interference filter, equipped with a 200 Watt mercury arc bulb (Lumen Dynamics), which started the reaction. The reaction kinetics were monitored via the reduction of the methyl 2-azidoacetate (azide) peak between 2080 and 2150 cm⁻¹ which exhibits a maximum at 2109 cm⁻¹. Using a Beer's Law type analysis, the area under the peak is directly proportional to the concentration of the species at a constant path length which was constant throughout the experiments at 0.1 mm. The decrease in the concentration of methyl 2-azidoacetate over the first two minutes of the reaction represented an average initial rate of the reaction and was calculated for each sample. An illustration depicting the decrease in the azide peak in using infrared spectroscopy is shown in Figure 2.3. All rate experiments were performed in triplicate.

2.2.3 Polymerizations

The polymer application experiments used bis(6-azidohexyl)(1,3phenylenebis(propane-2,2-diyl))dicarbamate (monomer 1; Figure 2.2), and 1-(Prop-2ynyloxy)-2,2-bis(prop-2-ynyloxymethyl)butane (monomer 2; Figure 2.2). The reactants were mixed stoichiometrically with respect to the azide and alkyne functional groups. A copper chloride N,N,N',N',N''-pentamethyldiethylenetriamine (PMDETA) ligand was synthesized¹⁴⁷ to act as the copper(II) source (Figure 2.2) which was characterized using elemental analysis and dissolved in trace (<1wt%) methanol. Irgacure 819 was used as the photoinitiator (Figure 2.2). The components were mixed under high speed using a DAC 150.1 FVZ-K Flacktek Speed Mixer. The conversion in these experiments were monitored using a Thermofisher IS-50 FTIR via tracking the alkyne near-IR peak¹⁴⁸ between 6430 and 6570 cm⁻¹ where the trifunctional alkyne has a peak at 6507 cm⁻¹. All polymer samples were placed between glass slides and separated with a spacer of 0.12 mm thickness. The structure of the monomers, catalyst and photoinitiators used in the polymerization system is shown in Figure 2.2.



Figure 2.1 Photo-CuAAC reaction system: 1-dodecyne reacts with methyl 2azidoacetate in the presence of copper sulfate pentahydrate and Irgacure 819 in DMF under 405 nm incident light to produce the triazole product.



Figure 2.2 Monomers, catalyst and photoinitiators used in the polymerization system. (1) bis(6-azidohexyl)(1,3-phenylenebis(propane-2,2-diyl))dicarbamate (2) 1-(Prop-2-ynyloxy)-2,2-bis(prop-2-ynyloxymethyl)butane (3) CuCl₂/PMDETA (4) Irgacure 819



Figure 2.3 The change in absorbance of the azide peak at between 2080 and 2150 cm⁻¹ over the first 10 minutes of a photo-CuAAC reaction using FTIR spectroscopy. The area under a reference peak at 2044 cm⁻¹ from the DMF solvent used is constant throughout the reaction.

2.3 **Results and Discussion**

The reaction kinetics and mechanism for the CuAAC reaction have been studied in detail since its discovery in 2002. Depending on the concentration of copper, the reaction rate dependence on reactant concentration follows one of two behaviors: firstorder rate dependence on the azide and alkyne concentrations at non-catalytic copper concentrations and roughly zero-order rate dependence on azide and alkyne concentration when copper is at catalytic concentrations⁵⁵.

rate
$$\left\{ \begin{array}{l} [C=C]^{1} [N_{3}]^{1} [Cu^{1+}]^{0} \\ [C=C]^{0} [N_{3}]^{0} [Cu^{1+}]^{2} \\ cat Cu \end{array} \right\}$$

The observed second power scaling of copper at catalytic concentrations has led to the hypothesis that a dinuclear copper intermediate is formed, which has been supported by DFT calculations¹⁴⁹ and, more recently, by direct experimental evidence^{57,58}. Copper(II) is typically formed in situ from copper(I) using an excess of a reducing agent, such as sodium ascorbate, which also helps in alkyne deprotonation¹⁵⁰. It has been shown that the reducing agent does not influence the kinetics of the reaction and can be used in large excess, suggesting that the production of copper(I) is not limiting in these traditional CuAAC reactions⁴⁹. Introducing photoinitiation to the CuAAC system can have several potential effects on the reaction pathway (Figure 2.4). **Potential Initiation Reactions:**

(1)	PI	$R^{\bullet} + O_2 \xrightarrow{k_0} R-O$	-0 [•]
(2)	PI	$R^{\bullet} + R^{\bullet} \xrightarrow{k_t} R-F$	र
(3)	PI $\frac{hv}{k_r}$	$R^{\bullet} + Cu^{2+} \xrightarrow{k_c} Cu^{2+}$	+
(4)	PI $\frac{hv}{k_r}$	$R^{\bullet} + Cu^{+} \xrightarrow{k_{co}} Cu$	(0)
(5)	2 Cu ⁺ – k _d	$rac{}{}$ Cu(0) + Cu ²⁺	
Potential Reactant Side Reactions:			

(6)
$$N_3 \longrightarrow \frac{hv}{k_{uv}} \longrightarrow N: + N_2$$

Figure 2.4 Potential reactions involved in photoinitiating the CuAAC reaction. Once the radicals are generated through light irradiation, they can either (1) react with oxygen forming peroxy radicals, (2) terminate by reacting with other radicals, or (3) reduce copper(II) into copper(I). (4) Copper(I) could then either be reduced further to form copper(0) or (5) react with another copper(I) molecule to yield copper(II) and copper(0) via disproportionation. (6) Finally, the azide could decompose into nitrene and nitrogen gas under UV or near UV-light.

Upon incident irradiation, a photoinitiator (PI) will form radicals (R•) that will subsequently undergo several presumed reactions. (1) The radical could react with oxygen (O₂), forming a peroxy radical as is prevalent in free radical polymerizations. These peroxy radicals have a much lower reducing potential than benzoyl or phosphinoyl radicals and would slow the reaction rate¹⁵¹. While oxygen inhibition is common in polymers involving phosphinoyl radicals¹⁵², at both low and high intensities oxygen was not observed to inhibit the photo-CuAAC system as shown in Figure 2.5. (2) The radical could react with another radical to undergo radical-radical termination (i.e., radical recombination). This reaction pathway is limited by the concentration of radicals produced at a certain time. (3) If the redox potential of the radical is sufficient, it can reduce copper(II) to copper(I), which will then enter the CuAAC reaction cycle as a catalyst; this the ideal or desired reaction pathway to initiate the CuAAC reaction. (4) Similarly, the radical can further reduce copper(I) to copper(0). Beyond side reactions of radicals, (5) copper(I) can undergo copper disproportionation in which two copper(I) molecules will react, forming copper(II) and copper(0)¹⁵³. (6) Finally, azide decomposition under UV or near UV-light is a potential reaction pathway in which the azide forms a reactive nitrene and nitrogen gas¹⁵⁴, With respect to this latter mechanism, methyl 2-azidoacetate was observed to not undergo significant decompositions in DMF when exposed to 405 nm light for 100 minutes of the reaction as shown in Figure 2.6.



Figure 2.5 Oxygen inhibition effects. Conversion of a system of 110 mM methyl 2azidoacetate, 110 mM 1-dodecyne, 10 mM copper and 10 mM Irgacure 819 in DMF after subjected to a freeze pump thaw cycle and 30 min of argon purging and without freeze pump thaw (none) at 2 mW/cm² (left) 20 mW/cm² (right). At both intensities, there is little difference between the conversions of these systems, indicating that oxygen inhibition does not play a significant role in the photo-CuAAC reaction.



Figure 2.6 Kinetics of methyl 2-azidoacetate decomposition in DMF over 100 minutes of reaction time using 10 mW/cm² of 405 nm light. The results show no significant decrease in the concentration of the azide, indicating that negligible azide decomposition occurred.

Rate law studies, where key components of the photo-CuAAC reaction are varied, reveal kinetic behavior that is different than that observed in traditional CuAAC reactions. While azide and alkyne concentration variations predictably had a negligible effect on the reaction rate, which is consistent with CuAAC kinetic behavior in the absence of accelerating ligands as shown in Figure 2.7. The copper concentration reaction dependence yields a near first-order scaling (1.15 \pm 0.08) for lower concentrations as shown in Figure 2.8.



Figure 2.7 The effect of varying methyl 2-azidoacetate (left) and 1-dodecyne (right) concentrations on the initial rate of the reaction with constant photoinitiator and copper(II) concentrations of 10 mM and 1-dodecyne of 110 mM at 1 mW/cm² and 20 mW/cm² of 405 nm light. The methyl 2-azidoacetate scaling was found to be (0.00 ± 0.01) and (0.05 ± 0.03) at 1 and 20 mW/cm² respectively. The 1-dodecyne scaling was between -0.1 and -0.26.



Figure 2.8 Copper and Irgacure 819 kinetic scaling effects. Varying copper(II) concentration (square) at constant photoinitiator concentration at 10 mM and varying photoinitiator concentration at constant copper concentration (circle) at 10 mM at 5 mW/cm2 of 405 nm light. The concentrations of 1-dodecyne and methyl 2-azidoacetate were kept constant at 110 mM. Copper(II) scaled to (1.15 ± 0.08) between 1 and 20 mM and shifted to (0.07 ± 0.08) beyond 20 mM. Irgacure 819 scaled to (1.07 ± 0.03) between 1 and 5 mM and shifted to (0.03 ± 0.03) beyond 5 mM.

While the first-order scaling in copper concentration is atypical for a CuAAC reaction, similar scaling has been previously observed where an accelerating ligand is included. This behavior was attributed to weak-donor environments in which the binuclear copper-ligand complex remains intact⁵⁰. In our system, it is unlikely that the first-order scaling is attributed to the reaction environment as DMF would constitute a strong-donor environment. Interestingly, the first-order scaling in copper has also been reported in other photo-initiated CuAAC reaction schemes. For example, Ritter and König reported a first-order scaling in copper(I) concentrations using dihydroflavin as a photoreducing agent¹²². Song et al. furthermore found a first-order dependence in copper concentrations using bulk photo-initiated CuAAC chemistries¹⁴⁶. This scaling

appears characteristic of photo-CuAAC reaction schemes that utilize an in situ photoinitiator.

At higher concentrations of copper(II), once the initial copper (II) concentration is roughly double the initial photoinitiator, there is an abrupt transition to near zerothorder kinetics. A scaling of (0.07 ± 0.08) with respect to initial copper (II) concentration is observed in this regime. We define the threshold value as the concentration in which the kinetics switches from first-order to zeroth-order. This transition likely accompanies the transition of copper(II) to a limiting reactant with respect to the photoinitiator. It also would imply that the formation of copper(I) is largely irreversible, as excess amounts are not required to continuously reduce the copper(II) back to copper(I). Furthermore, the zeroth-order kinetics copper(II) concentration threshold suggests that copper disproportionation (Figure 2.4, reaction 5) is slow relative to the photo-CuAAC reaction, since the addition of excess initial copper(II) would have shifted the equilibrium towards copper(I) formation and resulted in an increasing reaction rate rather than a zero-order plateau.

Figure 2.8, further reveals that the role of the photoinitiator on the kinetics of the photo-CuAAC system is dissimilar from a copper(II) reducing agent typically employed in CuAAC reactions. Again, a near first-order rate scaling of (1.07 ± 0.03) on the initial photoinitiator concentration is observed until a threshold of 5 mM photoinitiator is reached, where the scaling shifts to (0.03 ± 0.03) . This transition to zero-order kinetics implies that copper(II) has become the limiting initial reagent. This scaling is similar to the behavior observed above with varying initial copper(II) concentrations, and in this case the zero-order reaction rate threshold suggests that further reduction of copper(I) to copper(0) by reaction with radicals (Figure 2.4, reaction

4) is not significant. If further reduction was important to the initial kinetics, increasing the amount of photoinitiator would have decreased the initial reaction rate. The protection of the copper(I) species from further reduction could be due to the formation of a stable copper(I)-acetylide complex or the triazole acting as a ligand. While radicalradical termination (Figure 2.4, reaction 2) is most likely occurring at increased concentrations of photoinitiator, it also does not appear to affect the initial rate of the photo-CuAAC reaction. If this recombination reaction were influencing the initial rate of the photo-CuAAC reaction, an increase in initial photoinitiator concentrations would have decreased the initial reaction rate.

Figure 2.8 clearly demonstrates that the kinetic behavior is dictated by the amount and relative ratio of copper(II) and photoinitiator concentrations in the system. As discussed, several radical side reactions do not influence the rate of the reaction where the initial rate in a photo-CuAAC system is dependent on the formation of copper(I) via the reduction of copper(II) with photoinitiator radicals (Figure 2.4, reaction 3), which is justified through the threshold values obtained above. The threshold value in copper(II) concentration is always double the concentration of Irgacure 819, while the threshold value of Irgacure 819 is always half the concentration of copper(II) in the system, as depicted in Figure 2.9a and b. This result indicates that one photoinitiator molecule is capable of reducing two copper(II) molecules to copper(I) in our system, which is consistent with the capability of Irgacure 819 to cleave into four radicals³³, including two phosphinoyl radicals which have a strong copper(II) reducing potential. Moreover, the kinetics of the process are enhanced by increasing the concentration of copper(II) and photoinitiator given that the ratio between them remains constant (Figure 2.9c).



Figure 2.9 Copper(II)/Irgacure-819 ratio effects on the photo-CuAAC reaction using 110 mM methyl-2azidoacetate and 1-dodecyne in DMF at 10 mW/cm^2 (405 nm filtered light). (a) Adding copper(II) above its threshold value does not influence the reaction kinetics. Similar kinetic behaviour is observed when the concentration of photoinitiator is constant at 3 mM and copper(II) is increased from 7 mM to 15 mM (closed square and circle). The reaction rate of 25 mM of copper(II) and 15 mM of copper(II) at constant photoinitiator concentration at 7 mM is also the same (open square and circle). (b) Adding photoinitiator above its threshold value does not increase the reaction rate. The reaction rate of 3 mM Copper(II) with 3 and 7 mM of I-819 are identical (closed square and circle). The reaction rate of 7 mM Copper(II) with 7 and 15 mM of I-819 are also identical (open square and circle). (c) When both copper(II) and I-819 are increased in an equimolar ratio from 3 mM copper(II) and 3 mM I-819 (square) to 7mM copper(II) and 7 mM I-819 (circle) to 15 mM copper(II) and 15 mM I-819, the reaction rate increases.

Mechanistically, the first order results in copper(II) and photoinitiator concentration and their interdependence in influencing the reaction rate suggests that the rate determining step of this reaction, at high intensities, is the reduction of copper(II) to copper(I) (Figure 2.4, reaction 3). This assertion assumes that the rate of radical formation is faster than the rate of copper(II) reduction. However, since copper(II) to copper(I) reduction by radicals is known to be rapid, it remains unclear if the photoinitiator and copper(II) source are alternatively influencing the CuAAC cycle directly and differently than an *in situ* reagent such as sodiuim ascorbate would, which was found to not affect the CuAAC kinetics⁴⁹.

While the initial rates of the photo-CuAAC reaction are unchanged beyond the copper(II) and photoinitiator threshold values, the overall conversion of the reaction system is affected by the relative copper(II) to photoinitiator ratios present in the system. Increasing the concentration of initial copper(II) in the system above a threshold value of photoinitiator in the system does not affect the overall conversion of the reaction (Figure 2.10). This implies that disproportionation reactions play no significant role in the photo-CuAAC reaction. However, increasing the amount of photoinitiator relative to the copper(II) concentration threshold has a deleterious effect on the overall conversion (Figure 2.10). Excess photoinitiator is hypothesized to be reacting with copper(I) to form copper(0) at a later stage of the reaction (i.e., Figure 2.3, reaction 4); when a large excess of photoinitiator molecules was used, the solution turned a dark brown color after irradiating which is indicative of copper(0) formation. Increased radical recombination as the reaction progresses may also be occurring due to the large excess of photoinitiator radicals at high intensities. Indeed, when increasing the concentration of photoinitiator 40 times that of initial copper(II), the reaction exhibits a drastic decrease in the overall conversion where it plateaued at 20% conversion after only 25 minutes of reaction (Figure 2.11). This result further illustrates how the photoinitiator interaction with copper is different than an in situ reducing agent such as sodium ascorbate, which can be used in excessive quantities^{56,155}.



Figure 2.10 Final conversion effects of increasing copper(II) and photoinitiator concentrations in a photo-CuAAC system. (a) At a constant 1-dodecyne and methyl 2-azidoacetate concentration at 110 mM and Irgacure 819 concentration at 10 mM, adding copper between 10 mM and 100 mM resulted in a final conversion that ranged between 94 and 98%. (b) At a constant 1-dodecyne and methyl 2-azidoacetate concentration at 110 mM and copper(II) concentration at 10 mM, adding Iragacure-819 in the system between 10 mM 100 mM decreased the final conversion from 94% to 76% after 40 minutes.



Figure 2.11. Increasing the concentration of photoinitiator beyond that of copper results in a decreased overall conversion of the photo-CuAAC reaction system.

The photo-CuAAC reaction exhibits two different behaviors depending on the light intensity used (Figure 2.12). In the high intensity regime, the kinetic behavior, threshold values, and scaling of copper(II) and photoinitiator are unchanged as a function of intensity as shown in Figure 2.13. Intensity effects directly impact the rate photolysis the of radical formation in conventional of and thus rate photopolymerizations. A reaction rate intensity independence indicates that at intensities 5 mW/cm^2 and above, the rate determining step of the reaction is not dependent on the rate of radical formation. In the low intensity regime, the photo reduction must be occurring at similar rates to the CuAAC reaction, and as a result, the overall reaction rate has a much more complex dependence on the initial copper(II) and photoinitiator concentrations. Consequently, the copper(II) and photoinitiator scaling is altered, and furthermore the characterization of the reaction in terms of the initial ratio of copper(II) to photoinitiator is no longer possible.



Figure 2.12 The effects of varying intensity on the initial rate of the photo-CuAAC reaction. The concentration of Irgacure 819 and copper(II) were 10 mM and the concentration of 1-doedecyne and methyl 2-azidoacetate were constant at 110 mM each. The intensity did not significantly influence the kinetics above 5 mW/cm².



Figure 2.13 Initial rate of the photo-induced CuAAC reaction as a function of varying initial Cu(II) concentration (left) and photoinitiator concentration (right) using at 10 and 20 mW/cm² intensity of 405 nm. The other components in the reaction system were 110 mM of methyl 2-azidoacetate and 1-dodecyne and 10 mM of Irgacure 819 or Cu(II). Cu(II) initially scales to (1.20 ± 0.07) and (1.21 ± 0.06) at 10 and 20 mW/cm² respectively. After the concentration is increased above 20 mM of Cu(II), the scaling shifts to (0.03 ± 0.02) and (0.01 ± 0.09) at 10 and 20 mW/cm² respectively. The photoinitiator initially scales to (1.14 ± 0.01) and (1.17 ± 0.03) at 10 and 20 mW/cm² respectively. After the concentration is increased above 20 mM of Cu(II) and (-0.01 ± 0.05) at 10 and 20 mW/cm² respectively. After the concentration is increased above 10 mM of Cu(II) and (-0.01 ± 0.05) at 10 and 20 mW/cm² respectively.

In the low intensity regime, the photo-CuAAC system exhibits a delay before the onset of the decrease in azide concentration. While this induction period has been observed in other photo-CuAAC systems, it had been generally attributed to potential oxygen inhibition effects¹⁵⁶. Through argon purging experiments, there was no evidence of oxygen inhibition in our samples at low intensities. The induction period at low intensities could moreover be attributed to the slow kinetics of radical formation at low intensities; the photo-CuAAC reaction would require a build-up of radicals to convert copper(II) to copper(I). This is, however, unlikely since the kinetics of copper(II) to copper(I) conversion in the presence of phosphinoyl radicals for photo-CuAAC reactions was found to be extremely rapid¹⁵⁷. Furthermore, this period may be an indication that the triazole product acts as a ligand for the copper(I) species; once a small amount of triazole forms, autoacceleration of the reaction is achieved due to the stable copper(I) ions formed. Alternatively, an induction time has been observed in traditional CuAAC reactions, which was attributed to the nature of the copper-ligand and copper-anion interactions with the alkyne species as discussed by Jin et al¹⁵⁸. Finally, a relatively simple explanation of the induction period is that the copper(II) is quenching of the photoinitiating system. Therefore, as copper(II) is converted to copper(I), the reaction rate would accelerate as suggested in Figure 2.14. It should be noted that the quenching of photoinitiating ketones by metal cations (including copper cations) has been reported in literature^{159,160}.



Figure 2.14 Suggested photoinitiation scheme in which the copper(II) source can quench the photoinitiator triplet state (PI*) before it forms radicals. Once this inhibition is overcome, the photoinitiator (PI) can form radicals (R•) which then reduce copper(II) to copper(I) catalyzing the CuAAC reaction.

The induction period appears to be dependent on the absorbency and quantum yield of the photoinitiator used in a photo-CuAAC reaction as discussed by Tasdelen et al¹⁶¹. This would explain why the induction period is significantly reduced by increasing photoinitiator concentrations. Indeed, increasing the concentration of the photoinitiator increased the rate of radical generation which effectively shifts the intensity-driven threshold values as shown in Figure 2.15.



Figure 2.15 Photoinitiator concentration effects in the low intensity regime: Varying the concentration of Irgacure 819 from 2.5 mM to 70 mM at a constant copper(II) concentration at 10 mM and methyl 2-azidoacetate and 1-dodecyne constant at 110 mM. The intensity used was 0.5 mW/cm² of 405 nm filtered light. Increasing the concentration of photoinitiator from 2.5 mM to 70 mM decreased the inhibition time from 3 minutes to less than 15 seconds and increased the reaction rate significantly.

The kinetic trends in these solvent-based, model systems are also observed in solventless, bulk photopolymerizations that use copper ligands to catalyze the CuAAC chemistries. Since copper(II) is not miscible in the neat monomer systems, we use

CuCl₂/PMDETA along with Irgacure 819 to demonstrate the compositional variation effects in a network forming polymerization (i.e., the photo-CuAAC reaction of monomer 1 and monomer 2). The threshold value effects of Irgacure 819 is demonstrated in Figure 2.16, where increasing the concentration of photoinitiator in the system beyond a constant amount of CuCl₂/PMDETA (1 wt%) is negligible. However, when both copper(II) and photoinitiator concentrations are increased simultaneously at a 1:1 molar ratio, the kinetics of the reaction are notably increased as depicted in Figure 2.16.



Kinetic results in polymerizing systems using Irgacure 819 and Figure 2.16 CuCl₂/PMDETA along with monomers 1 and 2 as the reactants and at a constant intensity of 10 mW/cm² of 405 nm wavelength light and a sample thickness of 0.12 mm. The grey, shaded area represents the time (5 min) before the light was turned on. (a) Threshold value in photoinitiator applies in network forming systems. When the concentration of photoinitiator is increased beyond half that of copper(II), from a 1:2 mol ratio Irgacure 819:CuCl₂-PMDETA (square) to an equimolar ratio (circle) and then a 2:1 mol ratio (triangle), there was little increase in the reaction rate. (b) When the concentration of photoinitiator and copper(II) where increased in equimolar concentrations from a 0.5 wt% of Copper(II) (square) to 1 wt% Copper(II) (circle) to 3 wt% ratio (square), the rate of the reaction significantly increases.

Similar to model systems, the threshold value in intensity is observed in network forming systems, as shown in Figure 2.17. In contrast to other radical-initiated polymerizations^{162–164}, increasing the light intensity beyond a threshold value does not increase the polymerization rate. In our system this threshold was observed beyond 20 mW/cm² where the polymerization kinetics become independent of the rate of radical formation.



Figure 2.17 Varying intensity in polymer systems using Irgacure 819 and CuCl₂-PMDETA along with monomers 1 and 2 as the reactants using 405 nm wavelength and a sample thickness of 0.12 mm. The grey, shaded area represents the time (5 min) before the light was turned on. When the intensity was increased beyond 20 mW/cm², the reaction rate did not significantly change.

2.4 Conclusions

The kinetic behavior of the photo-CuAAC reaction shows two different regimes of behavior. In the first, the photoreduction of copper(II) is much faster than the kinetics of the CuAAC reaction. Here, the initial reaction rate is increased by increasing the concentrations of the photoinitiator until the photoinitiator is in excess, and zero-order behavior is observed. Near first-order kinetics is observed in with respect to copper(II) concentrations. Consequently, first-order behavior is also observed with respect to photoinitiator when copper(II) is in excess. This threshold behavior is indicative of the robust nature of the photo-CuAAC reaction in this regime as several potential side reactions appear to be largely suppressed and the reaction is highly selective towards forming the desired copper(I) catalyst. However, while using excess photoinitiator in the system does not affect the initial rate, it does significantly decrease the overall conversion of the reaction, implying that further reduction of copper(I) to copper metal does play a role in the kinetics. This behavior is significantly different from typical in situ reducing agents such as sodium ascorbate, which can be used in large excess when compared to the copper catalyst amount.

In the second regime, the copper(II) reduction reaction appears to occur on a similar timescale to the CuAAC reaction, which significantly complicates the observed behavior and the scale of the rate law with regards to the initial copper (II) and photoinitiator concentrations. Furthermore, an induction period is observed in these systems which can be significantly decreased by increasing the concentration of the photoinitiator used or the intensity of light. It is hypothesized that the induction period is due to copper(II) quenching of the triplet state of the photoinitiator.
The kinetic trends observed in the solvent system were extended to a solventfree polymer network system. This photopolymerization shows similar results to the solvent system kinetics, which further emphasizes the importance of the copper and photoinitiator threshold values and its impact on controlling the reaction rate in different photo-CuAAC reaction schemes. While the photochemical reduction used in the photocommon conventional CuAAC reaction shares some steps in with photopolymerizations, the nuances of the CuAAC reaction give it much different behavior. Unlike radical reactions, the zero-order behavior observed provides some interesting opportunities for applications requiring dark cure post exposure and low intensity curing. Furthermore, while this behavior does occur in the "high light intensity" regime reported here, it must be noted that these light intensities are one to two orders of magnitude less than that used in many industrial applications. This fact implies that were these materials to show better performance than conventional photopolymers, the curing chemistry should not limit their implementation.

Chapter 3

NORRISH TYPE(II) PHOTO-CuAAC POLYMERIZATIONS

This chapter contains results that were published in Chemical Communications in 2016¹⁷.

3.1 Introduction

The photo-CuAAC reaction requires the radical reduction of copper(II) to copper(I) following the irradiation of a photoinitiator. The photoinitiator can undergo one of two mechanisms: Norrish Type(I) and Norrish Type(II) reactions¹⁶. The Norrish Type(I) reaction, also known as an α -cleavage involving direct dissociation of the species into radicals capable of reducing copper(II) to copper(I). The Norrish Type(II) reaction is an electron transfer reaction and typically abstracts a hydrogen intermolecularly in the presence of a co-initiator (such as a tertiary amine) which forms radicals capable of reducing copper(II). A general schematic of these reactions is shown in Figure 3.1. While most commercially available photoinitiators are Type(I) initiators, they typically absorb in the UV-region. Irradiating under UV-light has shown to cause side reactions such as self-initiating monomers and degradation reactions. Azides, particularly, are susceptible to degradation under UV-light. This degradation has been taken advantage of in photo-induced azide-amine conjugation reactions¹⁶⁵. In this scenario, azides photo-decompose to form a reactive nitrene followed by ring expansion and reaction with the amine substrate^{166,167}. While the photo-CuAAC reaction has several favorable attributes such as direct spatial and temporal control over the reaction and enhanced reaction kinetics, these attributes are diminished when 365 nm or 405 nm light (i.e., UV or near UV-light) is irradiated onto the system. The loss of these characteristics is due to the emergence of bubbles forming within the polymeric film as photographed in Figure 3.2.



Norrish Type (I) Photoinitiating System

Figure 3.1 Norrish Type(I) vs Norrish Type(II) photoinitiation of the CuAAC reaction. In a Type(I) initiation, the photoinitiator undergoes intersystem crossing to form an excited state which then dissociates into two radicals. One or more of these radicals can then reduce copper(II) to copper(I). In a Type(II) initiation, the photoinitiator also undergoes intersystem crossing, but then typically abstracts a hydrogen from a co-initiator (CI). The result co-initiator radical can then reduce copper(II) to copper(I).



Figure 3.2 Photo-CuAAC polymer films using Irgacure-819 as the photoinitiator under [A] 365 nm light and [B] 405 nm light

3.2 Experimental Procedures

3.2.1 Materials

The following chemical compounds were used without further purification: bis(2,4,6-trimethylbenzyoyl)-phenylphosphineoxide (Irgacure 819) (Ciba), N,N,N',N',N''-pentamethyldiethylenetriamine (Sigma Aldrich), copper chloride (Sigma Aldrich), camphorquinone (Ciba), 4,N,N-trimethylaniline (Sigma Aldrich)

3.2.2 Polymerizations

The polymer application experiments used bis(6-azidohexyl)(1,3phenylenebis(propane-2,2-diyl))dicarbamate and 1-(Prop-2-ynyloxy)-2,2-bis(prop-2ynyloxymethyl)butane (monomers 1 and 2, Figure 3.3). The reactants were mixed stoichiometrically with respect to the azide and alkyne functional groups. A copper chloride N,N,N',N',N''-pentamethyldiethylenetriamine (PMDETA) ligand was synthesized to act as the copper(II) source which was characterized using elemental analysis and dissolved in trace (<1wt%) methanol. Irgacure 819, or camphorquinone with 4,N,N-trimethyl aniline, were used as the photoinitiator. The components were mixed under high speed using a DAC 150.1 FVZ-K Flacktek Speed Mixer. The conversion in these experiments were monitored using a Thermofisher IS-50 FTIR via tracking the alkyne near-IR peak between 6430 and 6570 cm⁻¹ where the trifunctional alkyne has a peak at 6507 cm⁻¹. All polymer samples were placed between glass slides and separated with a spacer of either 0.12 mm or 0.5 mm thickness. The structure of the monomers, catalyst and photoinitiators used in the polymerization system is shown in Figure 3.3. The decrease in the near-IR alkyne peak at 6507 cm⁻¹ is shown in Figure 3.4.



Figure 3.3 Monomers, catalyst and photoinitiators used in the polymerization system. (1) bis(6-azidohexyl)(1,3-phenylenebis(propane-2,2-diyl))dicarbamate (2) 1-(Prop-2-ynyloxy)-2,2-bis(prop-2-ynyloxymethyl)butane (3) CuCl₂/PMDETA (4) Irgacure 819 (5) Camphorquinone (6) 4,N,N-trimethyl aniline.



Figure 3.4 The change in absorbance of the near-IR alkyne peak at 6509 cm⁻¹ for the CuAAC polymer system before (left) and after irradiation (right).

3.2.3 Gas chromatography

A 0.5 gram sample of Bis(6-azidohexyl)(1,3-phenylenebis(propane-2,2diyl))dicarbamate was placed in a small argon purged chamber. Nitrogen and oxygen sensors were attached to a gas chromatographer (GC) instrument. The sample was then irradiated with either 365 or 470 nm light and the nitrogen:oxygen ratio was measured as a function of irradiation time.

3.2.4 UV-vis experiments

The UV-Vis spectroscopy analysis was performed by Abhishek Shete. A 1 mM solution of monomer **1** in *N*,*N*-dimethylformamide (DMF) was prepared. Absorbance spectrum between 270 and 500 nm⁻¹ was performed using a Thermofisher UV-vis Spectrophotometer (Evolution 260 Bio) in a 1 cm thick quartz cuvette. Real-time spectra

was recorded at both 365 nm (UV) light and 470 nm (blue) light at an intensity of 40 mW/cm^2 .

3.2.5 Dynamic mechanical analysis

The modulus and glass transition temperature were calculated using a Dynamic Mechanical Analyzer (DMA) Q800 from TA instruments. The temperature range was varied between 0 °C to 200 °C (3 °C/min rate) at a constant amplitude and frequency at 15 μ m and 1 Hz, respectively).

3.3 Results and Discussion

Bulk photo-polymerized CuAAC network systems had been typically initiated with UV-light (365 nm) or near-UV wavelengths of light (e.g. 405 nm) using an appropriate absorbance-matched photoinitiator species^{136,146,168}. As mentioned, continuous UV irradiation at these wavelengths can lead to the photo-decomposition of azide functional groups present on the monomers. While azide photo-decomposition is a relatively minor reaction compared to the azide-alkyne crosslinking reaction, bubbles are clearly observed in 0.5mm thick films formed as shown in Figure 3.2. At higher energies (lower wavelengths), however, the amount of bubbles decreased (Figure 3.2 A and B). While other factors could cause formation of nitrene gas in the presence of UV-light remained the main hypothesized cause of bubble formation. In order to test the

hypothesis several experiments were carried out as shown in Figure 3.5. First, Bis(6azidohexyl)(1,3-phenylenebis(propane-2,2-diyl))dicarbamate (monomer 1) was placed between glass slides and irradiated with 365 nm light at an intensity of 40 mW/cm² for 1 hour (Figure 3.5A). Bubbles were observed in the system and increased as a function of time, indicating that the azide monomer was responsible for bubble formation. To test the hypothesis of azide decomposition, two experiments were carried out. The first was performed by Abhishek Shete and involved tracking the UV-vis spectra of the azide monomer in DMF while irradiating with 365 nm light (Figure 3.5B). The spectra showed a decrease in the absorbance at 285 nm, corresponding to the azide peak. This decrease indicates that azide decomposition was occurring under UV-light. The second was performed using a gas chromatographer (Figure 3.5C). The azide monomer was irradiated solventless under both 365 and 470 nm of light. Only when irradiated with 365 nm light did the Nitrogen:Oxygen ratio increase, indicating the formation of Nitrogen gas due to azide decomposition (Figure 3.5D).

Wavelength selection is critical to avoid bubble formation in photo-CuAAC resins. Inspired by dimethacrylate polymerizations, a blue-light photoinitiating system was proposed using Camphorquinone (CQ) a photosensitizing cyclic ketone, which is a well-known visible light photoinitiator with peak absorption of 469 nm³⁵. CQ alone has been shown to photoinitiate CuAAC using a mercury lamp equipped with a 400-500 nm band filter for small molecules by Tasdelen et.al³⁷ and in bulk polymerization by Song et al.³² at elevated temperatures (35°C). In photopolymerization of vinyl monomers the use of a co-initiator amine species in conjunction with CQ has been utilized as a kinetic accelerator³⁸. Motivated by this approach, a novel CQ-amine photoinitiation system is developed.



Figure 3.5 [A] Monomer 1 irradiated under 365 nm light shows formation of bubbles over 1 hour of irradiation. [B] UV-vis spectra of monomer 1 dissolved in DMF as 365 nm light is irradiated. A decrease in the azide peak at 285 nm is observed as a function of irradiation time. [C] Schematic of monomer 1 irradiated under both 365 nm light and 470 nm.
[D] Production of bubbles were observed under the 365 nm and the eventual rupture led to a spike in the nitrogen to oxygen ratio as tracked by Gas Chromatography. No bubbles nor spike in the nitrogen to oxygen ratio was observed in the 470 nm system.

Mechanistically, the CQ-tertiary amine is a Norrish Type II photoinitiation system and follows a well-known two stage initiation process. Briefly, 470nm wavelength light excites the CQ to a singlet state during the n- σ^* transition. After an inter-system crossing (ISC) from the singlet to the triplet state, CQ interacts via electron transfer with the tertiary amine to form an excited complex (exciplex), which then extracts hydrogen from the amine to form a radical on the α -C atom of the tertiary amine¹⁶⁹ (as illustrated in. Figure 3.6A). The stability of this radical is critical in the H transfer process¹⁶¹. The radical on the amine then reduces copper(II) to copper(I) which in turn catalyzes the CuAAC reaction.

The polymerization kinetics of this system are moreover enhanced (Figure 3.6B). The amine was added to monomers in a 1:1 CQ:amine ratio at 0.7wt% each relative to the resin total mass. The resin was then polymerized under a 470 nm wavelength filtered light of 30mW/cm² intensity to yield a bubble free network that reaches over 90 percent conversion in less than 25 minutes (Figure 3.6C).



Figure 3.6 [A] Camphorquinone/tertiary amine photoinitiation scheme. [B] polymerization kinetics for a sample containing equimolar difuntional azide and trifunctional alkyne irradiated under 470 nm light under 30 mW/cm² in the presence of 1.5wt% copper(II)/PMDETA and 0.7wt% caomphorquinone and 4,N,N-trimethylaniline. The polymerization reaches >90% conversion in 25 minutes. [C] Bubble free photo-CuAAC polymer film using camphorquinon/4,N,N-trimethylaniline scheme under 470 nm.

The mechanical properties of the blue light photopolymerization CuAAC film were analyzed using a Dynamic Mechanical Analyzer (performed by Abhishek Shete). These properties were compared to that of a 70:30 BisGMA:TEGDMA film, photopolymerized using the same concentrations of camphorquinone and 4,N,N-trimethylaniline (Figure 3.7). This comparison was performed to better assess the suitability of the CuAAC network as a potential replacement for the BisGMA:TEGDMA dental resin. The modulus of the photo-CuAAC film was 2.8 GPa at room temperature (25° C) which is similar to that of the methacrylate at the same temperature at 3.2 GPa. Moreover, when plotting the tan(δ) as a function of temperature, the Tg is the temperature at which the tan(δ) has reached a maximum. Figure 3.7B shows that while the glass transition temperature of the CuAAC film is significantly lower than that of the methacrylate film, at 69°C and 154°C respectively, the CuAAC network exhibits a much narrower tan(δ) peak. This narrowness indicates that the CuAAC network is more homogenous than that of a methacrylate network, most likely owing to the step-growth polymerization nature of CuAAC photopolymers compared to the free-radical mechanism of the dimethacrylate polymerization.

To further investigate the suitability of the blue-light polymerized photo-CuAAC network as a dental material, OX50 silica was mixed into the formulations (at 10, 20, and 30 wt%) of both the CuAAC and dimethacrylate systems. The overall conversions of the reactions over 12 hours as well as the elastic modulus were assessed for each system as shown in Figure 3.8. The results show that, the CuAAC networks consistently reached near-full conversion regardless of the amount of silica as compared to the BisGMA:TEGDMA dimethacrylate system which did not exceed 70% conversion.



Figure 3.7 Dynamic mechanical analysis data for a CuAAC polymer film and a dimethacrylate (70:30 BisMGA:TEGDMA) film. Both samples polymerized by using 0.7 wt% camphorquinone and 0.7wt% 4,N,N-trimethylaniline and were irradiated under 30 mW/cm² of 470 nm light. Both samples were 0.5 mm thick. [A] The storage modulus as a function of time. The CuAAC film and the dimethacryalte film showed similar room temperature storage moduli at 2.8 and 3.2 GPA respectively. [B] The glass transition temperature was calculate by plotting tanδ as a function of temperature. The Tg of the CuAAC film is at 69°C and the BisGMA:TEGDMA film at 154°C.



Figure 3.8 [A] Comparison between final conversion (after 12 hours) of a CuAAC network polymerized with monomers (1) and (2) and a 70:30 BisGMA:TEGDMA network using varying amounts of OX-50 sillica. The CuAAC reaction's conversion was consistently above 95% conversion whereas the dimethacrylate system's conversion ranged between 60 and 70 percent conversion. [B] Comparison between the storage modulus of the CuAAC networks and BisGMA:TEGDMA networks at 0, 10 and 20 wt% of OX50 silica.

3.4 Conclusion

In order to subdue azide decomposition in photo-CuAAC polymer films, a novel Type(II) photoinitiating scheme is developed for photo-CuAAC polymerizations using blue light. This system shows many advantages over previous systems that depend on traditional Type(I) photoinitiators. Mainly, azide decomposition is avoided at 470 nm and no bubbles are observed in polymer films when camphorquinone/4-N,N trimethyl aniline are used. Moreover, the kinetics are accelerated where the reaction shows high

conversion (>90% in 25 minutes). Moreover, the resulting photo-CuAAC films exhibited high room temperature modulus, and a narrow glass transition temperature. Finally, using this photoinitating scheme, the CuAAC films were made into composites by mixing silica (OX50) into the resin formulation prior to polymerization. The kinetics of the reaction remained high (>95%) over 12 hours compared to analogous 70:30 BisGMA:TEGDMA composites which did not reach higher than 70% conversion on average.

Chapter 4

COPPER CATALYST LIGAND AND ANION EFFECTS

4.1 Introduction

Since its discovery in 2002, the copper(I) catalyzed azide—alkyne cycloaddition (CuAAC) reaction^{6,7} has been one of the most influential 'click' reactions¹ with applications in various fields such as organic synthesis,^{170–172} bioconjugation,¹⁷³ and polymers.^{18,111} Click reactions are typically robust in nature, easy to carry out, afford high yields, and exhibit excellent selectivity between reactive groups with limited or easily removable by-products. The copper(I) source is usually introduced directly by adding a copper(I) salt or through the use of a reducing agent, such as sodium ascorbate in conjunction with a copper(II) salt.^{56,150} In an effort to afford this reaction spatiotemporal control, several researchers have photoinitiated the CuAAC reaction through the use of an external photosensitizing or photoinitiating agent capable of reducing copper(II) to copper(I).^{34,122,124} The overall ability to dictate when and where a chemical reaction takes places using light is critical to multiple applications in materials science, such as photo-lithography⁵⁹, dental materials¹⁴⁴, self-healing¹⁰⁸, and stereolithographic 3D-printing¹⁷⁴. The advantages of using the light-induced CuAAC chemistry is no exception, and it has been especially successful in implementations such as biomaterials and composites.^{14,15,118,135,157}

Copper(II) chloride ligated to N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA) has been widely employed in photo-induced CuAAC step-growth polymerizations. The use of this nitrogen-based ligand is not only attributed to an enhancement in the stability of the copper(I) oxidation state,¹⁶⁸ but also an increase in

the solubility of copper in neat CuAAC resins. Nitrogen based ligands can moreover retard copper(I) disproportionation into copper(II) and copper(0)^{50,175}. The significance of nitrogen-based copper-ligands on reaction rates has been demonstrated in controlled and living polymerizations,^{176,177} specifically, atom transfer radical polymerizations (ATRP). In ATRP, the ability to control copper oxidation states is critical for the selectivity and kinetics of the reaction^[ref] where the activation rate constant of an ATRP reaction is heavily influenced by the type of ligand used^{178,179} While copper catalyst performance has been studied in both ATRP and CuAAC chemistries that are not light activated^{12,180–182}, there have been no efforts to understand catalyst performance and ligand effects in photo-mediated CuAAC polymerizations.

Herein, the reaction kinetics of photo-CuAAC polymerizations are assessed as a function of copper(II) species complexed with different polydentate amine ligands in both Norrish type(I) and type(II) photopolymerization schemes. The effects of the ligands and counter ions on the temporal control of the photo-CuAAC polymerization are assessed through evaluating the long-term stability of these copper complexes in the presence and absence of photoinitiators and light. Finally, the robustness of the photo-CuAAC polymerization is demonstrated to be solely dictated by the copper(II) source and ligand species present.

4.2 Materials and Methods

4.2.1 Materials

Copper(II) chloride [CuCl₂], copper (II) bromide [CuBr₂], copper (II) acetate [Cu(OAc)₂], copper(II) sulfate [CuSO₄], N,N,N',N'',N''-pentamethyldiethylenetriamine [PMDETA], tetramethylethylenediamene [TMEDA],

2,2'-bipyridine [BPY], and di-(2-picolyl)amine [DPA] 1,1,4,7,10,10hexamethylenetetramine (HMTETA) were used as received from Sigma Aldrich. Copper(II) bis(trifluoromethanesulfonyl)imide $[Cu(TFSI)_2]$ and tris[2-(dimethylamino)ethyl]amine [Me6TREN] were used as received from TCI America. Acetonitrile and methanol were used as received from Fisher Scientific. Anhydrous ethanol was used as received from Decon Laboratiories Inc. All ligands and monomers used in the study are shown in Scheme 1.

4.2.2 Copper Ligand Synthesis

Synthesis of CuBr₂-TMEDA: In a round-bottom flask, 1.28 g (~5.75 mmol) of CuBr₂ was dissolved in approximately 30 mL of methanol. A solution of 0.67 g (~5.75 mmol) of TMEDA in 10 mL of methanol was added to the CuBr₂/methanol solution dropwise. The reaction proceeded for 3 hours. The resulting green liquid was heated under reduced pressure to evaporate the solvent. The dark green powder was further dried under vacuum. The product was obtained in 89% yield (1.74 g). Elemental Analysis, Calculated (%): C, 21.22; H, 4.75; N, 8.25; Measured (%): C, 21.28; H, 4.65; N, 8.38 **Synthesis of CuBr₂-BPY:** In a round-bottom flask, 1.12 g (~5.0 mmol) of CuBr₂ was dissolved in approximately 40 mL of anhydrous ethanol. A solution of 0.78 g (~5.0 mmol) of BPY in 10 mL of anhydrous ethanol was added to the CuBr₂/EtOH mixture dropwise. The reaction proceeded for 18 hours. The resulting light brown solution was heated under reduced pressure to remove the solvent. The remaining light brown solid was further dried under vacuum. The product was obtained in 43% yield (0.82 g).

Elemental Analysis, Calculated (%): C, 31.65; H, 2.12; N, 7.38; Measured (%): C, 32.58; H, 2.21; N, 7.80

Synthesis of CuBr2-DPA: In a round-bottom flask, 0.224 g (~1.00 mmol) of CuBr₂ was dissolved in approximately 15 mL of anhydrous ethanol. A solution of 0.20 g (~1.00 mmol) of DPA in 10 mL of anhydrous ethanol was added to the CuBr₂/EtOH mixture dropwise. The reaction proceeded for 3 hours. The resulting blue precipitate was filtered from the solution. The remaining blue solid was further dried under vacuum. The product was obtained in 71% yield (0.30 g). Elemental Analysis, Calculated (%): C, 34.10; H, 3.10; N, 9.94; Measured (%): C, 34.34; H, 3.01; N, 10.02

Synthesis of CuBr₂-Me₆TREN: In a round-bottom flask, 0.097 g (~0.43 mmol) of CuBr₂ was dissolved in approximately 15 mL of anhydrous ethanol. A solution of 0.10 g (~0.43 mmol) of Me₆TREN in 10 mL of anhydrous ethanol was added slowly to the CuBr₂/EtOH mixture. The reaction proceeded for 3 hours, resulting in a green solution. The solution was heated under reduced pressure to evaporate the solvent. The remaining green solid was further dried under vacuum. The product was obtained in 87% yield (0.17 g). Elemental Analysis, Calculated (%): C, 31.76; H, 6.66; N, 12.35; Measured (%): C, 31.47; H, 6.69; N, 12.32

Synthesis of CuBr₂-HMTETA: In a round-bottom flask, 0.20 g (~0.87 mmol) of CuBr₂ was dissolved in 25 mL of anhydrous ethanol. A solution of 0.20 g HMTETA in 7.5 mL of ethanol was added to the reaction mixture dropwise. The reaction proceeded for 3 hours, was heated under reduced pressure, and kept to dry for 24 hours under vacuum to give a green solid. The product was obtained in 99% yield (0.39 g). Elemental

Analysis, Calculated (%): C, 31.76; H, 6.66; N, 12.35; Measured (%): C, 32.39; H, 6.59; N, 12.59

Synthesis of Cu(TFSI)₂-PMDETA: In a round-bottom flask, 0.194 g (~0.16 mmol) of Cu(TFSI)₂ was dissolved in approximately 15 mL of anhydrous ethanol. After stirring, 0.028 g (~0.16 mmol) of PMDETA was added to the solution. The proceeded for 3 hours, resulting in a blue solution. The solution was heated under reduced pressure to evaporate the solvent. The remaining blue solid was further dried under vacuum. The product was obtained in 63% yield (0.08 g). Elemental Analysis, Calculated (%): C, 19.59; H, 2.91; N, 8.79; S, 16.09; Measured (%): C, 18.51; H, 3.18; N, 8.40; S, 16.418 Synthesis of Cu(OTf)₂-PMDETA: In a round bottom flask, 0.10 g (~0.28 mmol) of Cu(OTf)₂ was dissolved in 20 mL of acetonitrile. After stirring, 0.048 g (~0.28 mmol) of PMDETA was added dropwise to the solution. The reaction proceeded for 6 hours, resulting in a dark blue solution. The solution was heated under reduced pressure to evaporate the solvent. The dark blue solid was dried under vacuum overnight. The product was obtained in 80% yield (0.118g g). Elemental Analysis, Calculated (%): C, 24.70; H, 4.33; N, 7.85; S, 11.99; Measured (%): C, 23.74; H, 4.47; N, 7.33; S, 11.15 The synthesis of CuBr₂ and CuCl₂ with PMDETA followed the procedure by Margaf et al.¹⁴⁷

Elemental Analysis CuBr₂-PMDETA, Calculated (%): C, 27.75; H, 5.84; N, 10.59; Measured (%): C, 28.19; H, 5.94; N, 11.16

Elemental Analysis CuCl₂-PMDETA, Calculated (%): C, 35.12; H, 7.53; N, 13.65; Measured (%): C, 33.99; H, 7.69; N, 13.41

All ligands and monomers used in this study are shown in Figure 4.1



Figure 4.1 Polydentate amine ligands and monomers used in this study.

4.2.3 Polymerization kinetics

An equimolar functional group ratio of AZ-1 and YNE-1 was used in all polymer samples. The monomers were added together with an equimolar concentration of copper(II) (1.15 mol% relative to azide mol functionality). Methanol was added to assist with solubility in the polymer sample but was later removed under high vacuum so that the total amount of methanol was less than 1 wt%. A 0.2 gram aliquot was then taken

and 1 wt% of camphorquinone was added to the reaction mixture. A DAC 150.1 FVZ-K Flacktek Speed Mixer was later utilized to mix the components under high speed. All polymerization samples were placed between glass slides separated by 0.11 mm plastic shims. An IS-50 Fourier Transform Infrared (FTIR) spectrometer (Thermofisher Scientific) was utilized to track the near-IR alkyne peak between 6430 and 6570 cm⁻¹ for real-time kinetics. The decrease in the alkyne peak area was converted to overall alkyne conversion in the system using a Beer's law analysis.

4.3 **Results and Discussion**

The copper(I) catalyzed azide-alkyne cycloaddition reaction is a conjugation reaction between an azide and alkyne in the presence of copper(I) as shown in Figure 4.2a. Photoreduction of copper(II) to copper(I) in CuAAC polymerizations occurs using either Norrish Type(I) or Type(II) photoiniating reactions (Figure 4.2b). The Norrish Type(I) reaction, also known as an α -cleavage reaction involves direct dissociation of the species into radicals capable of reducing copper(II) to copper(I). Since most Norrish Type(I) photoinitiators absorb in the UV-region, this makes the photo-CuAAC reaction susceptible to other side reactions, such as azide degradation¹⁷. Mechanistically, the Norrish Type(II) reaction is an electron transfer reaction and typically abstracts a hydrogen intermolecularly in the presence of a co-initiator. In the presence of a copper(II) species, these radicals can reduce copper(II) to copper(I). In the absence of

an external amine, this hydrogen can be extracted from another source, such as the amine-based ligand used in the CuAAC reaction.



Figure 4.2. A) Schematic of the photo-CuAAC polymerization. An alkyne functional group (blue) reacts with an azide functionality (red) in the presence of copper(I), forming a step-growth network with triazole linkages (purple). (B) The photoinitiation of the reaction occurs by one of two routes: Norrish Type(I) and Norrish Type(II) photoinitiation. In Type(I) initiation, the photoinitiator (shown as RCOR') undergoes intersystem crossing to form an excited state which then dissociates into two radicals. One or more of these radicals can then reduce copper(II) to copper(I). In Type(II) initiation, the photoinitiator also undergoes intersystem crossing, but then typically abstracts a hydrogen from a co-initiator (H-R''). The resulting co-initiator radical can then reduce copper(II) to copper(I).



Figure 4.3 Conversion profile between AZ₁ and YNE₁ of photo-CuAAC chemistries using 1.5wt% copper(II) bromide or chloride pre-ligated BPY and DPA respectivitely to a under 470 nm light at 30 mW/cm² in the presence of 1 wt% camphorquinone. Negligible reaction was observed in these systems over 2 hours.

The copper(II) aliphatic ligands were further tested for kinetic performance. Copper(II) bromide ligated to HMTETA displays the fastest kinetics where the average initial rate of polymerization was twice as fast with HMTETA as compared with PMDETA and Me6TREN (Figure 4.4A). While previous studies on non-photoinitiated CuAAC showed tridentate ligands have been favorable in catalyzing CuAAC reactions over tetradentate amines^{168,181} since tetradentate ligands coordinatively saturate the copper(I) source disfavoring copper(I)-alkyne coordination, the opposite trend is observed in photo-CuAAC polymerizations. One potential explanation for this discrepancy owes to the photo-CuAAC initiation mechanism in the absence of an accelerating amine (Figure 4.4D). Since the ligand is the only source of abstractable N- α -carbon hydrogens, a tetradentate ligand (HMTETA) is expected to exhibit faster kinetics than a tridentate ligand (PMDETA) due to the increase in availability of these abstractable hydrogens. While also a tetradentate ligand, Me6TREN is not as fast as HMTETA potentially due to steric hindrances caused by branching.



Figure 4.4 Conversion profile of a 1:1 stoichiometric mixture of AZ₁ and YNE₁ monomers in the presence of 1.5wt% copper(II) bromide pre-ligated to a multidentate amine, and under 470 nm light at 30 mW/cm², containing (a) 1 wt% camphorquinone, (b) 1 wt% Irgacure 819 and (c) 1:1 wt% camphorquinone:trimethylaniline. (d) Schematic of the Noorish Type (II) photoinitiation of CuAAC polymerizations with camphorquinone and a tertiary amine.

Cyclic voltammetry studies were performed in water to assess the complexes' redox potential (Figure 4.5). HMTETA showed a higher reducing potential (-0.045 V) compared to PMDETA and Me6TREN (-0.089 and -0.073 V respectively), providing additional insight into the rate enhancements of the copper(II) HMTETA-based ligand.

The high reducing potential of copper(II)/HMTETA is a viable explanation to why it exhibits the fastest kinetics when a type(I) photoinitiator, phenylbis(2,4,6trimethylbenzoyl)phosphine oxide (Irgacure 819), is employed which does not require hydrogen abstraction to reduce copper(II) (Figure 4.4b). Regardless of the type of photoinitiator used, HMTETA thus performs better kinetically than other multi-dentate ligands in photo-CuAAC polymerizations. This result shows the significance copper(II) to copper(I) reduction has in determining overall reactivity in photo-CuAAC polymerizations.

Another salient feature observed in photo-CuAAC reactions is a characteristic induction period, where no conversion takes place after light is commenced. The induction period in photo-CuAAC reactions has been attributed, mainly, to oxygen inhibition via oxidation of copper(I) to copper(II) at the early stages of the reaction¹⁵⁶ as well as copper(II) inhibition of the photoinitiator triplet state.^{145,159,160} This inhibition is hypothesized to depend on the quantum yield and absorbency of the photoinitiator. In addition to exhibiting the fastest kinetics, copper(II)/HMTETA also had the smallest induction period out of the three aliphatic ligands tested, suggesting that it is the best at protecting the copper(I) oxidation state in the neat polymerizations. It is furthermore possible that the ligands, through interaction with the triplet state of the photoinitiator, can be influencing this induction period. Finally, with the addition of 4,N,N-trimethylaniline, an accelerating amine, the inhibition period of all these reactions was reduced to less than one minute (Figure 4.4C), indicating an increased rate of the copper(II) ligand.



Figure 4.5 Cyclic voltammetry data for copper(II) bromide with different polydentate ligands in water using a 0.1 M Potassium phosphate buffer. Ag/AgCl was chosen as the reference electrode and the scan speed was 0.02 V/s.

The counter ion of the copper(II) ligand species plays a significant role in photo-CuAAC polymerization kinetics. Figure 4.6 shows the effect of bromide, chloride, bis(trifluoromethane)sulfonamide (TFSI), and trifluoromethanesulfonate (OTf) on the kinetics of the photo-CuAAC polymerization with AZ₁/YNE₁ and AZ₁/YNE₂, using PMDETA as the ligand and camphorquinone as the photoinitiator. Copper(II) bromide and chloride complexes exhibit faster kinetics than OTf and TFSI in the presence of two different multifunctional alkynes (YNE₁ and YNE₂) despite the similarly low basicity of the four anions. Basic anions can act as ligands favoring the formation of the copperacetylide, an important intermediate species of the CuAAC mechanistic cycle while disfavoring the formation of the bis(copper) acetylide complex¹⁵⁸. However, the effectiveness of the halides (chloride and bromide) compared to organic anions (TFSI and OTf) suggests that other factors are playing a role in the kinetics of neat photo-CuAAC polymerizations, such as copper(II) to copper(I) redox potentials, solubility of the copper species in the resin formulation, and the relative size of the counter anion. While halides are effective in increasing the rate of the photo-CuAAC reaction in neat polymerizations, this may not apply in organic media. For example, the bromide anion can have a strong inhibitory effect in organic media due to bromide's affinity to bind to copper(I) centers^{183,173} As an aside, the copper(II) acetate salt and ligands were tested for photo-CuAAC polymerization, but caused a reaction between AZ-1 and YNE-1 in the presence of methanol. Similar reaction behavior has been noted by Kuang et. al.¹⁸⁴ Interestingly, however, the reaction occurred in the absence of a photoinitiator and an external light source; this reaction was also observed with copper(II) acetylacetonate/PMDETA. The non-photoiniaited CuAAC polymerization in the presence of Cu(OAc) and Cu(AcAc) ligands indicates a loss of temporal control over the reaction.



Figure 4.6 Conversion profile between (**A**) AZ-1 and YNE-1 and (**B**) AZ-1 and YNE-2 using different equimolar amounts of copper(II) anion sources ligated to PMDETA in the presence of 1 wt% camphorquinone under 470 nm light at 30 mW/cm². The halides (bromide and chloride) exhibited the fastest reaction kinetics compared to triflate and bistriflimide ions.

Pre-ligation of the copper(II) salt with the amine before adding to the resin formulation is critical to enabling this reaction with temporal control. When copper(II) chloride was pre-ligated to PMDETA, no reaction was observed over 10 hours in the absence of a photoinitiator and an external source of light (Figure 4.7). When copper(II) chloride and the PMDETA were added separately in the reaction mixture, however, polymerization begun in the absence of an external light source and a photoinitiator in the system. This result suggests that as the nitrogen species and copper(II) source ligate in the presence of an alkyne, the formation of a copper(I)-acetylide complex occurs, starting the CuAAC reaction, where the nitrogen ligand can act as a base in deprotonating the alkyne³⁶. However, there is no initial source of copper(I) in this system. And while copper(II) reduction to copper(I) has been observed with copper(II) bromide TMEDA through Glaser-Hay coupling using excess TMEDA as a base¹⁸⁵, this mechanism is unlikely to be occurring in the system since the near-IR alkyne peak at 6509 cm⁻¹ remained unchanged in the absence of a multifunctional azide (Table 4.1, 9). Table 4.1 furthermore shows that no polymerization takes places in the absence of a ligand, or a copper(II) species (Table 4.1, 1-2). If the ligand species is not pre-ligated to the copper(II) before adding to the resin formulation, polymerization occurs with both PMDETA and HMTETA in the presence of both copper(II) bromide and chloride (Table 4.1, 3-6). If the copper catalyst is pre-ligated, no polymerization occurs (Table 4.1, 7-8). While the exact polymerization mechanism is under current investigation, these results demonstrate the importance of pre-ligation of the amine with the copper(II) salt in photo-CuAAC polymerizations to maintain the latency of initiation in the absence of light.

Table 4.1Polymerization results in the presence or absence of: AZ-1, YNE-1,
copper(II) source, an amine ligand, preligation, and camphorquinone with accelerating
amine. An external light source was not irradiated on these samples.

	AZ1	YNE1	Copper(II)	Ligand	Preligated	CQ/a mine	Polymerization?
1	+	+	$+ CuBr_2$	-	-	+	No
2	+	+	-	+ PMDETA	-	-	No
3 *	+	+	$+ CuBr_2$	+ PMDETA	-	-	Yes
4	+	+	$+ CuBr_2$	+ PMDETA	-	-	Yes
5	+	+	$+ CuBr_2$	+ HMTETA	-	-	Yes
6	+	+	$+ CuCl_2$	+ PMDETA	-	-	Yes
7	+	+	$+ CuBr_2$	+ PMDETA	+	-	No
8	+	+	$+ CuCl_2$	+ PMDETA	+	-	No
9	-	+	$+ CuBr_2$	+ PMDETA	-	-	No

* #3 used methanol as the solvent, whereas #4 used acetonitrile.



Figure 4.7 Conversion profile for the photo-CuAAC polymerization using equimolar amount of AZ-1 and YNE-1 comparing a pre-ligated copper(II) chloride PMDETA ligand vs a non-ligated copper(II) chloride catalyst where PMDETA was added separately. No reaction was observed in the preligated copper(II) complex over 10 hours, whereas near full conversion was observed with the non-ligated copper(II) source within 2 hours.

In one case, a pre-ligated copper-amine catalyst, CuBr₂/TMEDA, promoted the polymerization of AZ-1 and YNE-1 in the absence of light and photoinitiator. In an effort to understand this reaction, a model system, containing 100 mM of 1-dodecyne in methanol and 10 mM of CuBr₂/TMEDA was studied using NMR and UV-vis spectroscopy in methanol. The UV-vis spectra showed a steady decrease in the copper(II) concentration over 1000 minutes, which was not observed for either the

PMDETA or Me6TREN, as shown in Figure 4.8. It should be noted that no decrease in the copper(II) peak was observed in the absence of an alkyne (Figure 4.8D). ¹H NMR analysis of the identical systems in deuterated methanol, showed a decrease in the H- \equiv bond (2.18 MHz) and the emergence of new peak at 2.7 MHz when CuBr₂/TMEDA was used (Figure 4.9), indicating a potential reaction between the alkynyl -H and the copper ligand. ¹³C NMR analysis showed a complete disappearance of both alkynyl carbons C=C (69 and 85 ppm) (Figure 4.9). No change in the NMR spectra of CuBr₂/PMDETA and Me6TREN was observed (Figure 4.10).



Figure 4.8 UV vis spectra over 1000 minutes of 100 mM 1-dodecyne and 10 mM of (a) CuBr₂/TMEDA, (b) CuBr₂/PMDETA, (c) CuBr₂/Me6TREN and (d) CuBr₂/TMEDA without 1-dodecyne in methanol. A decrease in the peak between 600 and 800 nm was observed only for the copper(II) TMEDA ligand indicating copper(II) reduction in the presence of the alkyne.



Figure 4.9 [A] Change in ¹HNMR spectra at time=0 (red) to time=18 hours (blue) for a solution of 100 mM 1-dodecyne and 10 mM copper(II) bromide TMEDA in deuterated methanol. The NMR shows a decrease in the peak at 2.18 MHz and an appearance of a peak at 2.7 MHz. [B] Change in ¹³CNMR spectra at time=0 (top) to time=18 hours (bottom) for a solution of 100 mM 1-dodecyne and 10 mM copper(II) bromide TMEDA in deuterated methanol.



Figure 4.10 Change in ¹HNMR spectra at time=0 (red) to time=24 hours (blue) for a solution of 100 mM 1-dodecyne and 10 mM copper(II) bromide (A) PMDETA and (B) Me₆TREN in deuterated methanol. The NMR shows no change over time.

The initial hypothesis was that methanol was causing this reaction to take place. For, the reduction of copper(II) to copper(I) in alcoholic solvents has been documented in literature. Yamamoto suggested that alcoholic solvents can reduce some copper(II) sources to copper(I) where the alcohols can act as a reducing agent¹⁸⁶. Furthermore, Brotherton reports triazole formation from 2-picolylazide and phenylacetylene using only copper(II) salts in methanol¹⁸⁷. Kuang et al. also show that copper(II) acetate is excellent at catalyzing the CuAAC reaction with chelating azides¹⁸⁸. They suggest that copper(II) acetate reduces to copper(I) through an oxidative homocoupling of methanol into formaldehyde and hypothesize that such a mechanism and/or alcoholic reduction of copper(II) could be taking place in methanol. However, ¹³C NMR spectra shows no evidence of an aldehyde peak emergence at 200 ppm. Furthermore, a similar decrease in the copper(II) UV-vis peak was observed using chloroform as the solvent indicating that this behavior is not limited to alcoholic solvents. An alternative cause could be halide to metal charge transfer. Da Silva et al. report photoreduction of copper(II) to copper(I) due to halide to metal charge transfer for CuBr₂ in the presence of methanol when the solutions were irradiated under 350 nm light. It is moreover possible that ambient light conditions could be sufficient for copper(II) to copper(I) reduction over long periods of time due to halide to metal or ligand to metal charge transfer.

Finally, the UV-vis peak reduction behavior is not limited to the bromide anion and was observed with other anions such as TFSI. The exact mechanism with copper(II) TMEDA ligands in the presence of an alkyne and the reason from copper(II) reduction is under current investigation; however, using a copper(II) TMEDA catalyst in photo-CuAAC polymerizations prevents temporal control over the photo-induced CuAAC reaction. Copper(II) TMEDA ligands could alternatively be used as CuAAC initiators in organic media.

4.4 Conclusions

The use of different copper(II) catalysts in photo-CuAAC polymerizations can have an immense effect on the kinetic and chemical behavior of these systems. Pyridinebased copper(II) ligands show little reaction in photo-CuAAC, whereas aliphatic amines show enhanced kinetic performance. Most notably, however, the CuAAC reaction can lose its temporal control under certain conditions, such as the absence of pre-ligation, the use of certain amine-based polydentate ligands like TMEDA or the use of different anions such as acetate and acetylacetonate. While the photo-CuAAC reaction is considered an extremely robust and effective reaction, our results show that more consideration must be paid to the copper(II) source to fully optimize and manipulate the kinetics and behavior of this photoinduced polymerization, specifically relating to its spatial and temporal control characteristics.
Chapter 5

PHOTO-CUAAC POLYMERIZATION FOR ANION EXCHANGE MEMBRANES

5.1 Introduction

Polymeric ionic liquids (PILs) contain at least one ionic repeat unit which imparts the polymers with electrolytic properties, specifically ionic conductivity, while maintaining their mechanical stability and characteristics. PIL properties are typically tunable by ionic liquid monomer composition as well as anion and cation structure^{189–} ¹⁹¹. PILs are often highly hydroscopic and thus susceptible to dissolution in water-based applications (i.e., fuel cell membranes). The synthesis of crosslinked ionic networks has been employed to enhance mechanical stability¹⁹². Click chemistry offers a facile and robust monomer crosslinking strategy to make charged polymer networks. Click reactions, such as the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction^{6,7}, are extremely selective and high yielding organic reactions that can occur over a wide range of conditions^{10,18}. The copper(I)-catalyzed reaction between an alkyne and an azido functional group has already shown potential in the creation of PILs using two different synthetic routes: (1) the CuAAC polyaddition reaction and subsequent quaternization reaction with alkyl halides^{193–199} and (2) the direct reaction of azido-polymer side-groups with alkyne-functionalized ionic liquids²⁰⁰ (Figure 5.1). The rapid formation of a conductive polymer network with enhanced hydroxide conductivity by combining both concepts via a CuAAC polyaddition of multifunctional alkyne ionic monomers is shown in this chapter. Moreover, photoinitiation is achieved by converting copper(II) to copper(I) in the presence of a photoinitiating systems thus enabling spatial and temporal control with implications for the design and synthesis of functional polymeric materials as well as photopatterning. reaction have exhibited narrow glass transition temperatures and desirable thermomechanical properties at room temperature owing to the step-growth mechanism and presence of 1,2,3-triazole linkages, respectively^{135,201}. These triazole linkages are rigid in nature, shielding it from side reactions and protecting against hydrolytic cleavage and oxidation or reduction^{10,11}. Moreover, the photo-CuAAC polymerization shows rapid kinetics when compared with typical CuAAC reactions under optimized conditions^{145,146}. The work herein describes the synthesis of ion-conductive polymers from the photoinitiated CuAAC reaction, with potential applications in the design of hydroxide exchange membranes (HEMs). The PILs are synthetically facile, exhibit rapid conversions, and are ion-conductive.



Figure 5.1 Methods of synthesizing CuAAC based PILs include: (1) Postquarternization via reaction of the 1,2,3 triazole with methyl iodide and forming a triazolium cation, and (2) Direct addition of charge on the alkyne or azide backbone monomer and subsequent formation of the triazole.

5.2 Methods

5.2.1 Synthesis procedures

1,17-diazdio-3,6,9,12,15-pentaoxaheptadecane (**AZ-2**) was obtained in a two-step synthesis reaction:

$$HO\left[\begin{array}{c} O \\ 5 \end{array}\right]_{5} OH \xrightarrow{(1)} TSO\left[\begin{array}{c} O \\ 5 \end{array}\right]_{5} OTS \xrightarrow{(2)} N_{3}\left[\begin{array}{c} O \\ 5 \end{array}\right]_{5} N_{3}$$

(1) Hexaethylene glycol (4.01 grams, 14.1 mmol) and potassium hydroxide (5.97 grams, 106.5 mmol) were added to DCM. The reaction mixture was placed in an ice bath and tosyl chloride (5.39 grams, 28.3 mmol) was added. The reaction was cooled to room temperature after 2 hours and was allowed to react overnight. The mixture was then washed with water and extracted with DCM. The DCM layer was dried over sodium sulfate and concentrated under high pressure to obtain a viscous clear liquid (6.50 grams, 10.99 mmol) in 78% yield.

(2) To a round bottom flask purged with argon, the product from reaction (1) (3.00 grams, 5.1 mmol) was dissolved in 100 mL DMF. Sodium azide (1.25 grams, 19.2 mmol) was added to the reaction mixture which was then heated to 80 °C and kept for 24 hours. The reaction mixture was then cooled, and 200 mL of water added. The product was extracted with ethyl acetate (3 x 250 mL). The organic layer was dried over sodium sulfate, and concentrated under high pressure to obtain AZ-2 as a clear liquid

(1.05 grams, 3.16 mmol) in 62% yield. ¹H NMR (600 MHz, Chloroform-d) δ 3.64-3.72
(m, 20H), δ 3.39 (t, 4H.

YNE 2-Bromide 1,3-di(prop-2-yn-1-yl)-1H-imidazol-3-ium bromide: A procedure by Lang et al. was modified in the synthesis of dipropargyl imidazolium bromide ([DPIm][Br])²⁰². N-(trimethylsilyl)imidazole (20.005 grams, 143 mmol) was dissolved in 500 mL of acetonitrile and an excess of propargyl bromide (35 mL, 394 mmol; 80% in toluene) was added dropwise under stirring. The temperature of the mixture was increased to reflux and allowed to react for 48 hours. Subsequently, the reaction mixture temperature was reduced to -20 °C and the white solid precipitate filtered out. This was repeated 3 times. The solid precipitate was washed five times with acetone to remove unreacted reagents and dried under vacuum overnight to remove residual solvent and moisture. ¹H NMR (400 MHz, DMSO-d6) δ 9.35 (2, 2H), δ 7.87 (d, 2H), δ 5.21 (d, 4H), δ 3.87 (t, 2H).

YNE2: 1,3-di(prop-2-yn-1-yl)-1H-imidazol-3-ium*bis(trifluoromethane)sulfonimide :* Standard procedures for anion metathesis were followed for synthesis of YNE-2 from YNE-2 Bromide²⁰³. [YNE-2][Br] (6.876 grams, 30.7 mmol) and an equimolar quantity of lithium bis(trifluoromethane)sulfonimide (8.771 grams, 30.6 mmol) were dissolved in 25 mL of water and allowed to react at 80°C for 24 hours. The reaction mixture was subsequently cooled down and the TFSIform monomer phase separated from the mixture. The product, a pale yellow liquid, was separated and then washed several times with water prior to drying under vacuum overnight to yield purified YNE-2 in quantitative yield. ¹H NMR (400 MHz, DMSOd6) δ 9.35 (s, 2H), δ 7.87 (d, 2H), δ 5.21 (d, 4H), δ 3.87 (t, 2H).

YNE-3: N,*N*-dimethyl-N,*N*-di(prop-2-ynyl)ethane-1,2-diamine: The noncharged amine based dialkyne was synthesized from a procedure by Hao et al²⁰⁴. with modification: To a round bottom flask charged with argon, 1.2dimethylethylenediamine (3.70 g, 42 mmol) and potassium carbonate (17.3 g, 125 mmol) were added to 100 mL of anhydrous THF. The reaction mixture was cooled to 0°C. Propargyl bromide (10.0 g, 84 mmol) was then added dropwise. The reaction was then allowed to reach room temperature and kept overnight. The crude mixture was filtered, washed with water (200 mL) and the product was extracted with DCM (5 x 250 mL). The product was then concentrated under high pressure. Column chromatography was then performed (9:1 DCM:MeOH) giving 0.25 grams of the product (4% yield) as an orange liquid. ¹H NMR (400 MHz, CDCl₃) δ 3.45 (d, 4H), δ 2.61 (s, 4H), δ 2.35 (s, 6H), δ 2.24 (t, 2H).

BPOHD: 1,17-*bis*(4-decyl-1h-1,2,3-triazol-1-yl)-3,6,9,12,15pentaoxaheptadecane): To a round bottom flask, AZ-2 (0.500 grams; 1.5 mmol) and 1dodecyne (0.500 grams; 3.0 mmol) was added to 10 mL of DMF. Irgacure 819 (0.021 grams; 0.05 mmol) and CuSO₄.5H₂O (0.025 grams; 0.10 mmol) were added and the reaction mixture was stirred. Light (405 nm) was irradiated on the sample, and left to react for 24 hours. Ammonium hydroxide (100 mL) was added to the reaction mixture and the product was then extracted with ethyl acetate (3 x 100 mL) and washed with brine (3 x 100 mL) and dried with sodium sulfate. The product was then concentrated under high pressure. Column chromatography was then performed (19:1 DCM:MeOH), and the product was obtained as a white solid (0.55 grams, 55% yield). . ¹H NMR (400 MHz, MeOD) δ 7.44 (s, 2H), δ 4.50 (t, 4H), δ 3.85 (t, 4H), δ 3.60-3.70 (m, 16H), δ 2.70 (t, 4H), δ 1.71 (q, 4H), δ 1.25-1.40 (m, 28H), δ 0.81 (t, 6H).

All monomers, photoinitiators, catalysts, and triazole products used in this study are shown in Figure 5.2.



Figure 5.2 Monomer, catalyst, and initiator structures for ion-conductive network formation. **Monomers include**: Difunctional azide AZ-1 (1,17-diazido-3,6,9,12,15-pentaoxaheptadecane), trifunctional alkyne crosslinker YNE-1 (1-(prop-2-yn-1-yloxy)2,2-bis((prop-2-yn-1 yloxy)methyl)butane), charged difunctional alkyne YNE-2 (1,3-di(prop-2-yn-1-yl)-1H-imidazol-3-ium bis(trifluoromethane)sulfonimide), and non-ionic dialkyne YNE-3 (*N*,*N*-dimethyl-*N*,*N*-di(prop-2-ynyl)ethane-1,2-diamine).

Photoinitiating system includes: Catalyst CuCl₂/PMDETA, and the Type II Noorish photoinitiators camphorquinone and 4,*N*,*N*-trimethylaniline. **Model triazole is:** difunctional triazole, BPOHD {1,17-bis(4-decyl-1h-1,2,3-triazol-1-yl)-3,6,9,12,15-pentaoxaheptadecane)}

5.2.2 Polymerization kinetics

An AVIII nuclear magnetic resonance (NMR) spectrometer (600 MHz) was used to confirm the synthesis of all monomers. A Nicolet IS-50 Fourier Transform Infrared (FTIR) spectrometer (Thermo Fisher Scientific) was utilized to monitor the reaction kinetics. After 5 minutes, the light was irradiated onto the sample using an OmniCure Series 2000 lamp, filtered using a 470 nm band pass interference filter, and equipped with a 200 Watt mercury arc bulb (Lumen Dynamics), at an intensity of 30 mW/cm². The disappearance of the near-IR alkyne peak between 6430 and 6570 cm⁻¹ was monitored as a function of time reflecting reaction conversion.

5.2.3 Water uptake

All water uptake experiments were performed by Andrew Tibbits. Water uptake (WU) of networks was determined by the change in network weight after complete drying of a fully hydrated network. Specifically, given the mass of the network after 48 hours immersion in deionized water (m_{wet}) and the mass of the network after 24 hours drying at 60 °C (m_{dry}), the water uptake was determined from the following equation. All water uptake measurements were averaged from three distinct network samples.

$$WU = \frac{m_{wet} - m_{dry}}{m_{dry}} * 100\%$$

5.2.4 Conductivity measurements

An impedance and gainphase analyzer (Solartron SI 1260) coupled with a potentiostat/galvanostat (Solartron SI 1287) were used to measure fully hydrated ionic conductivity (σ) of photo-CuAAC networks in the longitudinal direction. Specifically, AC impedance spectroscopy with a four-electrode setup over a frequency range of 1Hz to 0.1 MHz at constant amplitude (5 μ A) was used to generate Nyquist plots for determination of the resistance (R) of the networks (i.e., the positive intersect of the real axis). Subsequently, the ionic conductivity was computed from the resistance using the following equation:

$$\sigma = \frac{L}{WdR}$$

where L is the distance between the two reference electrodes, W is the sample width, and d is the sample thickness. All networks were washed several times, immersed within Argon-purged deionized water and the hydroxide-form conductivity experiments performed in a carbon dioxide free glove-box. The results were replicated with three distinct network samples. The TFSI-form conductivity experiments were measured by Andrew Tibbits.

5.2.5 UV-vis spectorscopy

An Evolution 260 Bio UV-Visible Spectrophotometer from Fisher Scientific was used to monitor leaching of copper from ionic photo-CuAAC samples over time. A rectangular network sample was immersed in 15 mL of deionized water for 24 hours. The water was subsequently transferred to a 10 mm cuvette and UV-Vis analysis was performed over 500 to 800 nm. The network was re-immersed in a fresh 15 mL volume of deionized water for 24 hours and the process was repeated until UV-Vis showed no more leaching of copper (4 days).

5.2.6 Mechanical properties and analysis

TA Instruments Dynamic Mechanical Analyzer (DMA) Q800 at a temperature range from -35 °C to 45 °C (2 °C/min ramp rate and amplitude and frequency 5 μ m and 1 Hz, respectively) under tension mode was used for determination of elastic modulus and of networks along with thermomechanical properties. Each measurement was taken from three distinct network samples to ensure reproducibility after initial drying for water removal of samples at 60 °C for 24 hours. For the tensile strength measurements, an initial strain of 1% was introduced and the strain rate increased 1%/min. The subsequent strain was measured.

5.3 **Results and Discussion**

The structures of the comonomers are critical in enabling molecular mobility which facilitates ionic conductivity of the network structure in its hydrated state. A hydrophilic poly(ethylene glycol) (PEG)-containing difunctional azide (AZ-1) was chosen as the azide monomer (Figure 5.2). The use of a PEG backbone is hypothesized to enhance ionic conductivity properties in which they act as multivalent ligands²⁰⁵. Moreover, networks formed from PEG difunctional azides exhibit decreased modulus and glass transition temperature when compared to bulkier multifunctional azides that have traditionally been used in photo-CuAAC networks¹³⁶. Increased chain mobility, associated with low glass transition (Tg) polymer networks, facilitates increased ionic conductivity (Figure 5.3). A difunctionalized-imidazolium ionic liquid (YNE-2) was further synthesized for copolymerization with the crosslinker (YNE-1) and the PEG-containing difunctional azide (AZ-1). The imidazolium functionality was chosen as the ionic backbone due to its ease of synthesis and ability for incorporation into polymeric materials.



Figure 5.3 Comparison between glass transition temperatures of two component diazide-trialkyne networks (1:1 total azide:alkyne) for two different diazides: dicarbamate-based diazide AL-1 (red) and PEG-based diazide AL-2 (blue).

The counter ion of the ionic liquid monomer is critical to the success of the photopolymerization process. The bromide form of YNE-2 not only shows decreased solubility in the CuAAC resin, but exhibits negligible reactivity. This kinetic effect is further illustrated when reacting a monofunctional azide and alkyne in DMF as depicted in Figure 5.4A. While the bis(trifluoromethane)sulfonimide (TFSI)-based propargyl imidazole reaction reaches near full conversion within 3 minutes, the bromide-based imidazole shows insignificant reactivity for over an hour. The inhibitory nature of high

concentrations of the bromide ion to CuAAC chemistries has been documented in the literature and can be attributed to the strong affinity of bromide ions, when used in excess, to bind to the copper(I) centers in organic media^{36,183}. In contrast, the TFSI counter ion in the model system exhibits rapid kinetics. The TFSI-based difunctional alkyne, YNE-2, moreover shows excellent solubility in the resin formulation.

The ionic liquid monomer (YNE-2) is photopolymerized with the azide monomer, AZ-1, and alkyne crosslinker, YNE-1, to form a polymer network structure as illustrated in Figure 5.5. For these photopolymerizations, a Norrish Type (II) photoinitiating system was employed with camphorquinone and 4,*N*,*N*-trimethylaniline irradiated under blue light (470 nm) at 30 mW/cm². The visible light system is used to mitigate azide decomposition into nitrogen gas and nitrenes which can cause defects in the polymer network¹⁷. All networks are formulated with a 1 to 1 stoichiometric ratio between azide and alkyne monomers; however, the crosslink densities are tuned by controlling the ratio of trifunctional (YNE-1) and difunctional (YNE-2) alkynes in the formulation {E.g. 50:50 YNE-1:YNE-2 indicates 50 mol% of the 'ynes' are from the crosslinker (YNE-1) and 50 mol% from the ionic monomer (YNE-2)}.

The photopolymerization of the YNE-1/YNE-2 and AZ-1 formulation reaches full conversion in less than 30 minutes independent of the crosslink density (Figure 5.4B). The mechanical properties of the formulated polymer networks exhibits unconventional trends. As more YNE-2 is added to the formulation, a decrease in room temperature modulus in the rubbery regime is expected, since the elastic modulus is directly proportional to the network crosslink density. Surprisingly, however, all ion containing polymers possess comparable glass transition temperatures (Tg) ranging between -1°C and 3.5°C (Figure 5.6A).

While the Tg of a crosslinked network is mainly influenced by molecular mobility, the near-uniformity in the Tgs at different YNE-2:YNE-1 ratios suggests that an increase in charge density leads to an increase in glass transition temperature. When replacing YNE-2 with YNE-3, a structurally similar non-charged difunctional alkyne, the Tg decreases from 3°C to -15°C in a 50:50 YNE-1:(YNE-2 or YNE-3) network. This result supports that an increase in charge density causes an increase in glass transition temperature.

The photo-CuAAC networks are also expected to increase their water intake as the crosslink density decreases. However, the opposite trend is observed in which the characterized networks become increasingly hydrophobic with additional YNE-2 incorporation. When replacing YNE-2 with the control YNE-3, however, the water uptake of these membranes increases by an order of magnitude (from roughly 20 to 200 wt%) at similar YNE-1:(YNE-2 or YNE-3) compositions and is also much higher than that of the more crosslinked binary YNE-1/AZ-1 system. Thus, the decrease in water uptake in the YNE-2 system is attributed to the hydrophobicity of the bistriflimide counterion.

Bistriflimide anions are inherently hydrophobic and are expected to be poor ionconductors in water. The highest conductivity observed when using bistriflimide anions in the network was with a 50:50 YNE-1:YNE-2 formulation at 5.1 ± 1.6 mS/cm. This conductivity was around a 2 times greater than the control samples that contained no charged moiety, only YNE-1 and 50:50 YNE-1:YNE-3 (Figure 5.6B).



Figure 5.4 [A] FTIR conversion plots for the reaction between methyl-2-azidoacetate and a model ionic liquid monomer as a function of counterion. The data shows no reactivity for a bromide-form imidazolium monomer but rapid kinetics with the TFSI-form monomer. Reaction conditions were 50 mM of both the azide and the alkynyl ionic liquid, 10 mM CuSO4, and 10 mM Irgacure-819 photoinitiator in DMF. The reaction was conducted at with 405 nm visible light at 20 mW/cm². [B] Conversion plots for YNE-1:YNE-2 with AZ-1 networks showing the effect of changing the ratio YNE-2 to YNE-1 on the kinetics of the photopolymerization with an equimolar amount of AZ-1, 1.5 wt% CuCl2/PMDETA, 0.7 wt% camphorquinone, 0.7 wt% trimethylaniline using 470 nm light at 30 mW/cm². The reaction was not irradiated until 5 minutes after starting the experiment, as represented by the grey box.



Figure 5.5 Schematic of the formation of charged networks using photo-CuAAC chemistries



Figure 5.6 [A] Comparison between glass transition temperature and elastic modulus values when different ratios of the charged alkyne (YNE-2) and the non-charged alkyne (YNE-1) are used. The Tg does not change with changing YNE ratios, whereas the modulus decreases as more YNE-2 is added to the formulation. [B] Increase in conductivity when the bistriflimide YNE-2 is added to the formulation compared to the two controls (Only YNE-1 used, 50:50 YNE-1 to YNE-3).

The conversion of the counterion to a more hydrophilic counterion (i.e., hydroxide) is essential for water-mediated transport applications such as fuel cells. Different ratios of the YNE-1/YNE-2 formulation was converted to the hydroxide form by immersion of the TFSI-form network in 1M KOH for 48 hours membrane (HEM) as illustrated in Figure 5.7. While all formulations showed an increase in conductivity in the hydroxide form compared to the bistriflimide form (Figure 5.8A), the exchange of the networks from bistriflimide to hydroxide form for a 50:50 formulation showed the highest increase (5.1 ± 1.6 to 19 ± 3 mS/cm) was complemented by a modest increase in water uptake (23% to 50%). Similar immersion of a 50:50 YNE-1:YNE-3, non-ionic network in 1M KOH provided no measurable increase in the ionic conductivity or water. The networks were moreover dried and the tensile strength and strain was measured.

Exchanging TFSI with hydroxide showed very little to no change in tensile properties of the material (Figure 5.8B). These networks can withstand strains of over 30% without breaking. However, the ability of these networks to withstand high temperatures in alkaline conditions is moreover important for fuel cell membrane applications. Thus, these membranes were immersed in a 1M KOH solution under 60°C temperature for 7 days. The subsequent elastic modulus and tensile properties were measured and compared to that which were not heated. A two-fold decrease in the modulus, and an increase in the strain percent at break, from 30% strain to 100% strain, depict a loss of crosslink density caused by heating.



Figure 5.7 Schematic of the hydroxide exchange. The TFSI form of the polymer network is immersed into a 1M KOH solution.



Figure 5.8 [A] TFSI and Hydroxide form conductivity as a function of YNE-2 to YNE-1 ratios. [B] Tensile properties of the TFSI form charged CuAAC networks (50:50 YNE-2:YNE-1 ratio) remain unchanged before and after immersion in 1 M KOH for 48 hours. However, a decrease in crosslink density was observed after heating the network at 60°C.

To investigate the cause of the loss of crosslink density, a model difunctional 1,2,3-triazole, BPOHD (Figure 5.2), was synthesized by reaction of AZ-1 and 1-dodecyne.. CD₃OH using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard was prepared. 50 mM of BPOHD was then dissolved in the deuterated basic solution and placed in a sealable NMR tube to perform ¹H NMR degradation studies²⁰⁶. After the initial spectrum was taken, the tube was placed in an oven and heated to 60°C. After a week the ¹H NMR spectra did not change relative to the internal standard C₃H₉ peak as shown in Figure 5.9. This result indicates that the loss of crosslink density is attributed to the imidazolium group rather than the 1,2,3-triazole which is stable under the basic conditions and elevated temperatures.



Figure 5.9 ¹H NMR spectra of BPOHD in 1M KOH in CD₃OH. After heating the sample to 60°C using an oven, there was no change in the NMR spectra after one week.

A unique attribute of using photo-CuAAC chemistries for the formation of polymers is their ability to provide spatial and temporal control over network formation. As a simple demonstration, a non-charged CuAAC network containing thymol blue was photopatterned leaving a "J" shape empty. The 50:50 YNE-1:YNE-2 with AZ-1 CuAAC network also containing thymol blue was then filled into the "J" pattern and

polymerized by irradiating at 470 nm light in the presence of CuCl₂/PMDETA, camphorquinone, and 4 *N*,*N*-trimethylaniline (Figure 5.10). This polymerization yielded an embedded charged "J" shaped CuAAC PIL network within a non-conductive CuAAC network. Hence, while both these networks contained thymol blue, only the "J" shape changed colors to greenish-blue when immersed in 1 M KOH, due to successful hydroxide exchange.



Figure 5.10 Photopatterning of the charged photo-CuAAC membrane within a noncharged CuAAC membrane

5.4 Conclusion

In summary, the covalent incorporation of an alkyne-functionalized ionic liquid into a polymer network is achieved. The resultant membranes were formed from the single crosslinking step proceeding to quantitative conversion in less than 30 minutes. The network polymerization kinetics and Tg are largely independent of the composition of comonomers in the network while the water uptake and rubbery modulus decrease with increasing ionic monomer content. The ion exchange from bistriflimide to hydroxide converts the networks from hydrophobic to hydrophilic and enhances the ionic conductivity by a 4-fold increase, at various comonomer ratios. While the membrane's crosslink density decreased under elevated temperatures in basic media, this was attributed to the imidazolium functional group rather than the stable triazole resulting from the CuAAC polymerization. The spatial and temporal control of these reactions adds a unique benefit for the fabrication of ion-exchange membranes.

Chapter 6

FUTURE DIRECTIONS AND APPLICATIONS

6.1 Vitrimers

Thermosets, on the one hand, have many desirable traits, such as dimensional stability and mechanical integrity²⁰⁷. On the other hand, due to this architectural rigidity, they cannot be reprocessed or reshaped. In an effort to impart thermosets with this reprocessesability, polymer networks that contain exchangeable bonds were developed by Kloxin et. al^{208–211}. These networks were coined covalent adaptable networks (CANs). In brief, the exchangeable bonds in CANs can lead to dynamic crosslinks through interchanging chemical bonds under specific stimuli (e.g. light, temperature) while maintaining network integrity.

In 2011, Liebler et al. took advantage of a transesterification reaction in an epoxy polymer network. In addition to the classic glass transition temperature, Tg, the researchers observed a second transition temperature, Tv, which is due to bond rearrangements at higher temperatures. Tv represents a transition from a viscoelastic solid to a viscoelastic liquid^{212,213}. These permanent networks were coined vitrimers. The viscosity of vitrimers can be controlled by bond exchange reactions at higher temperatures allowing for the reprocessessing, repairing, and recycling of the polymer because of the the formation of new bonds. Due to the bond exchanges, these polymers further present rapid topological rearrangements and can undergo stress relaxation. The concept of associative bond exchange in a permanent polymer network is illustrated in Figure 6.1. A model transesterification exchange reaction between an organic alcohol and an ester is shown in Figure 6.2.



Figure 6.1 Schematic of a crosslinked network that can undergo bond exchanges, while preserving the total number of crosslinks.



Figure 6.2 Model transesterification reaction between a hydroxide and an ester. The R' group of the ester was exchanged with a R group of an organic alcohol.

Photo-CuAAC polymer networks can be formed efficiently and rapidly. In an attempt to create dynamic bonds in bulk CuAAC networks, the synthesis of a multifunctional alkyne containing ester linkages (YNE-E) and difunctional azides containing hydroxy groups (AZ-BPAOH and AZ-PEGOH) were synthesized (Figure 6.3). If both ester and hydroxy groups are present in the CuAAC network backbone, bond exchanges owing to transesterification could take place under elevated temperatures in the presence of a transesterification catalyst. As a control, AZ-PEG was synthesized which does not contain any hydroxy groups in its backbone.



Figure 6.3 Monomers synthesized and purchased for photo-CuAAC network vitrimers include: trip(prop-2-yn-1-yl) 2,2',2''-nitrilotriacetate (**YNE-E**), 3,3'-((propane-2,2-bis(4,1-phenylene))bis(oxy))bis(1-azidopropan-2-ol) (**AZ-BPAOH**), 1,16-diazido-4,7,10,13-tetraoxahexadecane-2,15-diol (**AZ-PEGOH**), and 1,17-diazido-3,6,9,12,15-pentaoxaheptadecane (**AZ-PEG**).

A proof of network formation experiment was performed in the absence of a transesterification catalyst. The polymerization kinetics of the reaction were tested between AZ-BPAOH and YNE-E using an equimolar amount of each, in the presence of 1wt% of CuCl₂/PMDETA and 1wt% camphorquinone and 4,N,N-trimethylaniline under 25mW/cm² of 470nm light. The polymerization kinetics were sluggish and the reaction conversion plateaued at ~60% after 200 minutes of reaction time as shown in Figure 6.4A. The slow kinetics are likely due to the extremely viscous nature of AZ-BPAOH. To increase polymerization kinetics and conversion in the proof of concept network, a PEG-based difunctional azide with pendent hydroxy groups was synthesized

(AZ-PEGOH). Using the same reaction conditions, AZ-PEGOH and YNE-E were polymerized and the reaction reached full conversion after 30 minutes (Figure 6.4B). Next, attempts to add a transesterification catalyst to the polymer mixture failed; tin(II) 2-ethylhexanoate reduced copper(II) to copper(I) before irradiation, which in turn crashed out of the solution, and 1,5,7-Triazabicyclodec-5-ene was insoluble in the resin formulation.



Figure 6.4. Photo-CuAAC polymerization kinetics using an equimolar azide to alkyne ratio of **[A]** YNE-E and AZ-BPAOH and **[B]** YNE-E and AZ-PEGOH. All samples contained 1wt% CuCl₂/PMDETA and a 1:1 camphorquinone:4,N,N-trimethylaniline ratio. Networks were tracked via real-time FTIR and initiated by irradiating blue light under 25 mW/cm²

Initial relaxation studies were performed on the polymer network after reaction AZ-PEGOH and YNE-E. Surprisingly, in the absence of a traditional transesterification catalyst, the polymer network relaxed at elevated temperatures (above 80°C) when compared to a control polymer network that use AZ-PEG and YNE-E which did not show any signs of relaxation (Figure 6.5). These measurements were performed by

Kaleigh Nicastro. The samples were exposed to a specific temperature for 5 minutes, followed by a 0.1% strain application and were recovered for either 20 minutes (Figure 6.5A) or 70 minutes (Figure 6.5B). The normalized relaxation modulus is the stress at time=t over initial stress. This result led to a hypothesis that the copper species can catalyze the transesterification reaction at elevated temperatures. The use of copper as a transesterification catalyst has been shown in literature^{214,215}. Recently, Connell et. al report transesterification side produces in methanol while performing atom transfer radical polymerization (ATRP) of methacrylate monomers in the presence of copper(I)/BPY and copper(I)/PMDETA²¹⁶.



Figure 6.5 Relaxation modulus as a function of time. A network formed from either [A] AZ-PEGOH and YNE-E or [B] AZ-PEG and YNE-E were allowed to rest at a specific temperature for 5 minutes, then 0.1% strain was applied and their stress measured over time. The normalized relaxation modulus is the stress at time=t over initial stress.

To fully assess the suitability of photo-CuAAC chemistries in vitrimer applications, the transesterification reaction in the presence of copper needs to be studied in more detail.

6.2 Self Catalyzed Copper Metal Organic Polyhedra Azide—Alkyne Cycloaddition

Metal Organic Frameworks (MOFs) are metallic ion species that are coordinated to an organic ligand to form 3-dimensional geometries^{217,218}. The most defining feature of a MOF is its porous nature. This porosity increases its surface area of active sites, allowing for applications in catalysis^{219–221}, selective gas separation and storage membranes^{222,223}, as well as drug delivery and biomaterials^{224,225}. Metal organic polyhedra (MOPs) are a subset of metal-organic materials and, while also having a porous nature as MOFs, they are exclusively topologically polehydral^{226,227}. Another advantage of using MOPs over MOFs in organic synthesis is that, due to their zero-dimensionality, MOPs are typically soluble in a wide variety of organic solvents such as DMF²²⁸.

Copper MOFs were first used as heterogeneous catalysts of CuAAC by Luz et al. in 2010²²⁹. A copper(2-hydroxypyrimidinolate) MOF was able to catalyze the reaction between benzyl azide and phenylacetylene where the reaction proceeded to full conversion without changing the integrity of the MOF structure. Recently, Bae et. al demonstrated their ability to photoinduce copper(II) to copper(I)/copper(0) through the use of a Copper-cuboctahedral MOP functionalized with coumarin, a triplet state quencher, in the presence of benzophenone²³⁰. They successfully applied this copper/MOP in a CuAAC reaction by irradiating it under UV-light for 3 hours.

Photo-CuAAC reactions provide a simple way of reacting an azido and an alkyne moiety while also enabling spatiotemporal control over the reaction. Building off previous studies of copper/MOP applications in CuAAC chemistries, using copper(II) MOPs in photo-induced CuAAC reactions can be acheived in the following ways. Figure 6.6 illustrates the goals from this project.

(1) Via conjugation reactions between an alkyne functionalized MOP and an azide,

(2) Via polymerization reactions by incorporating the copper(II) MOP into the network as a catalyst.

With the collaboration of the Eric Bloch group, a copper(II)-paddlewheel MOP functionalized with alkyne end groups (3.5 mmol of alkyne per 1 gram of MOP) was synthesized. Methyl 2-azidoacetate was then added to the MOP in DMF using an equimolar azide:alkyne ratio in the presence of 10 mM of Irgacure 819. 20 mW/cm² of 405 nm light was irradiated onto the sample and the kinetics were tracked via real-time FTIR by monitoring the azide peak between 2080 and 2150 cm⁻¹. Surprisingly, the azide—alkyne cycloaddition between the copper/MOP and azide proceeded to 75% conversion in 20 minutes under mild conditions (Figure 6.7). A control study containing no Irgacure 819 photoinitiator showed no conversion over 30 minutes.

(1) Reacting Functional Groups to MOPs



(2) Incorporation into Polymer Networks



Figure 6.6 Copper/MOP project goals consist of: (1) The Ability to reaction functional groups such as an azide (N) to a copper/MOP structure functionalized with alkynes (A). and (2) The use of a copper(II)/MOP as a catalyst for the formation of a CuAAC network and its subsequent incorporation into the network.



Figure 6.7 Conversion of azide peak in real-time FTIR for a reaction between methyl 2-azidoacetate and the alkyne functionalized copper(II) MOP in the presence of (blue squares) and absence (green circles) Irgacure 819 under 10 mW/cm² of 405 nm light. The reaction in the presence of Irgacure 819 proceeded to 75% conversion in less than 30 minutes. No reaction took place over the same timeframe in the absence of Irgacure 819. The grey, shaded area represents the time (5 min) before the light was turned on.

The copper/MOP was then assessed as a potential catalyst for CuAAC network formation. 1.5 wt% of copper/MOP was added to an equimolar concentration of monomers 1 and 2 (Figure 6.8) Camphorquinone and amine were used as the photoinitiating scheme. 20wt% of DMF was required to dissolve the copper into the resin formulation. The reaction reached full conversion, demonstrating the success of using the copper(II)/MOP as a homogenous catalyst in the photo-CuAAC polymerization (Figure 6.9)



Figure 6.8 Monomers used in the study consist of a urethane-based difunctional azide (1) and an ether based trifunctional alkyne (2)



Figure 6.9 Conversion of alkyne peak in real-time near-FTIR for a photoinduced CuAAC polymerization between monomers 1 and 2 using 1.5wt% of copper(II)/MOP as a catalyst and 1wt% of camphorquinone and 1wt% of trimethylaniline. The grey, shaded area represents the time (5 min) before the light was turned on.

While the initial results of incorporation of copper/MOP in photo-CuAAC systems are promising, more extensive studies relating to the mechanism of this reaction need to be performed. First, dynamic light scattering experiments would indicate if the copper/MOP retains its structure during and after the CuAAC reaction. Second, UV-vis experiments on the copper oxidation state during the course of the azide—alkyne cycloaddition need to be performed. Furthermore, successful incorporation of the copper/MOP and its stability in the azide—alkyne network will be performed. With control over porosity of the copper MOP in the network, applications can include gas separation membranes.

6.3 Synthesis Procedures

Tripropargyl nitrilotriacetate(YNE-E): To a nitrogen purged and oven dried 500 mLround bottom flask was added 100 mL of anhydrous DCM. Then nitrilotriacetic acid (1 g, 5.23 mmol) was added followed by HCTU (6.5 g, 15.71 mmol), TEA (2.19 mL, 15.71 mmol), and DMAP (63.8 mg, 0.53 mmol). After five minutes, propargyl alcohol (0.91 mL, 15.71 mmol) was added in one portion and the mixture was heated to reflux overnight while being monitored by TLC using a KMnO4 stain. Upon completion, DCM (200 mL) was added to the solution and the organic phase was extracted with sat. NaHCO₃ (2x 200 mL), H 2 O (4x 200 mL), and brine (1x, 200 mL). The organic phase was dried over MgSO4, filtered, and evaporated. The crude product was then purified using flash chromatography on silica gel (hexanes/ethyl acetate, 1:1) to afford 1.01 g (63.3% yield) of pure product as a slightly yellow oil. ¹H NMR (600 MHz, Chloroform-d) δ 4.72 (d, 6H), δ 3.76 (s, 6H), δ 2.49 (t, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 169.74, 77.25, 75.53, 54.88, 52.45.

1,16-diazido-4,7,10,13-tetraoxahexadecane-2,15-diol (*AZ-PEGOH*) was synthesized using a 2-step synthesis:



(1) 1,12-di(oxiran-2-yl)-2,5,8,11-tetraoxadodecane was synthesized using procedure from Xue-Ping et al²³¹.

(2) 1,12-di(oxiran-2-yl)-2,5,8,11-tetraoxadodecane (0.548 g, 20.9 mmol) and 2.5 equivalents of LiClO₄ (0.71 g, 51.2 mmol) were added to 50 mL of acetonitrile. 3 equivalents of sodium azide (0.447 g, 61.8 mmol) was added slowly. The reaction mixture was heated to 90°C and left to react for 72 hours. The reaction mixture was allowed to sit at room temperature and 150 mL of water was added. The reaction was extracted with ethyl acetate (3 x 100 mL) and dried over MgSO₄. The reaction was dried over reduced pressure to afford the product as a yellowish viscous liquid (0.401 g, 60% yield). [']H NMR (600 MHz, Chloroform-d) δ 3.45-3.8 (m, 18H), δ 3.32 (d, 4H), δ 1.75 (s, 2H).

3,3'-((propane-2,2-bis(4,1-phenylene))bis(oxy))bis(1-azidopropan-2-ol) was synthesized following a procedure by Gong et al¹³⁵.

Chapter 7

CONCLUSIONS

7.1 Overview

Photo-CuAAC chemistries offer a simple and rapid strategy for polymer network formation. The photoinitiation of the CuAAC reaction and its effect on the reaction kinetics is highly sensitive to reaction conditions, catalyst type and concentrations, and the overall photoinitiating scheme. The work presented outlines what factors influence the reaction and polymerization kinetics and how to fully implement this 'click' reaction effectively. Different avenues of utilization of this reaction, such as suitability for a dental resin material and as a polymer ionic liquids, is provided.

7.2 Conclusions

An understanding of the kinetic performance of photo-CuAAC chemistries was presented in chapter 2. The study provided insight on the complex mechanism and operation of the photo-induced CuAAC reaction in both solvent and bulk polymer systems. A discussion on how the reaction differs from traditional, non-photoinitiated CuAAC reaction was conducted. Specifically, the kinetic investigations of the photo-CuAAC reaction reveal: (1) a non-traditional copper concentration first-order scaling of the reaction; (2) a critical copper and photoinitiator threshold value, where the reaction switches to zeroth-order, which is dependent on their amounts and relative ratios; (3) a low-intensity behavior where the reaction exhibits an induction period accompanied by a kinetic acceleration; and (4) the universality of kinetics in a Norrish Type(I) photoinitiating scheme as demonstrated in both a solvent-based system and a nonsolvent, bulk photopolymerization reaction.

In chapter 3, defects, in the form of bubbles, are shown to form in crosslinked films that were synthesized neat (without solvent) using the photo-CuAAC reaction. These defects are due to azide decomposition into reactive nitrenes and nitrogen gas. While this decomposition is considered a side reaction, the production of bubbles limits the applicability of the reaction due to these defects. To overcome this problem, a novel Type(II) photoinitiating system was developed through using camphorquinone and a tertiary amine under incident blue light. The resultant polymer films were bubble free and exhibited rapid reaction kinetics. The versatility of the Type(II) photoinitiating system in polymer networks can lead to diversifying its applicability to include hydrogels, bioconjugations, and dental materials, to name a few.

In chapter 4, the kinetics of the CuAAC polymerization was assessed as a function of copper(II) amine-based ligands. Copper(II) bromide ligated with 1,1,4,7,10,10-hexamethylenetetramine (HMTETA) exhibited the fastest kinetics in both Norrish type(I) and type(II) photoinitiating systems. A characteristic induction period was observed with these polymerizations and is manipulated via adding an external tertiary amine or changing the counter anion of the copper(II) salt. Halides, specifically bromide and chloride, exhibit the fastest kinetics with the smallest induction period in comparison with organic anions (i.e., bistriflimide and triflate). The temporal control of the photo-CuAAC polymerization is further hindered if the copper(II) species used is not pre-ligated. This control is further minimized in the presence of certain anions such as acetates and specific ligands such as tetramethylethylenediamine (TMEDA). Overall,

the sensitivity of the photo-CuAAC polymerization kinetics and its robustness is shown to be directly correlated to copper catalyst ligands and copper(II) counter ions.

Overall, chapters 2 through 4 show that the photo-CuAAC chemistry has decent potential to be used in the resin formulation of dental materials. Chapter 2 demonstrates that photo-polymerization reaction rates and conversion can be reduced to less than 10 minutes under optimized copper(II) and photoinitiator concentrations. Chapter 3 depicts that this chemistry can be used with dental lamps which operate in the blue light region (470 nm) when camphorquinone and a tertiary amine are used. The reaction rates are rapid where near full conversion can take place over time. The mechanical properties of the resulting materials are glassy at room temperature and have moduli comparable to that of BisGMA and TEGDMA as used in dental composites. Finally, chapter 4 demonstrates that the reaction kinetics of photo-CuAAC polymerizations are highly affected by copper(II) anion and ligands used in the formulation. By manipulating the anion and the ligand (e.g., using HMTETA with bromide), the kinetics can be doubled compared to CuCl₂/PMDETA, which is commonly used in photo-CuAAC bulk polymerizations. While the kinetic enhancement is a positive result, more kinetic studies and optimizations should be performed in order to increase the polymerization rate even further so that it is as fast as the currently used dimethacrylate system.

Chapter 5 demonstrated the suitability of photo-CuAAC polymerizations to create polymer ionic liquids. The bulk polymerization of multi-functional azide and ionic alkyne monomers is performed to create charged polymer networks with triazole linkages in its backbone. Full conversion of these monomers is achieved within thirty minutes under mild irradiation conditions. The polymerization kinetics and ionic conductivity vary minimally as a function of the ratio of azide to alkyne monomers;
however, the facile exchange of hydrophobic anions for hydroxide yields hydroxide conductive polymer networks (>19 mS/cm) illuminating their potential as membranes in alkaline fuel cell applications. Finally, the charged polymerization is spatiotemporally controlled and can be easily photopatterned.

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Appendix A

ADDITIONAL CHARACTERIZATION

A1. ¹H NMR Spectra

All ¹H NMR spectra of synthesized monomers and products were obtained either from a Bruker AV 400 or AVIII 600NMR Spectrometer and are shown in Figures A1 through A7.



Figure A1 ¹H NMR spectra of Bis(6-azidohexyl)(1,3-phenylenebis(propane-2,2diyl))dicarbamate in CDCl₃



Figure A2 ¹H NMR spectra of -(Prop-2-ynyloxy)-2,2-bis(prop-2ynyloxymethyl)butane in CDCl₃



Figure A3 ¹H NMR spectra of 1,17-diazdio-3,6,9,12,15-pentaoxaheptadecane in CDCl_{3.}



Figure A4 ¹H NMR spectra of 1,3-di(prop-2-yn-1-yl)-1H-imidazol-3-ium in CD₆SO



Figure A5 ¹H NMR spectra of N,N-dimethyl-N,N-di(prop-2-ynyl)ethane-1,2diamine in CDCl₃



Figure A6 ¹H NMR spectra of 1,17-bis(4-decyl-1h-1,2,3-triazol-1-yl)-3,6,9,12,15pentaoxaheptadecane in CDCl₃



Figure A7 ¹H NMR spectra of 1,16-diazido-4,7,10,13-tetraoxahexadecane-2,15-diol in CDCl₃

A2. Copper ligand UV-Vis spectra

All UV-vis spectra were taken using an Evolution 260 Bio UV-Visible Spectrophotometer from Fisher Scientific. The samples contained 10 mM of the copper(II) ligand and were dissolved in methanol. Their spectra is shown in Figures A8 through A18.



Figure A8 CuCl₂/TMEDA UV-vis spectra



Figure A9 CuBr₂/HMTETA UV-vis spectra



Figure A10 Cu(OTf)₂/TMEDA UV-vis spectra



Figure A11 CuBr₂/PMDETA UV-vis spectra



Figure A12 CuBr2/TMEDA UV-vis spectra



Figure A13 Cu(TFSI)₂/TMEDA UV-vis spectra



Figure A14 Cu(OAc)₂/TMEDA UV-vis spectra



Figure A15 CuBr₂/Me6TREN UV-vis spectra



Figure A16 CuCl₂/PMDETA UV-vis spectra



Figure A17 Cu(OAc)₂/PMDETA UV-vis spectra



Figure A18 Cu(TFSI)₂/PMDETA UV-vis spectra

Appendix B

VINYL SULFONAMIDE THIOL-MICHAEL KINETICS FOR ON RESIN MACROCYCLIZATION OF PEPTIDES

B.1 Introduction

Peptide conjugation is a growing field in material science that allows for the facile synthesis of complex structures and functionalization. If the conjugation undergoes intramolecular reactions, this can result in cyclic peptides (macrocycles). These types of peptides exhibit increased stability and are more protected against degradation.

Click reactions offer an efficient way of peptide synthesis due to their highly efficient and selective nature¹. For the synthesis of macrocyclic peptides, two click chemistry reactions have been mainly used: The CuAAC reaction between an azide and alkyne functionality and Thiol-Ene additions between a thiol group and an electron rich alkene moiety^{2,3}. While highly selective, the CuAAC reactions typically require long reaction times for efficient peptide cyclization. The photoinduced thiol-ene reaction, while highly efficient, require high concentrations of photoinitiator along with high UV-light intensities, which is damaging to the peptides⁴.

Similar to thiol-ene chemistries, thiol-Michael reactions are reactions between a thiol and an alkene. The ene in this case, however, is electron deficient. While the reaction is used in conjugation of biological molecules, it has found limited use in the formation of cyclic peptides⁵.

B.2 Results and Discussion

The overall goal of this study was to assess the kinetic performance of different thiol-Michael acceptors. Maleimides and acrylates are commonly used in peptide chemistry due to their rapid kinetics⁶. Maleimides are, however, extremely sensitive to aqueous conditions where they degrade due to ring opening reactions². Acrylates are also susceptible to water degradation since they contain ester linkages³. To increase the stability of thiol-Michael acceptors, acrylamides have been utilized since they have a rigid amide bond that protects it from hydrolysis⁷. Acrylamides are, however, plagued with sluggish kinetics and low conversions⁸. Ideally, a hydrolytically stable and fast reacting thiol-Michael acceptor is needed for peptide macrocyclizations.

Recently the Bowman group have developed vinyl sulfonamides for the formation of thiol-Michael polymers⁹. These moieties exhibited increased stability as and were comparable to methacrylate networks. Furthermore, Dedová et al.¹⁰ used cross-coupled nucleic acids to proteins via thiol-Michael chemistries using vinyl sulfonamides which displayed stability under various conditions. Hence, due to the kinetic and mechanical stability of vinyl sulfonamides, they are a good candidate for peptide macrocyclization synthesis.

In an effort to evaluate kinetic performance of vinyl sulfonamides as thiol-Michael acceptors, model studies were performed to compare them to commonly used acceptors. The structures are shown in Figure B.1. Real-time FTIR analysis is used to track the conversion of the reaction based on the disappearance of the thiol-peak between 2485 and 2545 cm⁻¹ as shown in Figure B.2.



Figure B1 Model thiols (T1 and T2) and model enes (E1 through E6) used in the kinetic study.



Figure B2 FTIR spectra showing a decrease in the thiol peak (between 2485 and 2545 cm⁻¹) during the thiol-Michael reaction.

To test the effectiveness of vinyl sulfonamide as a thiol-Michael acceptor for peptide cyclization, six alkenes and two types of thiols were utilized for model kinetic studies. For the alkenes it was desired to compare vinyl sulfonamides to the most commonly used alkenes, acrylate and maleimide. Of these structures: Maleimide, E1, and methyl acrylate, E2, were chosen classical examples of kinetically rapid thiol-Michael acceptors. Other structures included a model secondary acrylamide, E3, and a secondary vinyl sulfonamide, E5 which was synthesized by Bryan Sutherland. In order to further assess structural kinetic effects of amines, a tertiary acrylamide, E4, and a tertiary vinyl sulfonamide, E6 was synthesized by Bryan Sutherland. Two thiols were selected for this kinetic study. First, an alkyl thiol, N-mercaptopropionate (T1), was chosen, as it is structurally similar to thiols used in polymeric systems. A cysteine-based thiol (T2) was chosen for biomaterial applications.

Figure B.5 illustrates the kinetics of the model study using 500 mM of the reactions (E and T) and 1.4 mol% of DBU in DMSO. As expected, the phenyl maleimide (E1) reacted to full conversion instantaneously after adding DBU (<30 seconds) for both T1 and T2. The rapid kinetic reactivity of maleimides is attributed to two main reasons: ring strain and the electron deficiency of the olefin from the neighboring carbonyl groups.³¹ In order to compare initial reaction rates, the average initial rate between 0 and 2 minutes was calculated (Figure B.5C and B.5D) ethyl acrylate (E2) showed rapid kinetics with both the alkyl and cysteine-based thiols with an initial rate of (212 ± 4) and (202 ± 3) mM/min respectively. In comparison, both acrylamides showed slow reaction kinetics and are two orders of magnitude slower than the acrylate. E3 exhiibited an initial rates at (2 ± 1) mM/min and (4 ± 3) mM/min when reacting with T1 and T2, respectively. Surprisingly, the tertiary acrylamide, E4, showed slightly improved reactivity for both T1 and T2 with an initial rate of (12 ± 3) mM/min and (15 ± 4) mM/min. The slow reactivity of acrylamides is attributed to a decrease in electronegativity of the amine compared with oxygen. Comparing secondary and

tertiary acrylamides it is believed that an induction and/or resonance effect reduces the stability of the enolate specie resulting in slower kinetics.

The vinyl sulfonamides (E5 and E6) exhibited faster reaction kinetics than the acrylamides. Vinyl sulfonamide E5 had an average initial rate of 99 ± 5 and 30 ± 3 mM/min with T1 and T2, respectively. An analogous trend in structural effects between secondary and tertiary amides that was seen in acrylamides was exhibited by the vinyl sulfonamides. Tertiary vinyl sulfonamide, E6, was more rapid than E5 with with initial rates twice to thrice as fast (167± 3 and 89± 1 mM/min for T1 and T2, respectively).



Figure B3 Reaction kinetics over 30 minutes with stoichiometric amounts of thiol [A] T1 and [B] T2 with alkenes E2(green), E3(black), E4(red), E5(blue), and E6(Purple). Not shown is E1 as it reacted to full conversion within the time of running the experiment (30 seconds). [C] shows the average initial rate of all the enes (E2 through E6) with T1 while [D] shows the average initial rate with T2.

B.3 Conclusion

Due to the results in the kinetic model study, current methods of macrocyclization using vinyl sulfonamides is underway using tertiary vinyl sulfonamides. The peptides are expected to exhibit stability in aqueous solutions and enhanced kinetics over analogous acrylamides.

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Appendix C

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