

CYCLOADDITION POLYMERIZATIONS

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A thesis submitted to the Faculty of the Graduate School of the University of Colorado in partial fulfillment of the requirement for the degree of Doctor of Philosophy, Department of Chemical and Biological Engineering, 2011

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ABSTRACT

Cycloaddition polymerizations

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Cycloadditions are a broad class of reactions where unsaturated species combine to form a cyclic adduct with reduced bond multiplicity. Consequently, unlike condensation reactions, no small molecule species are produced. This permits the formation of high molecular weight species and avoids plasticization. Furthermore, problems plaguing addition polymerization mechanisms such as reactions with water and oxygen are avoided. Despite such inherent advantages and widespread use in small molecule synthesis, cycloadditions have been seldom utilized by the polymer community. The unique reversibility of the Diels–Alder reaction received little mention until 2002, and the Huisgen cycloaddition was not widely utilized until the discovery of its copper catalysis in the same year. This work focuses on the synthesis, mechanisms, and unique attributes of cycloadditions for the fabrication of functional materials.

The Diels–Alder reaction was used to synthesize a network polymer with reversible crosslinks. When heated the polymer network depolymerizes and reverts to a liquid. Rheological and spectroscopic measurements demonstrate that the gel point temperature of the material is consistent with the extent of reaction predicted by the Flory–Stockmayer equation. Furthermore, in the gelled state a relaxation process occurs at the rate of bond cleavage in the material. The addition of magnetically susceptible particles causes the material to heat when placed in an electromagnetic field. The self-limiting nature of this heating process enables the material to achieve its native properties over ten cycles of fracture and repair. The reversible nature of the crosslinks also allows the material to function as a photoresist. The reversibility of the Diels–Alder adducts can be selectively eliminated using masked or focused laser light. Upon depolymerization the unexposed material is removed allowing for the fabrication of arbitrary two and three dimensional objects.

The photochemical catalysis of the CuAAC reaction via the radical mediated reduction of Cu(II) was also examined as a method of fabricating cycloaddition polymers. This approach affords comprehensive spatial and temporal control of the CuAAC reaction using standard photolithographic techniques. Advantageously, in this process the CuAAC reaction is the rate determining step, and undesirable side reactions of Cu(I) such as disproportionation, reduction of Cu(I) by radicals, and the reaction of Cu(I) with oxygen are avoided, likely by ligand protection. Such interactions explain the high fidelity of patterning in systems where rapid diffusion of the photogenerated catalyst would otherwise be expected.

To my father

ACKNOWLEDGMENTS

I would first like to thanks Sandia National Laboratories, the University of Colorado-Boulder, and the Department of Education for the funding my thesis through the Excellence in Science and Engineering Fellowship, and the GAANN Fellowship program.

I would like to thank the various members of the Bowman and Anseth groups for their guidance through many rank, dark, hot, cold, wet, stinky, always blue light deprived, occasionally explosive, and almost always smelly days in lab. Especially deserving of thanks are: Christopher Kloxin, Tim Scott, and Kathleen Schreck who answered no less than 1000 questions; Alan Aguirre whose REU project produced the ground work for my first publication; Youhua Tao who did much of the early work on the photo-click process; Cole DeForest who provided the confocal micrographs in chapter VI and performed the two-photon experiments described in chapter V; and Benjamin Fairbanks, Carmem Pfeifer, Robert McLeod and Richard Shoemaker who were of invaluable assistance when I occasionally ventured outside the basement.

I would like to thanks my committee members Jeffrey W. Stansbury, Douglas L. Gin, Daniel K. Schwartz, and Timothy F. Scott for their advice and guidance.

Finally, I would like to thank my advisor Christopher Bowman for his invaluable advice and constant encouragement when progress in both life and lab seemed most difficult.

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CHAPTER I: Introduction

Cycloadditions are a broad class of reactions where unsaturated species combine to form a cyclic adduct with reduced bond multiplicity.¹ Consequently, unlike condensation reactions, small molecule species are not produced, which permits the formation of high molecular weight species and avoids plasticization of the product. Furthermore, problems plaguing addition polymerization mechanisms such as reactions with water and oxygen are avoided. As such, cycloadditions are well suited for both polymer synthesis and modification.

Despite such inherent advantages and widespread use in small molecule synthesis,² cycloadditions have been seldom utilized by the polymer community as evidenced by their near or complete omission in the tomes of the field,^{3,4} and their rare use in commercial products.⁵ The unique reversibility of the Diels–Alder reaction received little mention until 2002,⁶ and the Huisgen cycloaddition was not widely utilized until the discovery of its copper catalysis in the same year.^{7,8} Both reactions have subsequently received considerable attention since the emergence⁹ and popularization^{10,11} of the “click chemistry” paradigm.

Click chemistry emphasizes modular, high yield reactions that occur under simple conditions. The core tenant of click chemistry is an emphasis on properties rather than

reactions. Thus, chemistry takes a back seat to ultimate structure of the material and enables non-chemists to create elaborate structures with ease. An example would be the synthesis of block copolymers from monomers of dissimilar reactivity and solubility.¹¹ Cycloadditions, such as the Huisgen and Diels–Alder reactions fit the click criteria and were among the first click reactions identified.⁹

A chief criticism of click chemistry has been that it is merely an exercise in rebranding.¹¹ For example, two reactions frequently associated with it, the Diels–Alder and Huisgen reactions (**Figure 1**) are frequently used in organic synthesis, and were discovered in 1928 and 1893, respectively^{12, Michael, A. cited in 13}. Early practitioners in the polymer community focused on synthesizing high molecular weight linear polymers from these reactions.^{14,15, reviewed in 13 and 16} As a result, few functional materials were created or well understood. However, examination of a small number of recent publications shows workers producing diverse materials such as oligonucleotide labels,¹⁷ oriented molecular wires,¹⁸ and Janus particles all from these reactions.¹⁹ While much of the chemistry behind these reactions may be old, the goals and implementations are indeed often new.

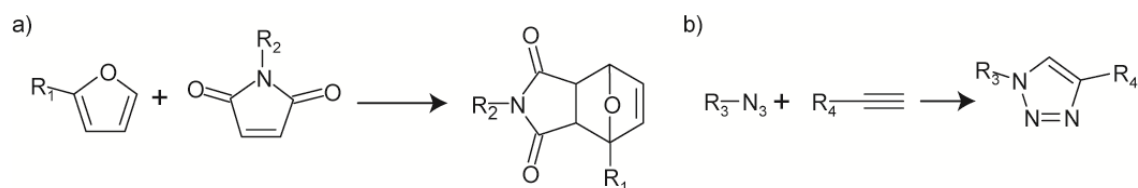


FIGURE 1 | a) The Diels–Alder reaction of furan and maleimide. b) The Huisgen cycloaddition of azide and alkyne functionalities. Only the 1,3,5-triazole, the sole product of the copper catalyzed variant, is shown.

Unlike small molecule chemistry, temporal control of a reaction is often important in the synthesis and modification of polymer networks and functional materials. Coatings, adhesives, metamaterials, contact lenses, dental materials, and photoresists^{20,21} all utilize patterned reactions, while techniques such as parallel protein synthesis,²² cell encapsulation,²³ tissue engineering,²⁴ and 3D prototyping^{25,26} also rely on them. The ability to spatially and temporally control a reaction greatly extends its capabilities and ultimate utility.

The Diels–Alder reaction

The Diels–Alder reaction is a [4+2] cycloaddition occurring between a conjugated diene and olefin, typically termed a dienophile. One of the most studied reactions in organic chemistry, it is the subject of more than 17,000 papers.¹¹ The Diels–Alder reaction possesses broad utility in chemical synthesis because of its ability to form both carbon and heteroatom bonds while tolerating a variety of reaction conditions and solvents. Mechanistically the Diels–Alder reaction is pericyclic, and the reactivity of diene and dienophile pairs is well understood by frontal molecular orbital theory. The most reactive pairs have a minimal gap between the HOMO of the diene and the LUMO of the dienophile. The resulting adduct is usually a mixture of the *endo* and *exo* regioisomers. Often the *exo* product is kinetically favorable while the *endo* product is thermodynamically favorable. This balance often results in the slow conversion from one form to the other.

The superb attributes of the Diels–Alder reaction allow it to be used as a click type reaction for the fabrication or functionalization of complex macromolecular structures.²⁷ Unlike other click reactions, the Diels–Alder reaction is often reversible and can be used for synthesizing materials containing dynamic covalent bonds.^{16,28,29} While all bimolecular

reactions are in principle reversible, few reactions are robust enough to synthesize a polymer that can be repeatedly polymerized and depolymerized. Often, the chief difficulty is the high temperature decomposition reaction common to all organic materials. Such problems are also observed in polymers formed by addition mechanisms where the ceiling temperature is not readily observed because of reactions with atmospheric oxygen.⁴ Other problems include crystallization, vitrification, side reactions, and the loss of a small molecule. Workers have explored many potential reactions: 1,3-dipolar cycloadditions,³⁰ nucleophilic addition reactions,³¹⁻³³ dimerization of nitroso groups³⁴ and carbenes,³⁵ [2+2] cycloadditions,³⁶ alkoxyamine bond scission,³⁷ and ring opening reactions.³⁸ Unfortunately, only a handful of Diels–Alder reactions have emerged as robust systems capable of tolerating repeated cycling outside of carefully controlled conditions.^{6,39-41}

Three potential routes to Diels–Alder polymer networks have been demonstrated in the literature: the polymerization of multifunctional monomers,¹⁴ the crosslinking of linear polymers,¹⁵ and the incorporation of Diels–Alder adducts into monomeric species and a subsequent polymerization via another reaction.⁴² Each approach has a significant impact on the resulting behavior of the gel and is an important design consideration.

When a crosslinked material is formed, the substituent species transform from a liquid to a solid. First, bimolecular and then oligomeric materials are formed by the coupling reaction. Eventually, the non-linear nature of the polymerization reaction results in the formation of a single molecule that percolates the sample and the weight average molecular weight diverges.³ This critical connectivity transition from a liquid to a solid is referred to as

the gel point, and assuming equal reactivity of functional groups the extent of reaction at the gel point, p_c , can be predicted by the Flory–Stockmayer equation,⁴³⁻⁴⁷

$$p_c = \frac{1}{[r(f_a-1)(f_b-1)]^{1/2}} \quad (1)$$

where r is the stoichiometric ratio of functional groups, f_a is the number of functional groups per monomer a (its functionality), and f_b is the functionality of monomer b . Equation (1) reveals that as the functionality of each species increases, the gel point is reduced.

Uniquely in a polymer network formed from the Diels–Alder reaction, the equilibrium constant, K , provides a direct relationship between the conversion and temperature at which the gel point occurs. Defining the equilibrium constant in terms of the conversion, p , the initial concentration, c_0 , of the limiting functional group, and the ratio of the initial concentrations of limiting and excess functional groups, r , gives K as,

$$K = \frac{rp}{c_0(1-p)(1-rp)} \quad (2)$$

Using the relationship between the Gibbs free energy and the equilibrium constant,

$$\ln K = \frac{-\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} \quad (3)$$

the relationship between the heat of reaction, $\Delta H^\ddagger$, entropy of reaction, $\Delta S^\ddagger$, and the temperature, T , can be derived to be:

$$T = \frac{\Delta H^\ddagger}{\Delta S^\ddagger - \frac{1}{R} \ln \frac{rp}{c_0(1-p)(1-rp)}} \quad (4)$$

where R is the gas constant. Thus, at the gel point the conversion, p_{gel} , the gel point temperature, T_{gel} , is

$$T_{gel} = \frac{\Delta H^\ddagger}{\Delta S^\ddagger - \frac{1}{R} \ln \frac{rp_{gel}}{c_0(1-p_{gel})(1-rp_{gel})}} \quad (5)$$

Equation (5) reveals that as long as the heat of reaction is negative, a unique temperature exists above which the network will not exist. Equation (5) also shows that the gel point temperature depends on both the nature of the chemistry utilized (heat and entropy of reaction) and the functionality of the monomers which controls the gel point conversion. Consequently, species that gel at low conversions may decompose by other irreversible reactions before a temperature is reached where the system can be driven far enough backward to reverse the gelation process. As such, highly functionalized polymers or oligomers bearing tens to hundreds of pendant functional groups are more difficult to revert to a liquid than less functionalized species. As such, the polymerization of small multifunctional monomers is the easiest way to make a material that is capable of reverting to a liquid from a solid.

While thermodynamics predicts the gel-point temperature, kinetic considerations are also important in describing the mechanical behavior of materials formed by the Diels–Alder reaction. Gels are classified as either strong or weak gels based on their behavior on an infinite timescale.⁴⁸ Strong gels are formed by irreversible bonds and do not possess any terminal relaxation mechanism. As such, they possess a finite zero frequency elastic modulus. Weak gels are formed by reversible interactions that impart a terminal relaxation mechanism occurring at the frequency of bond scission. Thus, while a weak gel may possess an elastic modulus on a finite time scale, it vanishes on an infinite time scale. Weak gels are typically formed by non-covalent interactions such as hydrogen bonding⁴⁹ and pi stacking.⁵⁰ Classically, gels formed by covalent bonds are assumed to be strong gels, although Toplansky demonstrated the relaxation behavior of disulfide linkages in vulcanized rubber.⁵¹ Thus, measurements at a single frequency⁵²⁻⁵⁵ are only appropriate for describing the

mechanical properties over the time scale of the measurement. As the rate of relaxation in these systems can be frustratingly slow, an understanding of chemical kinetics is necessary to describe the behavior of these materials.

Applications of the Diels–Alder reaction

Polymers formed by the Diels–Alder reaction are useful for applications that require the mechanical properties of a typical polymer network, but simultaneously benefit from a lack of permanence in the structure typical of a conventional thermoset. An associated potential disadvantage of these materials that must be considered is their long-term creep behavior that, depending on the specific chemical nature of the covalent adaptable network (CAN), may lead to long-term changes in the material shape, particularly for those materials held under stress during their implementation. The creation of an easily recyclable material that possesses the characteristics of a thermoset has been a motivating idea since the inception of Diels–Alder based polymers¹⁴ and a number of systems have been synthesized that are readily manipulated post-polymerization.^{14,37,56,57,58} Such materials have been employed in so-called hot-melt applications, such as hot-melt inks⁵⁹ and hot-melt adhesives,^{55,60} where the material is manipulated in a heated liquid-state and then cooled to produce a crosslinked solid.

Electronic components are often protected from the environment in a thermoset encapsulate. If the component is found to be faulty after encapsulation, rework of the circuit requires shearing off the component and the thermoset encapsulate. Accordingly, the use of thermoreversible materials that are easily removed has been explored as alternative encapsulates and anisotropic conductive adhesives.⁶⁰⁻⁶² Interestingly, in such applications the

reverse reaction can be driven far from equilibrium by flushing sol fraction away with solvent. As a consequence, it is no longer necessary to drive the material past the conversion required for reverse gelation, rather only a sufficient rate of the reverse reaction is required. This strategy enables the use of polymers that are highly functionalized with crosslinking groups.

Thermoreversible crosslinks have also been used to align dendritic non-linear optical chromophores to achieve high electrical optical coefficients.^{63,64} Crosslinking of the dendrimers reduces the free volume, improving the long term stability of the material. Furthermore, the reversible nature of the Diels–Alder reaction permits the materials to be cured until alignment is achieved. It is also possible to incorporate a second chromophore, without inducing phase separation that improves the poling efficiency.⁶⁵ Thermoreversible materials have also been employed as the cladding material in light guides and other electro-optic devices.⁶⁶

More recent work has been directed at the use of thermoreversible bonds for creating self-healing or mendable materials.^{6,39,54,58,67} Self-healing materials possess the ability to recover their initial mechanical properties after damage. On small size scales healing is nearly universal in polymers due to reptation of polymer chains though this behavior is severely limited in crosslinked polymer networks;⁶⁸ however, macroscopic crack healing is always a significantly more difficult challenge. Autonomic self-healing schemes, where monomer is encapsulated in spheres, fibers, or channels and is released upon fracture to flow and subsequently polymerize in the crack, have been shown to be successful, but suffer from a limited number of healing cycles as the monomer is depleted.⁶⁹ While polymers

incorporating reversible bonds do not permit macroscale autonomous healing, they do offer a simpler approach to healing. For cracks where two surfaces are in close contact, bond rearrangement alone permits material healing. Chen et al.^{6,39} synthesized multifunctional furan and maleimide monomers and demonstrated, for a material above its gel point, 50% fracture toughness recovery after initial fracturing and 41% after a second fracture.⁶ Second generation materials by the same group recovered approximately 80% of their initial fracture toughness after two subsequent sample fracture and healing cycles.³⁹ Since reverse gelation in thermal CANs results in material flow, complete mechanical strength recovery is possible provided that irreversible side reactions, particularly common at elevated temperatures, are suppressed. Unfortunately, reverse gelation also results in slump or deformation in the overall material shape; thus, for many structural applications, near gel reversion is more desirable.

The copper-catalyzed azide–alkyne cycloaddition and the radical mediated reduction of Cu(II)

Like the Diels–Alder reaction, the Huisgen cycloaddition is an old reaction. It reemerged as a powerful synthetic tool after the discovery of the copper-catalyzed azide–alkyne cycloaddition (CuAAC).^{7,8} While the Huisgen cycloaddition is sluggish for most alkynes, a rate acceleration of approximately 10^7 is achieved by the addition of Cu(I), and high yields are then readily obtained.⁷⁰ Furthermore, the invisibility of azides and alkynes to many functional groups, the ability to use a variety of solvents, and the reaction's tolerance of a wide pH range⁷¹ facilitate reliable results in diverse applications. Telechelic azide and alkyne polymers are readily synthesized by controlled radical polymerization techniques such as atom transfer radical polymerization (ATRP)⁷⁰ and reversible addition fragmentation chain transfer polymerization (RAFT).⁷² These advantages have ultimately led to a “Lego-like”

approach to the fabrication of complex macromolecular structures,¹¹ and the CuAAC reaction has become ubiquitous.^{10,70,73}

Typically, Cu(I) is added directly as a copper salt,⁸ formed by the reduction of copper sulfate pentahydrate via ascorbic acid,⁷ or generated by the comproportionation of copper metal and Cu(II).⁷¹ Spatial control of the CuAAC reaction has been limited to surfaces, using techniques such as microcontact printing⁷⁴ and scanning-probe lithography.⁷⁵

An alternative approach to spatial and temporal control is photolithography, where masked or focused light is applied to a photoresist, causing a chemical reaction that changes the resists solubility.⁷⁶ Frequencies employed range from the infrared to soft x-ray region, although the visible to deep UV range corresponds to the electronic transitions in many molecules and is more commonly used. Negative photoresists that form polymer in irradiated areas typically utilize one of two reaction motifs: photochromic groups can undergo cycloadditions such as the [2+2] cycloaddition of cinnamate,³⁶ or a chain process can be initiated via the generation of an active species.

A limited reactant and reaction set has traditionally been directly photopolymerized; primarily, radicals and carbocations can be used to initiate the polymerization of a variety of olefins. Photochemical Huisgen cycloadditions are symmetry forbidden,⁷⁷ the CuAAC reaction is believed to proceed via a stepwise process,⁷¹ and neither reaction is initiated by common active species. Thus, conventional photochemical mechanisms fail in their ability to initiate this reaction. A limited solution that has been implemented utilizes the protection of a strained cyclo-octyne via a propenone. The propenone can be cleaved by UV light and

subsequently the cyclo-octyne undergoes a Huisgen cycloaddition.⁷⁸ In addition to the inherent limitation requiring the synthesis of strained cyclopropenones, one photon is required for each reaction event, whereas chain reactions enable a single photon to lead to the reaction of tens to millions of coupling events.

Another solution is the generation of Cu(I) as an active species. Such an approach would extend spatial control to all materials developed to date. One possible component of such a methodology was developed in the work of Sakamoto *et al.* who demonstrated the radical mediated generation of copper nanoparticles from Cu(II).⁷⁹ Conceivably, if appropriate conditions were utilized, the transiently generated Cu(I) would catalyze the Huisgen cycloaddition.

Research Overview

In this thesis research was conducted to explore the utility of cycloaddition reactions for the synthesis of polymer networks. Both the Diels–Alder reaction and the copper-catalyzed azide–alkyne cycloaddition (CuAAC) were studied. Spectroscopic experiments were conducted to demonstrate these reactions, and explore their mechanisms, while mechanical measurements examined the relationship between the underlying chemical reactions and the material properties. Both reactions were utilized in the fabrication of functional materials owing to efficient bond formation and tolerance of other functional groups, which allowed their modular use in a number of potential applications.

Following this introduction and the objectives laid out in the next chapter, chapters three through five detail the use of the Diels–Alder reaction for synthesizing polymers and

creating functional materials. The superb nature of the Diels–Alder reaction is demonstrated in a variety of applications. In chapter three a polymer network is synthesized using the Diels–Alder reaction. Fourier transform infrared (FTIR) spectroscopy is used to determine the equilibrium conversion as a function of temperature and reaction kinetics. These results are coupled with dynamic mechanical analysis to examine the gel point and explore the relationship between the chemical and mechanical properties of the material. Chapter four examines the combined use of ferromagnetic particles and an alternating magnetic field for remotely heating the polymer examined in chapter three. The self-controlled nature of the heating process allows the composite material to be healed from multiple fractures without changes in the mechanical properties. In chapter five a polymer formed by the Diels–Alder reaction is utilized as a photoresist, in a process termed “photofixation.” The benefits of utilizing a crosslinked material as a photoresist are demonstrated in both conventional lithography and for microstereolithography.

Chapters six and seven explore the radical mediated reduction of Cu(II) as a method for catalyzing the CuAAC. In chapter six the use of conventional photoinitiators for generating Cu(I) and catalyzing the CuAAC reaction is demonstrated. It is shown that this process enables spatial and temporal control of the reaction, allowing for both the patterning of hydrogel formation and the *in situ* functionalization of hydrogels. In chapter seven the mechanism of the reaction is examined by a series of initial rate experiments. Several side reactions thought to consume Cu(I) are shown not to play a role in the mechanism, while the interactions of Cu(I) ligands present in the system are found to be important to both the mechanism and the spatial control of the reaction.

REFERENCES

- (1) McNaught, A. D.; Wilkinson, A. *IUPAC. Compendium of Chemical Terminology*; 2nd ed.; Blackwell Scientific Publications: Oxford, 1997.
- (2) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Elmsford, 1990.
- (3) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, 1953.
- (4) Odian, G. *Principles of Polymerization*; 3rd ed.; John Wiley and Sons, Inc.: New York, 1991.
- (5) Maier, G. *Macromol. Chem. Phys.* **1996**, *197*, 3067-3090.
- (6) Chen, X. X.; Dam, M. A.; Ono, K.; Mal, A.; Shen, H. B.; Nutt, S. R.; Sheran, K.; Wudl, F. *Science* **2002**, *295*, 1698-1702.
- (7) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.-Int. Edit.* **2002**, *41*, 2596-2599.
- (8) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
- (9) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Edit.* **2001**, *40*, 2004-2021.
- (10) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Comm.* **2007**, *28*, 15-54.
- (11) Barner-Kowollik, C.; Inglis, A. J. *Macromol. Chem. Phys.* **2009**, *210*, 987-992.
- (12) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98.
- (13) Huisgen, R. *Angew. Chem.-Int. Edit. Engl* **1963**, *2*, 565-598.
- (14) Craven, J. M. Cross-linked Thermally Reversible Polymers Produced from Condensation Polymers with Pendant Furan Groups Cross-linked with Maleimides USPTO 3435003 1966.
- (15) Canary, S. A.; Stevens, M. P. *J. Polym. Sci. Part A* **1992**, *30*, 1755-1760.
- (16) Engle, L. P.; Wagener, K. B. *J. Macromol. Sci. R. M C.* **1993**, *C33*, 239-257.
- (17) Schoch, J.; Wiessler, M.; Jalschke, A. *J. Am. Chem. Soc.* **2010**, *132*, 8846-8847.
- (18) Luo, L.; Frisbie, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 8854-8855.
- (19) Chen, R. T.; Muir, B. W.; Such, G. K.; Postma, A.; McLean, K. M.; Caruso, F. *Chem. Commun.* **2010**, *46*, 5121-5123.
- (20) Bowman, C. N.; Kloxin, C. J. *AIChE J.* **2008**, *54*, 2775-2795.
- (21) Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int. Edit.* **2010**, *49*, 1540-1573.
- (22) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767-773.
- (23) Koh, W.-G.; Revzin, A.; Pishko, M. V. *Langmuir* **2002**, *18*, 2459-2462.
- (24) Martens, P. J.; Bryant, S. J.; Anseth, K. S. *Biomacromolecules* **2003**, *4*, 283-292.
- (25) Neckers, D. C. *Polym. Eng. Sci.* **1992**, *32*, 1481-1489.
- (26) Young, J. S.; Fox, S. R.; Anseth, K. S. *J. Manuf. Sci. Eng.-Trans. ASME* **1999**, *121*, 474-477.
- (27) Dag, A.; Durmaz, H.; Kirmizi, V.; Hizal, G.; Tunca, U. *Polym. Chem.*, *1*, 621-623.
- (28) Kloxin, C. J.; Scott, T. F.; Adzima, B. J.; Bowman, C. N. *Macromolecules* **2010**, *43*, 2643-2653.
- (29) Sanyal, A. *Macromol. Chem. Phys.*, *211*, 1417-1425.
- (30) Jones, G. O.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 1333-1342.
- (31) Chang, J. Y.; Do, S. K.; Han, M. J. *Polymer* **2001**, *42*, 7589-7594.
- (32) Wagener, K. B.; Murla, M. A. In *American Chemical Society, Polymer Preprints, Division of Polymer Chemistry*; ACS: 1989; Vol. 30, p 287-288.
- (33) Wagener, K. B.; Engle, L. P. *Macromolecules* **1991**, *24*, 6809-6815.

- (34) Pazos, J. Polymers Coupled by Nitroso Groups USPTO 3872057 1975.
- (35) Kamplain, J. W.; Bielawski, C. W. *Chem. Commun.* **2006**, 1727-1729.
- (36) Chung, C. M.; Roh, Y. S.; Cho, S. Y.; Kim, J. G. *Chem. Mat.* **2004**, *16*, 3982-3984.
- (37) Higaki, Y.; Otsuka, H.; Takahara, A. *Macromolecules* **2006**, *39*, 2121-2125.
- (38) Miyagawa, T.; Shimizu, M.; Sanda, F.; Endo, T. *Macromolecules* **2005**, *38*, 7944-7949.
- (39) Chen, X. X.; Wudl, F.; Mal, A. K.; Shen, H. B.; Nutt, S. R. *Macromolecules* **2003**, *36*, 1802-1807.
- (40) Boul, P. J.; Reutenauer, P.; Lehn, J. M. *Org. Lett.* **2005**, *7*, 15-18.
- (41) Reutenauer, P.; Boul, P. J.; Lehn, J. M. *Eur. J. Org. Chem.* **2009**, 1691-1697.
- (42) Heath, W. H.; Palmieri, F.; Adams, J. R.; Long, B. K.; Chute, J.; Holcombe, T. W.; Zieren, S.; Truitt, M. J.; White, J. L.; Willson, C. G. *Macromolecules* **2008**, *41*, 719-726.
- (43) Flory, P. J. *J. Am. Chem. Soc.* **1941**, *63*, 3083-3090.
- (44) Flory, P. J. *J. Am. Chem. Soc.* **1941**, *63*, 3091-3096.
- (45) Flory, P. J. *J. Am. Chem. Soc.* **1941**, *63*, 3096-3100.
- (46) Stockmayer, W. H. *J. Chem. Phys.* **1943**, *11*, 45-55.
- (47) Stockmayer, W. H. *J. Chem. Phys.* **1944**, *12*, 125-131.
- (48) de Gennes, P. G. *Scaling Concepts in Polymer Physics*, 1979.
- (49) Cordier, P.; Tournilhac, F.; Soulie-Ziakovic, C.; Leibler, L. *Nature* **2008**, *451*, 977-980.
- (50) Ajayaghosh, A.; George, S. J. **2001**, *123*, 5148-5149.
- (51) Stern, M. D.; Tobolsky, A. V. *J. Appl. Phys.* **1946**, *17*, 406-406.
- (52) McElhanon, J. R.; Russick, E. M.; Wheeler, D. R.; Loy, D. A.; Aubert, J. H. *J. Appl. Polym. Sci.* **2002**, *85*, 1496-1502.
- (53) Liu, Y. L.; Chen, Y. W. *Macromol. Chem. Phys.* **2007**, *208*, 224-232.
- (54) Zhang, Y.; Broekhuis, A. A.; Picchioni, F. *Macromolecules* **2009**, *42*, 1906-1912.
- (55) Tian, Q.; Yuan, Y. C.; Rong, M. Z.; Zhang, M. Q. *J. Mater. Chem.* **2009**, *19*, 1289-1296.
- (56) Liu, Y. L.; Hsieh, C. Y. *J. Polym. Sci. Pol. Chem.* **2006**, *44*, 905-913.
- (57) Adzima, B. J.; Aguirre, H. A.; Kloxin, C. J.; Scott, T. F.; Bowman, C. N. *Macromolecules* **2008**, *41*, 9112-9117.
- (58) Murphy, E. B.; Bolanos, E.; Schaffner-Hamann, C.; Wudl, F.; Nutt, S. R.; Auad, M. L. *Macromolecules* **2008**, *41*, 5203-5209.
- (59) Paine, A. J.; Hamer, G. K.; Tripp, C. P.; Bareman, J. P.; Mayer, F. M.; Sacripante, G. G. Phase change ink compositions USPTO 5,844,020 1998.
- (60) Small, J. H.; Loy, D. A.; McElhanon, J. R.; Saunders, R. S. Method of making thermally removable polymeric encapsulants USPTO 6,271,335 2001.
- (61) Iyer, S. R.; Wong, P. K. Anisotropic conductive adhesives compositions USPTO 5,840,215 1998.
- (62) Iyer, S. R.; Wong, P. K. Die attach adhesive compositions USPTO 5,973,052 1999.
- (63) Shi, Z.; Hau, S.; Luo, J.; Kim, T. D.; Tucker, N. M.; Ka, J. W.; Sun, H.; Pyajt, A.; Dalton, L.; Chen, A.; Jen, A. K. Y. *Adv Funct Mater* **2007**, *17*, 2557-2563.
- (64) Enami, Y.; Derosé, C. T.; Mathine, D.; Loychik, C.; Greenlee, C.; Norwood, R. A.; Kim, T. D.; Luo, J.; Tian, Y.; Jen, A. K. Y.; Peyghambarian, N. *Nat. Photonics* **2007**, *1*, 180-185.
- (65) Kim, T. D.; Luo, J.; Ka, J. W.; Hau, S.; Tian, Y.; Shi, Z.; Tucker, N. M.; Jang, S. H.; Kang, J. W.; Jen, A. K. Y. *Adv. Mater.* **2006**, *18*, 3038-3042.
- (66) Jen, K.-Y.; Luo, J.; Liu, S. Thermally reversibly crosslinkable polymer as cladding for electro-optic devices USPTO 7,346,259 2008.
- (67) Bergman, S. D.; Wudl, F. *J. Mater. Chem.* **2008**, *18*, 41-62.

- (68) Wool, R. P. *Soft Matter* **2008**, *4*, 400-418.
- (69) White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. *Nature* **2001**, *409*, 794-797.
- (70) Meldal, M. *Macromol. Rapid Commun.* **2008**, *29*, 1016-1051.
- (71) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Amer. Chem. Soc.* **2005**, *127*, 210-216.
- (72) Quemener, D.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. *Chem. Commun.* **2006**, 5051-5053.
- (73) Sumerlin, B. S.; Vogt, A. P. **2009**.
- (74) Spruell, J. M.; Sheriff, B. A.; Rozkiewicz, D. I.; Dichtel, W. R.; Rohde, R. D.; Reinhoudt, D. N.; Stoddart, J. F.; Heath, J. R. *Angew. Chem. Int. Edit.* **2008**, *47*, 9927-9932.
- (75) Paxton, W. F.; Spruell, J. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 6692-6694.
- (76) Roffey, C. *Photogeneration of Reactive Species for UV Curing*. John Wiley and Sons: West Suffex, 1997.
- (77) Padwa, A. *Angew. Chem. Int. Edit. Engl.* **1976**, *15*, 123-136.
- (78) Poloukhine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G.-J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769-15776.
- (79) Sakamoto, M.; Tachikawa, T.; Fujitsuka, M.; Majima, T. *Chem. Mater.* **2008**, *20*, 2060-2062.

CHAPTER II: Objectives

This thesis explores methods for conducting, controlling, and utilizing cycloaddition polymerizations in polymer networks. Two reactions are examined in detail: the Diels–Alder reaction of furan and maleimide along with its accompanying retro reaction; and the copper catalyzed azide–alkyne cycloaddition (CuAAC). These reactions are employed to synthesize several functional materials: thermally reversible covalent adaptable networks (CANs), electromagnetic field responsive polymer composites, photoresists, and spatially patterned hydrogels. This thesis tests the hypothesis that cycloadditions are well-understood, efficient, and modular reactions, and that such attributes enable the facile synthesis of polymeric materials with unique properties.

To test these hypotheses, I have outlined these specific aims:

- 1) Synthesize a crosslinked polymer network using the Diels–Alder reaction, and use this material to,
 - i. Measure the thermodynamic and kinetic constants of the Diels–Alder reaction between furan and maleimide, and relate these constants to polymer properties;

- ii. Examine hysteresis heating as a mechanism for remotely controlling depolymerization and repeatedly healing damage by this mechanism; and
 - iii. Create a photoresist based on the concept of photofixation in which light will be used to locally prevent the retro Diels–Alder reaction.
- 2) Examine the radical mediated reduction of Cu(II) as a method for catalyzing the Huisgen cycloaddition. Employ this system to develop temporal and spatial control of the CuAAC reaction and to gain a mechanistic understanding of the photoreduction of Cu(II), the CuAAC reaction, and the relationship between the two processes.

While a number of crosslinked polymers have been prepared using the Diels–Alder reaction, to date none have been thoroughly characterized. Typically, spectroscopic measurements have been qualitatively analyzed and dynamic mechanical tests have utilized single frequency experiments that are incapable of accurate gel point determination. The synthesis of such a network will allow the exploration of the interrelationship of the chemical and mechanical properties of the material to be established. Understanding this relationship will allow for the successful implementation of Diels–Alder based polymer networks in functional materials. This embodiment will include being able to create materials that can be repeatedly healed from fractures and developing crosslinked materials that are capable of functioning as a photoresist. In both cases classes of materials developed to date can be improved by a thorough understanding of the impact of the underlying chemistry on the material properties.

The second objective seeks to establish a method for spatially and temporally controlling the CuAAC reaction. Various workers have sought to gain spatial control of the reaction by utilizing dip pen lithography, soft lithography, or other approaches. While successful in part, all of the techniques to date are limited to surface reactions, or require lengthy synthetic routes that are not amenable to all materials. Moreover, photolithographic steps employing other reactions are requisite in most schemes. Alternatively, the radical mediated reduction of Cu(II) promises to be a universal route to spatial control of the CuAAC reaction that employs common equipment and techniques. The development procedures for patterning technique for the CuAAC reaction will allow a vast array of materials and chemical species already developed to be readily patterned. Examination of the mechanism will allow for improvements to the protocol, such as increased reaction kinetics, possible methods for reducing the required concentration of copper, or other mechanism for reducing the cytotoxicity of the reaction.

Combined the objectives seek to demonstrate that cycloaddition reactions are efficient and modular reactions for the synthesis of functional polymeric materials with controlled and desired properties.

CHAPTER III: Rheological and chemical analysis of reverse gelation in a covalently crosslinked Diels–Alder polymer network*

Abstract

A network polymer, incorporating dynamic and reversible crosslinks, was synthesized using the Diels–Alder reaction. Fourier transform infrared (FTIR) spectroscopy was used to characterize the reaction rate and thermodynamic equilibrium over a broad temperature range. Equilibrium conversion of the furan and maleimide varied from 74% at 85°C to 24% at 155°C, demonstrating significant depolymerization via the retro-Diels–Alder reaction. The gel point temperature, as determined by rheometry using the Winter–Chambon criterion, was 92°C, corresponding to a gel point conversion of 71%, consistent with the Flory–Stockmayer equation. The scaling exponents for the complex moduli, viscosity, and plateau modulus, in the vicinity of the gel point, were determined and compared with experimental and theoretical literature values. Further, the material exhibited a low frequency relaxation owing to dynamic rearrangement of crosslinks by the Diels–Alder and retro-Diels–Alder reactions.

Introduction

Traditionally, thermosets are irreversibly crosslinked polymeric networks possessing essentially infinite molecular weight that cannot be melted, molded, or dissolved.¹ Such materials are durable and find use in a wide array of applications such as adhesives,^{2,3} coatings,^{4,5} dental materials,^{6,7} and composites.^{8,9} In contrast, the incorporation of reversibly labile functionalities into the polymer backbone enables manipulation of network connectivity and allows behavior analogous to melting, molding, and dissolution through depolymerization to low molecular weight species. This reversion significantly extends the capabilities and utility of these crosslinked materials. Furthermore, polymers that contain

*Published in *Macromolecules*, **2008**, 23, 9112-9117. Experiential information and a detailed reaction model is provided in Appendix A.

reversible linkages have been used to create stimulus responsive polymers that display novel properties such as shape memory,^{10,11} crack healing,^{12,13} and stress relief.¹⁴

In principle, most polymerizations are reversible; however, realizing depolymerization often leads to complete and irreversible degradation of the polymer network. Certain polymers, including those created by radical and ionic polymerization, often depolymerize when heated above a ceiling temperature. Ceiling temperatures are typically quite high and, at such temperatures, irreversible degradation of other molecular structures generally occurs.¹⁵ In condensation polymerizations, condensate removal favors the forward reaction, thus the retro-reaction is only achieved when the condensate is present in significant quantities. Consequently, polymers such as polyacrylhydrazones undergo dynamic network rearrangement, but do not revert to monomer,¹⁶ and exotic approaches are required to create systems that undergo a sol-gel transition, but do not exhibit dynamic network rearrangement in the gel state.¹⁷

The Diels–Alder (DA) reaction, a [4+2] cycloaddition between a diene (e.g., furan) and dieneophile (e.g., maleimide), is thermally reversible via the retro-Diels–Alder (rDA) reaction (**Figure 1**).¹⁸ The DA reaction is attractive as a reversible linkage as the rDA reaction occurs at moderate temperatures and does not liberate a small molecule. The subject of more than 17,000 papers, the DA reaction is well studied,¹⁹ but its use in polymer chemistry is comparatively limited. Nevertheless, a variety of macromolecular structures have been synthesized utilizing the DA reaction of maleimides and furans, including linear polymers,²⁰ networks,^{12,13,21,22} hydrogels,²³ and dendrimers.²⁴ Moreover, DA adducts have been incorporated into monomers bearing other polymerizable functionalities, allowing

DA/rDA reactions to be exploited in materials polymerized via common mechanisms such as the reaction between epoxy and amine functionalities,²⁵ and free-radical (meth)acrylate polymerizations.^{26,27}

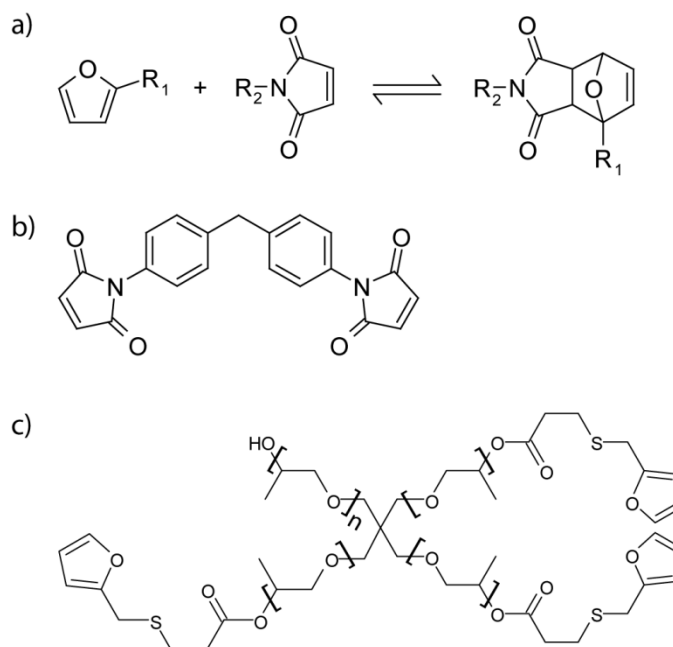


FIGURE 1 | a) The Diels–Alder/retro-Diels–Alder reaction between a functionalized furan and maleimide. Polymer networks are formed when the Diels–Alder pathway is utilized in monomers with multiple reactive functionalities. The monomers used include: (b) DPBM, and (c) PPTF.

Network reversibility owing to the rDA reaction has been demonstrated through solubility studies,^{21,25,28} however, the temperature dependence of the equilibrium constant, and therefore conversion, in these networks remains relatively unexplored. Typically, polymers above their glass transition temperature have sufficient molecular mobility to reach thermodynamic equilibrium when sufficient time is allowed for completion of the reaction. Accordingly, in polymers formed by the DA reaction, the final conversion is a function of temperature, as demonstrated in linear polymers crosslinked by the DA reaction.²⁹

The molecular weight evolution during a step-growth polymerization, such as a DA polymerization, proceeds geometrically and is accompanied by an exponential increase in viscosity. Moreover, for systems capable of crosslinking, the material undergoes gelation, a critical point that occurs when a single macromolecule first spans the sample, and the material transitions from a liquid sol to a solid gel. The creation of a macromolecular gel is accompanied by a divergence in the viscosity and an emergence of an elastic modulus. Typically, as the reaction proceeds, the elastic modulus increases until complete conversion is achieved or the material vitrifies. The mechanical properties of all polymeric materials vary with temperature as they pass through transitions such as crystallization, glass transition, or other molecular relaxations. Unlike conventional, non-reversible networks, the crosslink density of polymers containing DA adducts is dependent on the temperature, leading to the establishment of a gel point temperature.

The gel point conversion for the step-growth polymerization between maleimide and furan monomers is well-predicted by the Flory–Stockmayer equation,

$$p_g = \frac{1}{\sqrt{r(1-f_M)(1-f_F)}}, \quad (1)$$

where p_g is the gel point conversion, r is the stoichiometric ratio, and f_M and f_F are the degree of functionality for the maleimide and furan monomers, respectively.^{30,31} The gel point conversion is shifted by changing either the monomer functionality or the stoichiometric ratio and determined experimentally using rheometry to compare with the predicted value. Observation of a material's complex response to an oscillatory shear stress allows application of the Winter–Chambon criterion,

$$G'(w) \sim G''(w) \sim w^u, \quad (2)$$

which states that the real and imaginary moduli follow identical power law frequency scaling at the gel point, for $\omega < 1/\tau_0$ where τ_0 is the characteristic relaxation time of the smallest molecular species.³² The gel point conversion for an irreversible polymerization is typically determined by quenching the reaction, leading to a trial-and-error process. Nevertheless, several researchers have performed accurate mechanical measurements near the gel point, validating the Winter–Chambon criterion in a rheometer.^{33–35} Others have utilized off-stoichiometric monomer ratios so that the gel point is achieved near the final conversion.³⁶ Khan et al. monitored the polymerization of thiol-ene resins using rheometry and inferred the conversion at the gel point by IR spectroscopy.³⁷ In contrast, DA-based networks display inherent coupling of conversion and temperature, thereby allowing fine and reversible control of the conversion near the gel point, all within a single sample.

Here, the reversible reaction between furan and maleimide functionalities is exploited to examine the complex interplay between the Diels–Alder equilibrium, kinetic limitations associated with the mobility in the crosslinked network, the glass transition, and the sol-gel transition using IR spectroscopy and rheometry over a broad temperature range. The mechanical properties of the material are also examined using rheometry as a function of temperature, and therefore conversion, which facilitates the examination of several theoretical descriptions of the gelation process.

Results

Furan conversion (as determined by FTIR spectroscopy) versus time for PPTF-DPBM copolymerizations at several temperatures is shown in **Figure 2a**. FTIR spectroscopy enables facile determination of both furan and maleimide conversion

independently and simultaneously; however, as the functionalities are consumed at equal rates in the DA reaction, for clarity, maleimide conversions are not shown. Whereas the polymerization reaction rate increases monotonically with cure temperature, the ultimate conversion is not monotonically dependent on the temperature. As the polymerization proceeds, there is an increase in the crosslinking density and the glass transition temperature (T_g); however, once the T_g of the polymerizing material equals or exceeds the temperature (T_{cure}), mobility limitations become significant and thus the polymerization rate is severely reduced, i.e., the network vitrifies. Typically, higher cure temperatures result in greater conversions until T_{cure} exceeds the ultimate attainable T_g at full conversion.³⁸ The increased maximum conversion when the polymerization temperature is raised from ambient to 60°C is attributed to a delay in the onset of vitrification at the higher temperature. While it might be expected that vitrification should be further delayed at 80°C, a decrease in the conversion is observed. As the polymerization temperature is increased above approximately 45°C, the reaction transitions from kinetic control (a consequence of vitrification) to thermodynamic control associated with the attainment of the equilibrium reaction extent as dictated by the thermodynamics of the DA reaction. This transition can be inferred from **Figure 2b** where, below 45°C, vitrification limits the attainable conversion; whereas, above 45°C, the DA reaction is at or near thermodynamic equilibrium.

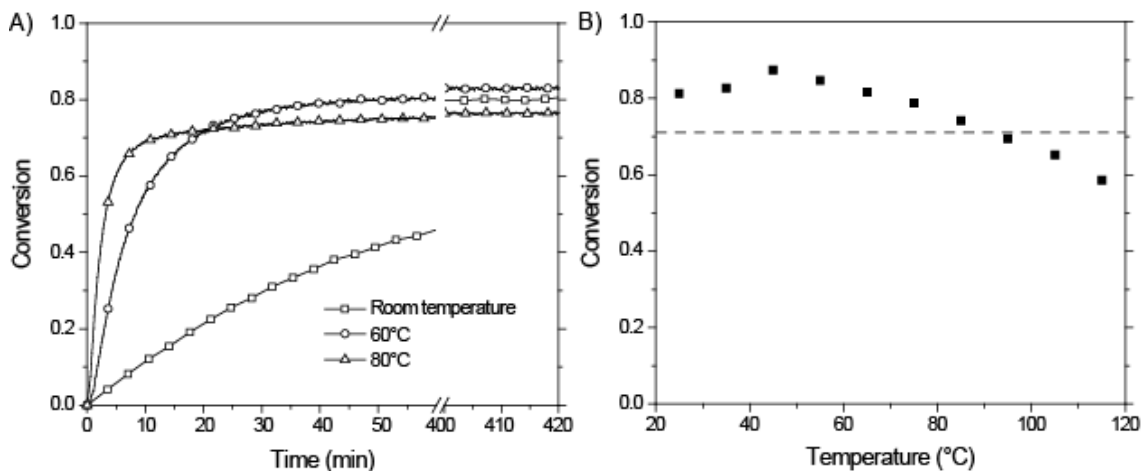


FIGURE 2 | (a) Fractional furan conversion during isothermal polymerizations of 1:1 stoichiometric mixtures of PPTF and DPBM, at various temperatures. (b) Ultimate furan conversion after PPTF-DPBM polymerization. The dashed line represents the gel point conversion predicted by the Flory–Stockmayer equation, where $f_M = 2$ and $f_F = 3$ (i.e., bismaleimide and trifuran). Maleimide conversions are identical and not plotted for clarity.

Figure 2b illustrates that, above 45°C, as the temperature is raised, the equilibrium is increasingly driven from the DA adduct to the reactants, via the rDA reaction. The gel point conversion, as predicted by the Flory–Stockmayer equation (1), is 0.707 for bismaleimide-trifuran polymerization; from the conversion data, the gel point temperature can be estimated to be $92.5 \pm 0.5^\circ\text{C}$ (Figure 2b). Moreover, the temperature range neighboring the gel point temperature is well within the thermodynamically controlled reaction regime, allowing facile examination of the gel point without complications associated with vitrification.

The equilibrium conversion is further decreased to 24% at 155°C; however, an irreversible side reaction becomes apparent at higher temperatures. At long residence times, above 120°C, the maleimide peak area begins to decrease, while the furan peak area increases. This decrease in the maleimide peak area likely can be attributed to maleimide homopolymerization, initiated at high temperature as demonstrated by Hopewell et al.,³⁹

which is accompanied by a corresponding increase in furan concentration as the loss of maleimide drives the equilibrium further towards the reactants.

The equilibrium constant for the reaction between a maleimide (M) and a furan (F), producing a DA adduct (A),

$$K = \frac{[A]}{[F][M]} = \frac{p}{c_0(1-p)^2}, \quad (3)$$

can be calculated for a stoichiometric mixture of reactants using the conversion, p (see **Figure 3**), and the initial concentration of either reactant, c_0 . A plot of the natural logarithm of the equilibrium constant versus inverse temperature, $1/T$, allows the heat of reaction (ΔH_r°) and entropy of reaction (ΔS_r°) to be determined from the slope and intercept. The heat and entropy of reaction were found to be -40 ± 1 kJ/mol and -102 ± 3 J/K/mol, respectively. This calculated heat of reaction is significantly lower than the reported values (ranging from -84 to -104 kJ/mol) given for reactions between substituted furans with maleic anhydride,⁴⁰ however, it compares favorably with an estimate of ~ 32 kJ/mol for the kinetically favored endo conformation of a furan-maleimide adduct.⁴¹

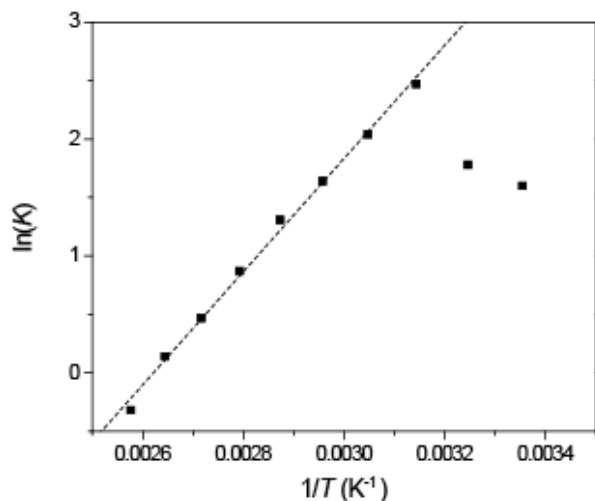


FIGURE 3 | A plot of the natural logarithm of the equilibrium constant (in M^{-1}) versus reciprocal temperature, allows determination of the heat and entropy of reaction through the van't Hoff equation. The fit excludes the data at low temperature where vitrification is evident, preventing the DA reaction equilibrium from being achieved.

The rate of consumption of furan by reaction with the maleimide is written as

$$\frac{d[F]}{dt} = -k_f[F][M] + k_r[A] \quad (4)$$

where k_f and k_r are the forward and reverse rate constants, respectively. For a stoichiometric mixture of furan and maleimide, the reverse rate constants were determined at 25, 45, 60, and 80°C (see Supporting Information). The pre-exponential factor and activation energy for the retro DA reaction are determined from an Arrhenius plot to be $5.6 \pm 0.3 \times 10^9 \text{ s}^{-1}$ and $88 \pm 2 \text{ kJ/mol}$, respectively (see **Figure 4**). Activation energies of 102 to 114 kJ/mol have been measured for substituted furans and benzoquinones,⁴² suggesting that the measured value is reasonable. The Arrhenius parameter determination allows for the adduct half-life to be expressed as a function of temperature,

$$t_{1/2} = \frac{\ln(2)}{k_r} = \frac{\ln(2)}{A_r \exp(-\frac{E_a}{RT})} \quad (5)$$

The adduct half-life, and thus the half-life of a crosslink, at the gel-point (i.e., 92.5°C) is calculated to be approximately 600 seconds, demonstrating the dynamic nature of the DA

crosslink. The Arrhenius temperature dependence significantly decreases the reaction rate, and at 66°C the adduct half-life is approximately one order of magnitude longer. At room temperature the adduct half-life is on the order of days.

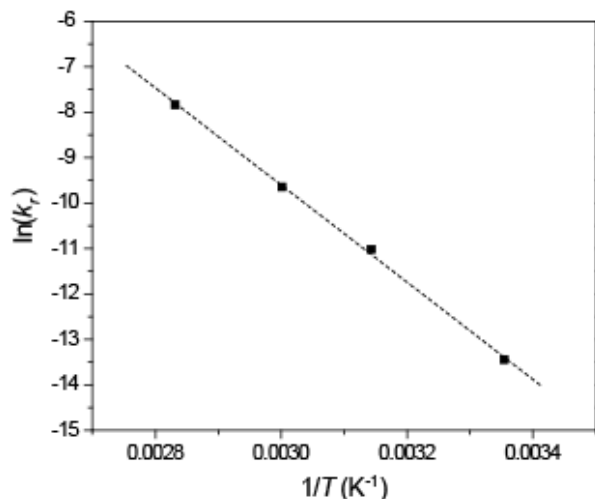


FIGURE 4 | An Arrhenius plot of the natural logarithm of the reverse DA rate constant (in s^{-1}) versus reciprocal temperature. The dashed line represents a fit of the data that allows the pre-exponential factor and activation energy to be determined from the intercept and slope, respectively.

Rheometry

The application of a small-amplitude sinusoidal deformation to a material yields a complex response, where the modulus is separable into the storage or elastic modulus, G' , and the loss or viscous modulus, G'' . Here, the behavior of the DA material at low temperatures, or high conversions, is that of a typical crosslinked polymer,⁴³ demonstrating a constant value for the elastic modulus at low frequency (i.e., a plateau modulus, G_p) as seen in a frequency sweep at 75°C for the PPTF/DPBM network (**Figure 5**). As temperature increases, a drop-off in the low-frequency modulus occurs, and a cross-over in the elastic and viscous moduli is observed (F), demonstrating liquid-like behavior and relaxation at long timescales. Typical chemical gels form irreversible bonds; however, DA crosslinks are

dynamic, constantly breaking and reforming over timescales dictated by the DA reaction kinetics and mobility restrictions, resulting in continuous network rearrangement on timescales associated with the temperature-dependent kinetics described above for the DA and rDA reactions. This low frequency behavior is analogous to that displayed by physical gels, such as gelatin,⁴⁴ which are connected by chain entanglements and other weak associations such as hydrogen bonds or ionic interactions, allowing network relaxation at long timescales. Network rearrangement has the consequence of adding a lower frequency bound to the Winter–Chambon criterion (2), corresponding to the longest relaxation time of the network, τ_L . It should be noted that the relaxation in the DA network, as determined by the $G'-G''$ cross-over at 87°C, occurs on, the same order of magnitude, $10^2 - 10^3$ s, as the half-life of the adduct determined from the kinetics.

Several distinguishing mechanical properties of the DA material, readily observed by rheometry, can be used to characterize its sol and gel states (see **Figure 6**). When the DA material is heated to 95°C, above the gel point temperature (i.e., below the gel point conversion), the viscous modulus is greater than the elastic modulus, characteristic of a liquid-like sol. Conversely, the elastic modulus is greater than the viscous modulus at 87°C for most of the frequency range, characteristic of a solid-like gel. At 91°C, the similar scaling of the elastic and viscous moduli with frequency indicates that the material is near the gel point as defined by the Winter–Chambon criterion, eq. (2).

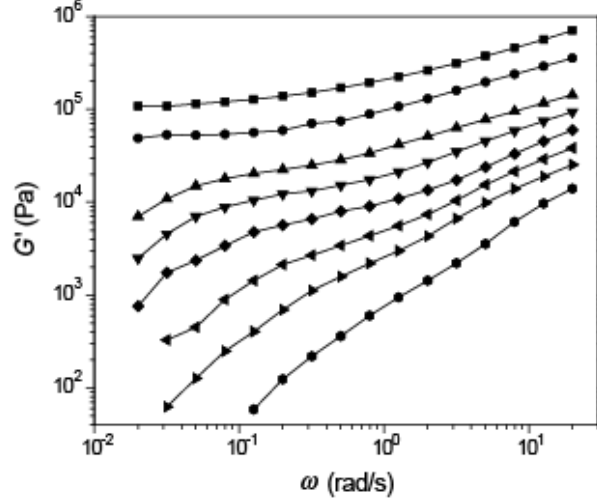


FIGURE 5 | Elastic modulus versus frequency for a PPTF/DPBM network. Frequency sweeps were performed at 75 (■), 80 (●), 85 (▲), 87 (▼), 89 (◆), 91 (◄), 93 (►), and 95°C (●).

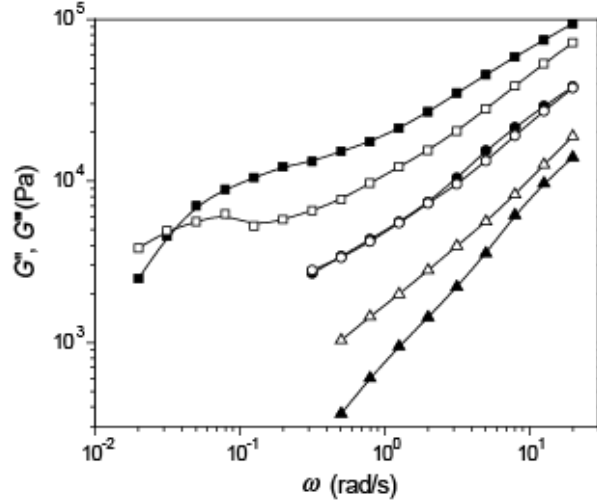


FIGURE 6 | Elastic (filled symbols) and viscous (open symbols) moduli versus frequency at temperatures above (95°C, ▲ and Δ), near (91°C, ● and ○), and below (87°C, ■ and □) the gel point temperature.

The Winter–Chambon criterion, eq. (2), can be re-expressed in terms of the ratio of the viscous to elastic modulus (i.e., the loss tangent or $\tan \delta$) which, at the gel point, demonstrates frequency independence. A plot of constant frequency loss tangent curves versus temperature (**Figure 7**) reveals an intersection that precisely marks the gel point. The gel point temperature was thus determined to be $92.1 \pm 0.2^\circ\text{C}$, corresponding to a

conversion of $70.9 \pm 0.5\%$, in excellent agreement with the gel point conversion predicted by the Flory–Stockmayer equation (1). Whereas other researchers have demonstrated some extent of reverse polymerization at raised temperatures, to our knowledge, this is the first clear demonstration of a temperature controlled sol-gel transition in crosslinked DA polymers, in the absence of a solvent. For example, high temperature ^{13}C -NMR spectroscopy performed on crack-healing DA materials demonstrated reversion to 70% conversion; however, the tetrafulan-trimaleimide system used in that work would require a reversion to 40.1% conversion to achieve reverse gelation, indicating that “softening” and “re-mendability” was achieved exclusively through network rearrangement rather than liquid flow.¹²

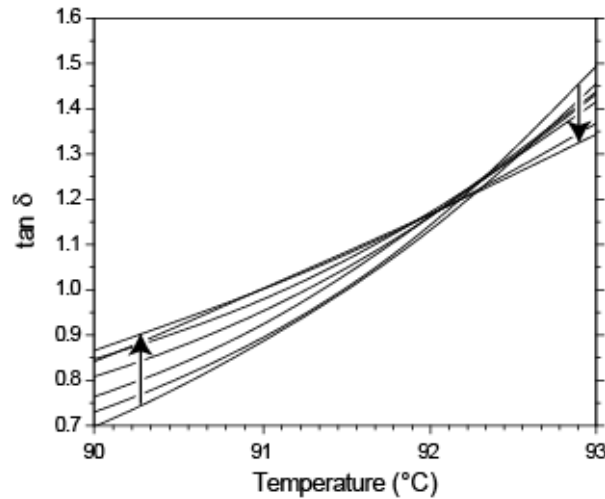


Figure 7 | The loss tangent is shown for several frequencies between 0.63 and 10 rad/s. Frequency independence (i.e., a cross-over) occurs at 92.1°C. The upper and lower frequency limits are within the valid range of the Winter–Chambon criterion, where $1 < 1/\tau_0$. Direction of arrows indicate increasing frequency.

The frequency cross-over in loss tangent determines the frequency scaling of the storage and loss moduli, ω , through the relationship,⁴⁵

$$\delta = \frac{u\pi}{2}, \quad (6)$$

yielding $u = 0.56 \pm 0.02$. As the conversion approaches the gel point from the sol phase (i.e., the liquid side of **Figure 8**), the viscosity divergence is described by the power law,

$$\eta \sim |\epsilon|^{-s}, \quad (7)$$

while the emergence of a plateau modulus, beyond the gel point (i.e., the solid side of **Figure 8**), is described by the power law,

$$G_p \sim |\epsilon|^t, \quad (8)$$

where ϵ is the relative distance from the gel point,

$$\epsilon = \frac{p - p_g}{p_g}, \quad (9)$$

and s and t are characteristic scaling exponents.

The diverging and subsequent emerging nature of the viscosity and modulus, respectively, in the vicinity of the gel point are shown in Figure 8. A zero shear modulus is not observed in DA networks owing to their long-time relaxation, and is thus supplanted by the corresponding plateau modulus as determined by the inflection point in the elastic modulus. The plateau modulus was normalized by the temperature to eliminate the entropic contribution ($G \sim T$, i.e., via rubber elasticity) and fit to equation (8) (dashed line, Figure 8), yielding $t = 1.23 \pm 0.03$. The viscosity was fit to equation (7) (solid line, Figure 8) and normalized by the activation energy (i.e., $\eta \exp(\frac{E_a}{RT})|\epsilon|^{-s}$), yielding $s = 1.4 \pm 0.2$.

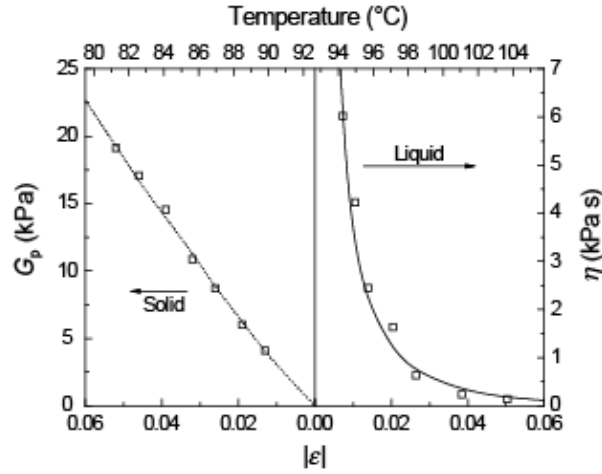


FIGURE 8 | The plateau modulus (left) and the viscosity (right) as a function of the relative distance from the gel point and temperature. The lines indicate the fits of the data to (7) and (8) on the liquid- and solid-side, respectively.

The scaling exponents u , s , and t are the foundation for a universal description of gelation. Several theories attempt to predict these exponents, an overview of which is shown in **Error! Reference source not found.** Mean field approaches have been used, but are typically successful only at high values of ϵ or when the distances between branch points are large, e.g., vulcanization.^{31,46,47} De Gennes' electrical-mechanical analogy establishes an equivalent scaling of the modulus and macroscopic conductivity and, unlike mean field theory, predicts the divergence of the viscosity.⁴⁸ The Rouse model describes linear polymers as a series of identical beads and springs, and assumes hydrodynamic interactions are screened at sizes smaller than the monomer level. The Rouse model can be extended to describe networks and has been shown to predict the scaling exponents successfully when the distance between network junctions is small.^{49,50}

TABLE 1 | Experimental and theoretical values of scaling exponents associated with gelation.

				Ref.
Mean Field	1	0	3	31,51
Electrical-Mechanical Analogy	0.72	0.75	1.9	48,51
Rouse Model	0.67	1.3	2.6	49
Experiment	0.56 ± 0.02	1.4 ± 0.2	1.23 ± 0.03	-

For the DA material, the frequency scaling of the elastic and viscous moduli at the gel point, u , is most similar to the Rouse model prediction. For other systems, experimental values have been observed to be in the range of 0.19 to 0.92.^{52,53} Deviations of u from the Rouse model prediction have been suggested to occur because of chain overlap,^{47,50} and the discrepancy between the measured value and the Rouse model may occur because the molecular weight of the PPTF monomer is sufficient to allow chain overlap. Such behavior would be manifest by a value of u less than that predicated by the Rouse model.

The viscosity scaling exponent s agrees well with both the Rouse model prediction and literature values.^{34,54} It should be noted, however, that the error indicated for s only reflects random error and not the systematic error in the gel point conversion, which can have considerable impact on the scaling determination. As the scaling exponents (i.e., u , s , and t) are interdependent and are related through

$$t = \frac{su}{1-u}, \quad 47,50,53 \quad (10)$$

the experimentally determined values for the exponents n and s can be used to calculate the plateau modulus exponent, yielding $t = 1.8 \pm 0.3$. This value is inconsistent with the experimentally determined value for t , which could simply be due to the sensitivity of the exponents to the precise location of the gel point conversion.

Conclusions

A crosslinked polymer was formed by the DA reaction between furan and maleimide moieties, and the furan conversion was measured using FTIR spectroscopy. Below 45°C, vitrification limited the ultimate attainable conversion, while above 45°C, the final conversion is determined by the thermodynamic equilibrium. At sufficiently elevated temperatures, the equilibrium shift through the retro-DA reaction results in depolymerization and reverse gelation. The gel point temperature of the material was determined by the Winter–Chambon criteria to be $92.1 \pm 0.2^\circ\text{C}$, which, in conjunction with spectroscopic data, is consistent with the gel point predicted by the Flory–Stockmayer equation for trifuran-bismaleimide system. The DA adduct half-life was on the same order of magnitude as the longest relaxation time for the network at 87°C, further illustrating the dynamic nature of the DA crosslink. The rapid and temperature dependent reversible DA reaction enables facile manipulation of conversion and thus allows the scaling exponents n , s , and t to be determined in the vicinity of the gel point. These exponents were found to be similar to other values in the literature; however, they were not consistent with values predicted from mean field theory, electrical-mechanical analogy, or the Rouse model.

Networks formed by the Diels–Alder reaction have been proposed for remendability, recyclability, and removability, properties that are not accessible in

conventional thermosets. The crack healing ability of these networks can be attributed to the constant breaking and reforming of crosslinks, which allows affected areas to form new crosslinks. Furthermore, because the reaction is controlled by thermodynamics over a large temperature range, the crosslinking density can be controlled and these materials can be removed and recycled by reversion to low molecular weight species. These results not only demonstrate the utility of the Diels–Alder reaction in polymer science, but they also illustrate the potential of reversibly labile crosslinks for the creation of novel materials.

REFERENCES

- (1) Billmeyer *Textbook of Polymer Science*; John Wiley and Sons: New York, 1984.
- (2) Kloosterboer, J. G. **1988**, *84*, 1-61.
- (3) Hoyle, C. E.; Lee, T. Y.; Roper, T. **2004**, *42*, 5301-5338.
- (4) Oshima, A.; Abe, K.; Kameda, N.; USPTO, Ed. US, 1976.
- (5) Decker, C. **2002**, *23*, 1067-1093.
- (6) Anseth, K. S.; Newman, S. M.; Bowman, C. N. In *Biopolymers II* 1995; Vol. 122, p 177-217.
- (7) Lu, H.; Stansbury, J. W.; Bowman, C. N. **2004**, *20*, 979-986.
- (8) Urabe, H.; Wakasa, K.; Yamaki, M. **1990**, *1*, 163-170.
- (9) LeBaron, P. C.; Wang, Z.; Pinnavaia, T. J. **1999**, *15*, 11-29.
- (10) Inoue, K.; Yamashiro, M.; Iji, M. **2005**, *62*, 261-267.
- (11) Lendlein, A.; Jiang, H. Y.; Junger, O.; Langer, R. **2005**, *434*, 879-882.
- (12) Chen, X. X.; Dam, M. A.; Ono, K.; Mal, A.; Shen, H. B.; Nutt, S. R.; Sheran, K.; Wudl, F. **2002**, *295*, 1698-1702.
- (13) Chen, X. X.; Wudl, F.; Mal, A. K.; Shen, H. B.; Nutt, S. R. **2003**, *36*, 1802-1807.
- (14) Scott, T. F.; Schneider, A. D.; Cook, W. D.; Bowman, C. N. **2005**, *308*, 1615-1617.
- (15) Odian, G. *Principles of Polymerization*; 3rd ed.; John Wiley and Sons, Inc.: New York, 1991.
- (16) Ono, T.; Nobori, T.; Lehn, J. M. **2005**, 1522-1524.
- (17) Yurke, B.; Lin, D. C.; Langrana, N. A. In *DNA Computing* 2006; Vol. 3892, p 417-426.
- (18) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley and Sons: New York, 1992.
- (19) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction*; John Wiley and Sons: New York, 2002.
- (20) Gousse, C.; Gandini, A. **1999**, *48*, 723-731.
- (21) Canary, S. A.; Stevens, M. P. **1992**, *30*, 1755-1760.
- (22) Imai, Y.; Itoh, H.; Naka, K.; Chujo, Y. **2000**, *33*, 4343-4346.
- (23) Chujo, Y.; Sada, K.; Saegusa, T. **1990**, *23*, 2636-2641.

- (24) Szalai, M. L.; McGrath, D. V.; Wheeler, D. R.; Zifer, T.; McElhanon, J. R. **2007**, *40*, 818-823.
- (25) McElhanon, J. R.; Russick, E. M.; Wheeler, D. R.; Loy, D. A.; Aubert, J. H. *J. Appl. Polym. Sci.* **2002**, *85*, 1496-1502.
- (26) Heath, W. H.; Palmieri, F.; Adams, J. R.; Long, B. K.; Chute, J.; Holcombe, T. W.; Zieren, S.; Truitt, M. J.; White, J. L.; Willson, C. G. **2008**, *41*, 719-726.
- (27) Long, B. K.; Keitz, B. K.; Willson, C. G. *J. Mater. Chem.* **2007**, *17*, 3575-3580.
- (28) Gousse, C.; Gandini, A.; Hodge, P. **1998**, *31*, 314-321.
- (29) Chang, B. T. A.; Dubois, D. A.; Ming, F.; Gelles, D. L.; Iyer, S. R.; Mohindra, S.; Tutunjian, P. N.; Wong, P. K.; Wright, W. J. In *Electronic Components and Technology Conference, 1999. 1999 Proceedings. 49th* 1999, p 49-55.
- (30) Flory, P. J. **1941**, *63*, 3083-3090.
- (31) Stockmayer, W. H. **1943**, *11*, 45-55.
- (32) Winter, H. H. **1987**, *27*, 1698-1702.
- (33) Adolf, D.; Martin, J. E.; Wilcoxon, J. P. **1990**, *23*, 527-531.
- (34) Hodgson, D. F.; Amis, E. J. **1991**, *131*, 913-920.
- (35) Lairez, D.; Adam, M.; Emery, J. R.; Durand, D. **1992**, *25*, 286-289.
- (36) Lairez, D.; Adam, M.; Raspaud, E.; Emery, J. R.; Durand, D. **1992**, *90*, 37-42.
- (37) Chiou, B. S.; English, R. J.; Khan, S. A. **1996**, *29*, 5368-5374.
- (38) Enns, J. B.; Gillham, J. K. **1983**, *28*, 2567-2591.
- (39) Hopewell, J. L.; Hill, D. J. T.; Pomery, P. J. **1998**, *39*, 5601-5607.
- (40) Dewar, M. J. S.; Pierini, A. B. **1984**, *106*, 203-208.
- (41) Rulisek, L.; Sebek, P.; Havlas, Z.; Hrabal, R.; Capek, P.; Svatos, A. **2005**, *70*, 6295-6302.
- (42) Jurczak, J.; Kawczynski, A. L.; Kozluk, T. **1985**, *50*, 1106-1107.
- (43) Ferry, J. D. *Viscoelastic Properties of Polymers*; 3 ed.; John Wiley and Sons, 1980.
- (44) Nijenhuis, K. T. In *Thermoreversible Networks* 1997; Vol. 130.
- (45) Michon, C.; Cuvelier, G.; Launay, B. **1993**, *32*, 94-103.
- (46) de Gennes, P. G. *Scaling Concepts in Polymer Physics*; Cornell Univeristy Press: Ithaca and London, 1979.
- (47) Lusignan, C. P.; Mourey, T. H.; Wilson, J. C.; Colby, R. H. **1999**, *60*, 5657-5669.
- (48) de Gennes, P. G. **1976**, *37*, L-1.
- (49) *Dynamic Scaling for Polymer Gelation*; Rubenstein, M.; Colby, R. H.; Gillmor, J. R., Eds.; Springer-Verlag: Berlin, 1989; Vol. 30.
- (50) Lusignan, C. P.; Mourey, T. H.; Wilson, J. C.; Colby, R. H. **1995**, *52*, 6271-6280.
- (51) Devreux, F.; Boilot, J. P.; Chaput, F.; Malier, L.; Axelos, M. A. V. **1993**, *47*, 2689-2694.
- (52) Scanlan, J. C.; Winter, H. H. **1991**, *24*, 47-54.
- (53) Durand, D.; Delsanti, M.; Adam, M.; Luck, J. M. **1987**, *3*, 297-301.
- (54) Guo, L.; Colby, R. H.; Lusignan, C. P.; Howe, A. M. **2003**, *36*, 10009-10020.

CHAPTER IV: Externally Triggered Healing of a Thermoreversible Covalent Network via Self-limited Hysteresis Heating*

Thermosets are assumed to be crosslinked by irreversible covalent bonds that break only during material fracture or destructive decomposition.¹ Once a crack is formed, either by a fabrication defect, mechanical deformation, or material fatigue, the material's strength rapidly deteriorates, generally necessitating its replacement. However, thermoreversible covalent adaptable networks are novel materials capable of undergoing a *reversible* gel-to-sol transition because they are crosslinked by thermoreversible bonds.² Herein, we use the terms sol and gel as per the polymer definitions where the gel represents the infinite macromolecular network and sol represents the portion of the material that is not attached to the macromolecular network. Covalent crosslinks are an order of magnitude stronger than hydrogen bonds, yet they permit the material to be reversibly transitioned from a crosslinked solid to a non-gelled oligomeric state.³ As a result, the material is both mechanically strong and readily able to heal fractures and other defects.^{4,5} Unfortunately, thermoreversible healing mechanisms are often limited by irreversible side reactions that occur at elevated temperatures (well beyond the sol-to-gel transition temperature).² Additionally, strategies for selectively heating a material that is either spatially confined or surrounded by other thermally sensitive materials have their own set of challenges. In this communication, we demonstrate the fracture healing of a novel Diels–Alder (DA)

*Published in *Advanced Materials*, **2010**, 22, 2784-2787. Experimental information is available in Appendix B.

crosslinked network embedded with magnetically susceptible particles that heat in the presence of an electromagnetic field. This responsiveness allows the material to be heated *in situ* while also exploiting the self-limiting heating behavior of ferromagnetic particles, which minimizes irreversible reactions. As a consequence the material is unchanged even after ten cycles of fracture and repair, achieving its native properties after each and every fracture and repair cycle. Furthermore, while photocuring in many optically opaque materials is intractable, the electromagnetic fields used in this study are not readily absorbed. Thus, our approach allows for an externally triggered depolymerization and subsequent polymerization in materials such as composite laminates.

Two strategies dominate the field of self-healing materials: systems that release reactive monomers at the site of fracture⁶ and networks that heal via reversible covalent bond rearrangement.^{4,5} Monomer releasing systems heal in response to damage without external intervention; however, few are capable of more than a single healing event unless complex lithographic fabrication is utilized.^{7,8} In contrast, reversible networks are inherently capable of healing multiple fracture events.^{4,5} Many reversible networks are thermally triggered, typically by placing the sample in a convection oven. Additionally, *in situ* temperature control methods are possible for composite materials, including resistance heating,⁹ photothermal particle heating,¹⁰ and hysteresis heating.^{11,12} Hysteresis heating is one of several heating mechanisms that occur when a ferromagnetic material is placed within an alternating magnetic field.¹³ Unlike the other two strategies, hysteresis heating does not require internal circuitry nor does it suffer from light attenuation. By selecting appropriate frequencies and particle sizes, the heating mechanism is limited to Néel relaxation. Above the Curie temperature of the material, the magnetic susceptibility vanishes and heating

ceases. Thus, unlike super paramagnetic effects or induced currents, hysteresis heating provides a self-limiting mechanism that is precisely controlled by the Curie temperature of the susceptible material. While common ferromagnetic materials, such as Ni, Fe, and Co, are unsuitable for organic materials as their Curie temperatures are well above the temperature where irreversible polymer decomposition occurs (i.e., 358, 770, and 1130 °C, respectively)¹³ chromium IV oxide possesses a Curie temperature of 113 °C,¹⁴ making it an ideal candidate.

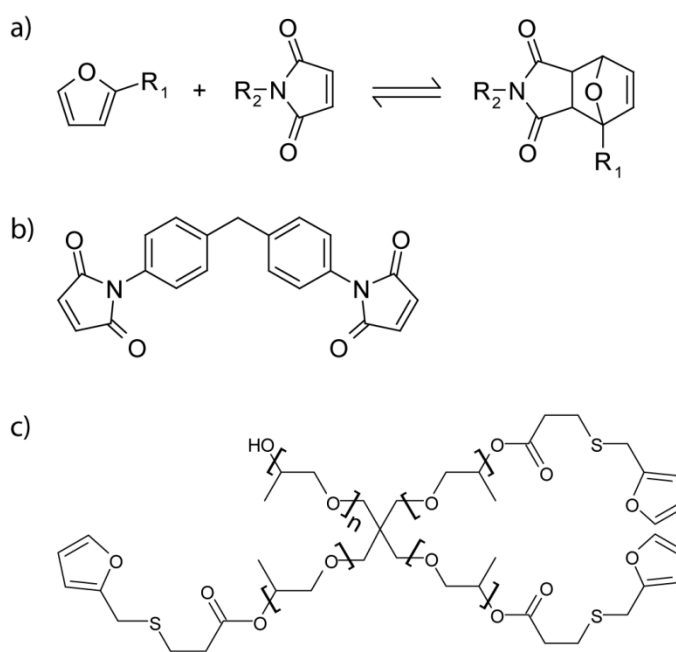


FIGURE 1 | (a) Diels–Alder reaction between furan and maleimide functionalities. At lower temperatures equilibrium favors the forward reaction, resulting in bond formation and gelation. At elevated temperatures the retro-Diels–Alder reaction is favored, and the bond is reversibly broken. The monomers used in this work were (b) 1,1'-(methylenedi-4,1-phenylene) bismaleimide (DPBM) and (c) pentaerythritol propoxylate tris(3-(furfurylthiol)propionate) (PPTF).

Figure 1 shows the monomers used in this communication, a trisfuran, PPTF, and a bismaleimide, DPBM, possess a gel point temperature of 92 °C,² which is well below the Curie temperature of chromium oxide (113 °C). The alternating magnetic field precludes the

use of a thermocouple for bulk temperature measurement, and consequently, an infrared pyrometer was used to measure the composite surface temperature. **Figure 2** shows the steady-state temperature reached by a polymer composite as a function of the magnetic field strength for several compositions of chromium IV oxide. For a given particle concentration each data set is divided into three regions: a low steady-state temperature region that is below a critical magnetic field strength; a high steady-state temperature region that is above a critical magnetic field strength; and a transition between these behaviors that displays path dependence or hysteresis.

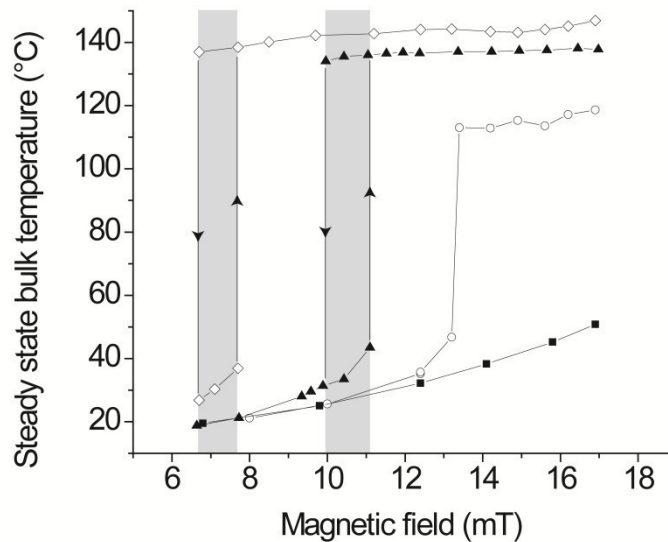


FIGURE 2| The steady state temperature of three different compositions of CrO_2 particles in a thermoreversible polymer network is shown as a function of the applied magnetic field strength (0.0 % wt. (■), 0.1 % wt. (○), 1.0 % wt. (▲), and 10.0 % wt. (◇)). The grey boxes denote regions where the system shows path dependence. Samples initially at an elevated temperature will not cool to the lower temperatures, unless brought to field strengths lower than the left side of the box. Samples at lower temperatures will not reach elevated temperatures, unless brought to field strengths greater than the right side of the box.

Below a critical magnetic field strength (left of the grey box in Figure 2), both the hysteresis heating and resistive heating of the coil produce a slight temperature rise. Despite internal water cooling, the coil temperature increases linearly with power owing to AC

resistive heating. As a consequence, the thermal gradient at the sample boundary decreases, causing a small rise in the bulk temperature, observed in samples with no particles. Above a critical magnetic field strength (right of the grey box in Figure 2) the steady-state temperature becomes nearly independent of the applied field, with a slight temperature rise, again associated with coil resistive heating. Further investigation reveals that the steady-state temperature in this region has a weak dependence on the particle concentration. A 0.1 % wt. loading results in a maximum steady state temperature of ~ 120 °C, while a 10.0 % wt. loading results in a maximum steady state temperature of 146 °C, which is approaching the temperature observed in the bulk material, 149 °C. Interestingly, all of these temperatures are above the Curie temperature of chromium IV oxide, suggesting either the presence of impurities in the particles, such as chromium III oxide, or viability of another heating mechanism, such as by induction via particle agglomerates. Between the lower and upper critical field strengths (within the grey box in Figure 2) there is a large path dependent shift between low and high steady state temperature regimes, respectively. For example, increasing the field strength in a 1.0 % wt. sample from 9.6 to 11.1 mT, results in a temperature rise of 29.6 to 43.5 °C. However, decreasing the field strength from 11.5 to 11.1 mT, results in a steady-state temperature decrease from 126 to 119 °C, rather than the expected 43.5 °C. This path dependence demonstrates the non-linear temperature effect of heat generation in chromium IV oxide coupled with the heat transport in the surrounding medium.

When heated to 110 °C the material shows liquid-like behavior with a viscosity twice that of glycerol (~ 3 Pa·s). Accordingly, upon activation in a radio frequency field at a suitable strength, the material with 1.0 % wt. CrO_2 readily flows and rapidly wets a teflon

mold, as shown in **Figure 3**. This process is readily repeatable, allowing the material to be repeatedly cycled between gel and sol states, which enables the material to be reshaped multiple times. Numerous cycles can be achieved because the rate of irreversible side reactions is minimal at the temperatures reached by the hysteresis heating mechanism.

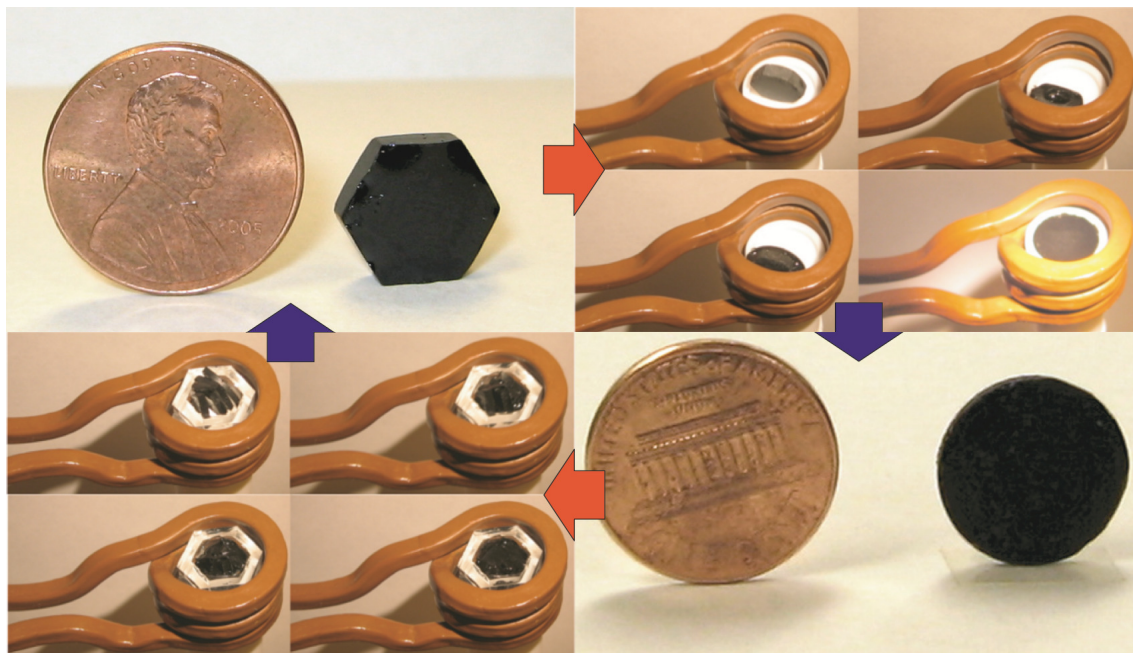


FIGURE 3 | A thermoreversible covalent adaptable network is shown being cycled between gel and liquid states so that it can be reshaped. (Upper left) Sample of PPTF/DPBM with 1.0 % wt CrO₂ cast as a hexagonal flat. (Upper right) The hexagonal sample is placed in a mold and heated by a ~ 15 mT field at 390 hz for ~ 150 s. Pictures are numbered sequentially as the sample depolymerizes and flows to fill the differently shaped mold. (Lower right) After shutting off the field and allowing the sample to cool, the round flat shown can be removed from the mold. (Lower left) The round flat is then fractured and placed in the hexagonal mold and heated using the same magnetic field. After cooling the hexagonal flat is recovered.

Suitable reactions for creating reversible covalent adaptable network are limited, as such a reaction must be readily reversible, have products and reactants that lack competing reactions, and be tolerant of environmental conditions. Several materials, such as polyalkylhydrazones,^{15,16} cycloadducts of [2+2] cycloadditions,¹⁷ and alkoxyamines¹⁸ (also see

review by Engle¹⁹), have been used to create reversible covalent bonds in polymers; however, only the Diels–Alder and [2+2] cycloaddition have been employed in crack healing systems.

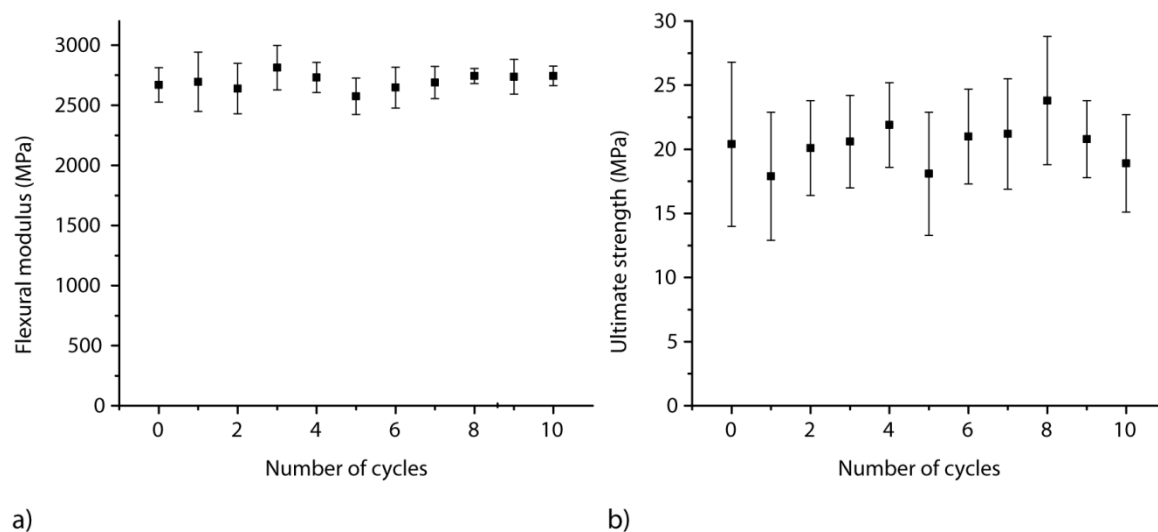


FIGURE 4| The flexural modulus (a) and ultimate strength (b) of a PPTF/DPBM sample with 1.0 % wt CrO₂ after ten cycles of being fractured and repaired. No significant change is observed in either material property, demonstrating the ability of this material to repeatedly heal damage.

To demonstrate the reversibility of our system and its inherent ability to heal damage, the flexural modulus and ultimate strength of the material were measured over ten heating and fracturing cycles. In these experiments complete recovery of the flexural modulus and ultimate strength was demonstrated, as shown in **Figure 4**. This result compares favorably with other Diels–Alder polymers that have been shown to recover 80 % of fracture toughness though two cycles,^{4,5} and also with systems employing the [2+2] cycloaddition that recovered 26 % of the flexural modulus.¹⁷ Furthermore, healing via the gel-to-sol transition is advantageous as it negates the problem of perfectly aligning the fractured surfaces. Alternatively, monomer releasing materials have been shown to recover 75 % of fracture load in microcapsule systems that heal a single fracture event.⁶ The microvascular network approach has been shown to permit healing of the sample over 30

fracture cycles, with an average 50 % recovery of the fracture toughness.⁸ The thermoreversible chemical bond approach also shows advantages over the reptation based healing that occurs in many thermoplastics. For example, poly(methyl methacrylate) composites employing ferrimagnetic $\gamma\text{-Fe}_2\text{O}_3$ particles as a magnetic susceptor showed complete recovery of the Young's modulus and reduced elastic modulus over six cycles; however, this material required 24 times the amount of heating time to heal.²⁰

The incorporation of magnetically susceptible particles in a thermoreversible chemical gel results in a material that undergoes a reversible gel-to-sol transition when placed in an alternating magnetic field. The gel-to-sol transition allows the material to flow, and upon cooling macroscopic fractures are healed. Unlike other self-healing materials, this approach is both repeatable and rapid, without requiring reactants to be dispersed in the material or a detailed mechanical microstructure. The self-limiting nature of the heating mechanism further protects the system from irreversible degradation during multiple healing cycles. While reversible chemical gels have inherent limitations, such as thermal stability, in appropriate applications they provide a successful route towards creating materials and devices that can be readily repaired instead of being discarded upon crack formation or material failure. The ability of electromagnetic fields to penetrate optically thick composite materials combined with the ability of such materials to be repeatedly heated and healed could prove particularly important in applications where large polymer composites, such as wind turbines and helicopter rotors, are subjected to repeated stresses, and the fatigue induced cracks must be healed to prevent catastrophic failure.

REFERENCES

- (1) Billmeyer *Textbook of Polymer Science*; John Wiley and Sons, 1984.
- (2) Adzima, B. J.; Aguirre, H. A.; Kloxin, C. J.; Scott, T. F.; Bowman, C. N. *Macromolecules* **2008**, *41*, 9112-9117.
- (3) Israelachvili, J. *Intermolecular and Surface Forces*; Academic Press: London, 2002.
- (4) Chen, X. X.; Dam, M. A.; Ono, K.; Mal, A.; Shen, H. B.; Nutt, S. R.; Sheran, K.; Wudl, F. *Science* **2002**, *295*, 1698-1702.
- (5) Chen, X. X.; Wudl, F.; Mal, A. K.; Shen, H. B.; Nutt, S. R. *Macromolecules* **2003**, *36*, 1802-1807.
- (6) White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. *Nature* **2001**, *409*, 794-797.
- (7) Toohey, K. S.; Sottos, N. R.; Lewis, J. A.; Moore, J. S.; White, S. R. *Nat. Mater.* **2007**, *6*, 581-585.
- (8) Hansen, T. S.; Daugaard, A. E.; Hvilsted, S.; Larsen, N. B. *Adv. Mater.* **2009**, *21*, 4483-4486.
- (9) Park, J. S.; Takahashi, K.; Guo, Z. H.; Wang, Y.; Bolanos, E.; Hamann-Schaffner, C.; Murphy, E.; Wudl, F.; Hahn, H. T. *J. Compos. Mater.* **2008**, *42*, 2869-2881.
- (10) Serksen, S. R.; Mensing, G. A.; Ng, M.; Halas, N. J.; Beebe, D. J.; West, J. L. *Adv. Mater.* **2005**, *17*, 1366-1368.
- (11) Ahmed, T. J.; Stavrov, D.; Bersee, H. E. N.; Beukers, A. *Compos. Pt. A-Appl. Sci. Manuf.* **2006**, *37*, 1638-1651.
- (12) Suwanwatana, W.; Yarlagaadda, S.; Gillespie, J. W. *Compos. Sci. Technol.* **2006**, *66*, 2825-2836.
- (13) Bozorth, R. M. *Ferromagnetism*; IEEE Press: Piscataway, NJ, 1978.
- (14) Kittel, C. *Introduction to Solid State Physics*; John Wiley and Sons, Inc.: New York, 1996.
- (15) Ono, T.; Fujii, S.; Nobori, T.; Lehn, J. M. *Chem. Commun.* **2007**, 46-48.
- (16) Deng, G.; Tang, C.; Li, F.; Jiang, H.; Chen, Y.
- (17) Chung, C. M.; Roh, Y. S.; Cho, S. Y.; Kim, J. G. *Chem. Mat.* **2004**, *16*, 3982-3984.
- (18) Higaki, Y.; Otsuka, H.; Takahara, A. *Macromolecules* **2006**, *39*, 2121-2125.
- (19) Engle, L. P.; Wagener, K. B. *J. Macromol. Sci. R. M C.* **1993**, *C33*, 239-257.
- (20) Corten, C. C.; Urban, M. W. **2009**, *21*, 5011-5015.

CHAPTER V: Photofixation lithography in Diels-Alder Networks*

Abstract

Photoresists generally utilize a change in solubility upon irradiation to subsequently “develop” a patterned image. In this work, a novel photolithographic resist that utilizes a light sensitive, reversibly crosslinked polymer network scaffold is demonstrated. Reversibly crosslinked networks are formed by the Diels–Alder reaction of furan and maleimide. Spatio-selective fixation of the crosslinks by radical reactions renders them irreversible within a well-defined, light exposed region. Subsequent reversion of the crosslinks in the unexposed regions to monomer yields a patterned image. Both two and three dimensional patterning is demonstrated, producing features as small as 2 microns. The use of a reversibly crosslinked resist provides several key advantages including solventless preparation, reduced diffusion of the active species, and the ability to pattern arbitrary three dimensional shapes.

The ability to selectively carry out chemical reactions using light to spatially and temporally control the reaction plays a key role in many modern technologies including as microfluidic devices,¹ metamaterials,² artificial tissues,³ parallel protein synthesis techniques,⁴ 3D prototyping,^{5,6} and microchip fabrication.⁷ Conventional photolithography begins with the preparation of a photoactive thin film cast onto a substrate, typically using spin coating techniques, followed by heat to remove the solvent. A pattern is then transferred to the photoresist using actinic masked or focused laser light. The resulting image is developed by immersion in a solvent which selectively removes the undesired material. Enhanced pattern resolution is a continuing goal as researchers attempt to attain smaller feature sizes. There are a number of subtle process variations that have been employed to reach this goal, such as the use of block copolymers to increase the pattern density,⁸ or deactivation techniques that allow sub diffraction feature sizes to be achieved.^{9,10}

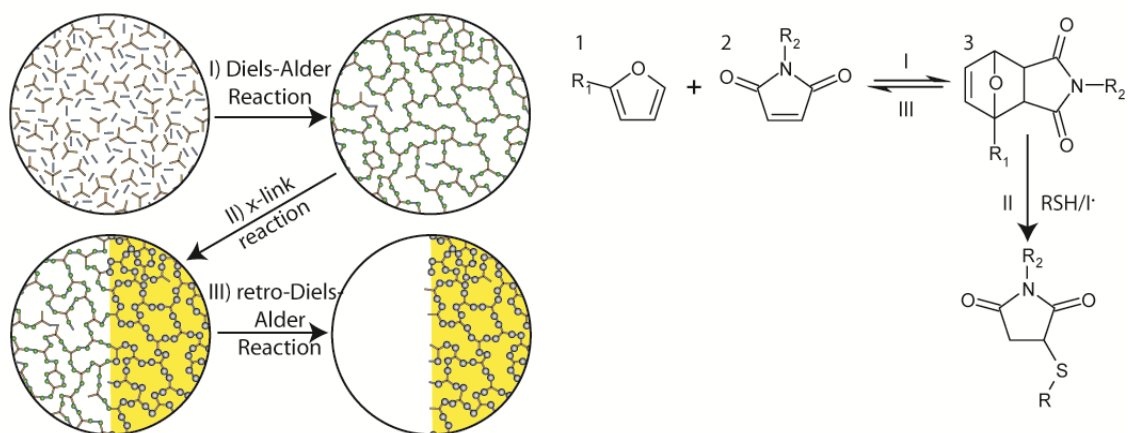
*Experimental information available in Appendix C.

Photoresists are generally classified as being negative or positive tone resists.¹¹ Positive tone resists are rendered soluble by irradiation, typically due to degradation or modification of the polymer polarity, while negative tone resists utilize polymerization or crosslinking reactions to render them insoluble after irradiation.⁷ Photosensitive polymers can be prepared that undergo direct photolysis (i.e. poly methyl methacrylate) or that are polymerized by simple photochemical reactions (i.e., cinnamate or azide-olefin coupling);¹² however, such approaches are inefficient and require at least one photon to be absorbed for each reaction event. Photoresist sensitivity is greatly enhanced when an active species, such as a radical, carbocation, or acid, is photochemically generated and propagates through the reaction medium to initiate or catalyze a series of reactions.¹³ The chief drawback of such an approach is that the active species can diffuse away from the area of interest, thus reducing the resolution of the photoresist. As modern photolithography is heading towards sub 38 nm resolution, molecular diffusion limitations pose an even greater problem.^{14,15} Furthermore, state of the art photolithographic techniques are approaching the characteristic size of the linear polymers employed in common resists. As such, alternatives including molecular glasses have been proposed for their decreased size.¹⁶

To improve resolution we propose carrying out the patterning reaction within a polymer network scaffold, where the diffusivity of the active species is significantly retarded and the smallest characteristic size is reduced to the distance between crosslinks. While conventional chemically crosslinked networks are insoluble, infusible, and inherently incapable of functioning as a reversible scaffold, networks formed using reversible reactions are readily able to depolymerize. Thus, patterning reactions can be carried out when the scaffold is in a crosslinked state, where diffusion of active species is reduced and where the

formation of three dimensional objects is facilitated. Subsequently, the unexposed scaffold can be removed in a later processing step.

In considering approaches to achieve these goals, a wide variety of reversible reactions that have been utilized to crosslink polymer networks were considered.^{17,18} However, among those reactions, few are as robust or possess the unique behavior of the Diels–Alder reaction between furan(1) and maleimide(2). Upon heating of reacted structures, the resulting adduct (3) readily undergoes a retro-Diels–Alder reaction to recover (1) and (2). Thus, polymer networks formed by the Diels–Alder reaction can be alternated between polymerized (i.e., crosslinked) and depolymerized states simply by decreasing or increasing the temperature.¹⁹ If the Diels–Alder adduct participates in a subsequent reaction, then the reversibility of this crosslink is eliminated. Thus, if one were to spatio-selectively trigger such a reaction of the adduct, that location within the scaffold would be permanently ‘fixed’. Fortuitously, the adduct (3) bears a superficial resemblance to norbornene, a vinyl group that exhibits excellent reactivity within the thiol-ene and other radical reactions. By introducing a photoinitiator and a thiol-functional species into the formulation, the Diels–Alder scaffold is readily photofixed wherever the material is irradiated. Upon heating the material, the unexposed regions revert to their uncrosslinked or even monomeric state and are easily removed, leaving the irreversibly crosslinked scaffold wherever the sample was exposed to light. **Figure 1** illustrates this negative tone ‘photofixation’ process and the accompanying chemical reactions, while **Figure 2** shows the specific species examined.



Figures 1 | A schematic of the photofixation process is shown with the accompanying chemical reactions. I) First, a crosslinked polymer is formed by the thermoreversible Diels–Alder reaction between multi-functional furan (1) and maleimide (2) monomers. II) The crosslinks formed by the resulting oxy-norbornene groups (3) are then selectively converted to irreversible crosslinks by the radical reactions with thiol molecules freely suspended in the polymer network. III) The pattern is then developed by selectively removing the remaining material containing reversible bonds via the retro-Diels–Alder reaction.

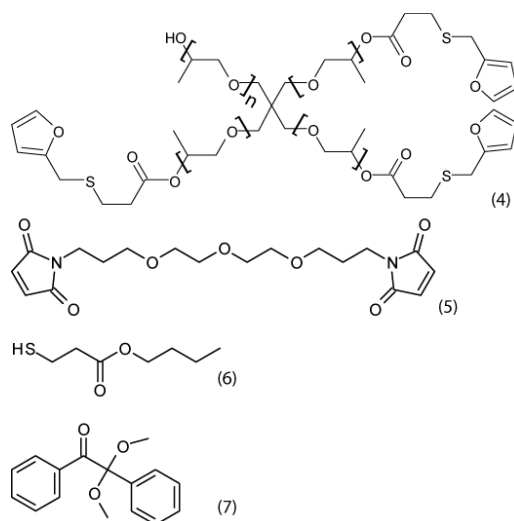


Figure 2 | The specific species used throughout this manuscript.

One interesting aspect to this proposed scheme is that the thiol can potentially undergo the base-catalyzed Michael addition with maleimide. This ‘click’ reaction is often employed in protein functionalization²⁰ owing to its ease and high yield. However, in the absence of a nucleophile or base, the thiolate anion is never formed preventing the Michael

addition reaction from occurring.²¹ Therefore a stoichiometric mixture of (4), (5), and (6) with 1% weight of the photoinitiator (7) was prepared and a 1/100th molar equivalent of HCl added. After heating for 7 hours at 80°C the reaction reached steady state. IR spectroscopy showed that 86% of the furan and 88% of the maleimide has been consumed (**Figure 3**). The nearly equimolar consumption of both species suggests that the strong acid effectively eliminates the Michael addition. Consequently, a mixture of maleimide, furan, thiol, acid, and photoinitiator could be prepared, and then baked to form a hard film, retaining its photosensitive properties for at least several weeks. Depending on the desired thickness, such films can be prepared without the need of a solvent.

Upon irradiation, photolysis of the initiator produces radicals. IR spectroscopy revealed the consumption of 40% of the Diels–Alder adducts, while nearly all of the free maleimide was consumed. The particular thiol used in these experiments (6) is not IR active, and its conversion is unknown. In separate experiments utilizing a different maleimide and thiol, the combined extent of reaction of the maleimide and adduct exceeded that of the thiol suggesting that coupling of all three components occurs (see Supporting information). Regardless of the exact pathway followed, these reactions form a significant number of irreversible crosslinks that prevent reverse gelation.

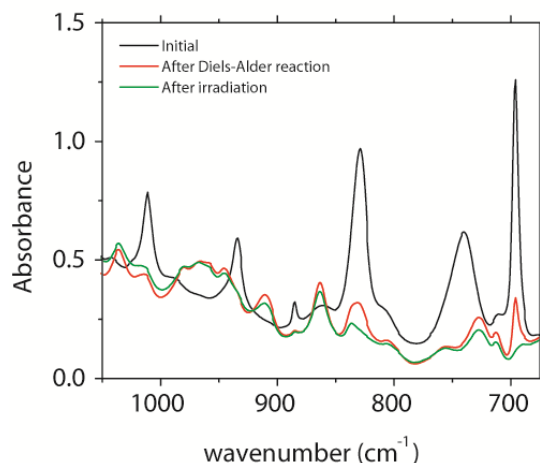


Figure 3| After 4 hours at 80°C the IR spectrum shows the consumption of furan (1012 cm^{-1}) and maleimide (690 $^{-1}$) as well as the formation of the Diels-Alder Adduct (920 $^{-1}$). Approximately 86% of the furan and 88% of the maleimide have been consumed, demonstrating effective suppression of the Michael addition. After irradiation, all of the free maleimide and 40% of the adduct is consumed.

When the material is selectively irradiated using masked light the crosslinking reactions are restricted to the irradiated area. Thus when such a sample is immersed in a heated solvent and the retro-Diels–Alder reaction occurs, and an image is developed (**Figure 4**). Using a collimated medium pressure mercury lamp in conjunction with a chrome mask in contact mode features as small as 2 microns were readily fabricated. The resolution of this process is severely limited by both the quality of the masks and the collimation of the lamp, and more modern approaches are required for increased resolution. Development is facilitated by the use of furfuryl alcohol as a solvent. Not only does this naturally derived solvent possess a high boiling point,²² but the monofunctional furan reacts with free maleimide to shift the equilibrium away from crosslink formation and towards the formation of low molecular weight, non-crosslinked oligomers and monomers.

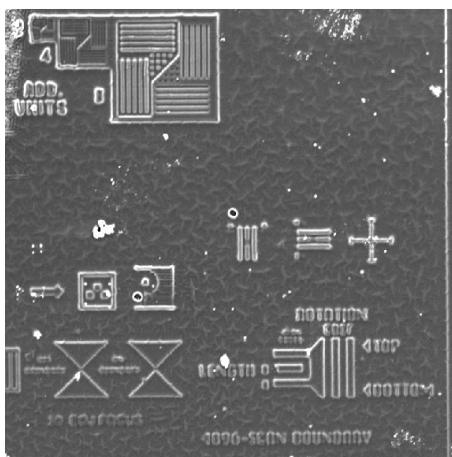


Figure 4| The increased crosslinking density in the irradiated areas results in the development of an image after the unreacted material is removed by the retro-Diels–Alder reaction. Features as small as 2 microns were readily produced in both thin films (< 1 micron) that were stripped completely to the glass, and in thicker films (~10 micron) where the etching proceeds 1-2 microns into the film (as shown in the SEM micrograph).

While the state of the art of two-dimensional lithography has moved to the nanometer realm, the fabrication of three dimensional structures on the micron size scale presents significant challenges. Unlike two dimensional lithography three dimensional features must be built up layer by layer in a bath of liquid monomer when using a negative tone resist.²³ Each underlying layer must support the next layer to be written and as such, support structures are required for overhanging features which would otherwise undergo settling from densification associated with the polymerization. These support structures are easily removed in macroscale rapid prototyping applications; however, they are not readily removed or formed for smaller structures. While complex shapes are possible with conventional approaches,²⁴ arbitrary three dimensional shapes that require overhanging features typically cannot be written with current negative tone materials. Positive tone photoresists overcome this difficulty²⁵ and are efficient for writing channels and other features where minimal material needs to be removed and where the hollow regions of the structure are interconnected with exits. However, the efficiency of removing large amounts

of material for other applications is problematic. The use of a photoresist that is a crosslinked solid therefore represents a significant advantage as the need for supporting structures is eliminated and complex structures can all be written prior to the removal of any material.

The sample formulation utilized for the previous experiments proved equally useful for the microstereolithographic applications. We found that the UV photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA, 7) possess an adequate 2-photon cross-section utilizing a 740 nm pulse femtosecond laser. Upon irradiation, the refractive index changed, allowing immediate visualization of written shapes within the surrounding material by confocal microscopy (**Figure 5**). After heating the sample in furfural alcohol, the unexposed material depolymerized and the written features could be recovered by careful filtration from the developing liquid.

The Diels–Alder reaction has been demonstrated as a viable approach to creating photofixation-based negative tone resist. The addition of a small amount of strong acid allows the Diels–Alder reaction between furan and maleimide to occur in the presence of thiol and a photoinitiator. After curing, the films are stable and may be later irradiated using masked or focused laser light to induce irreversible crosslinking reactions within the material. The retro-Diels–Alder reaction subsequently allows the material in the non-irradiated areas to be selectively removed, resulting in the development of an image or three dimensional shape. The use of a reversibly crosslinked polymer network as a photoresist has a number of potential advantages. It is expected that diffusion of the active species in such systems will be significantly retarded enhancing the feature resolution. Further, as the starting materials

are low viscosity monomers thin films can be prepared without the use of volatile organic solvents. It is also theoretically possible that the use of solvents could be eliminated in the image development step as well. As such, photofixation lithography presents a powerful new approach to patterning polymeric materials.

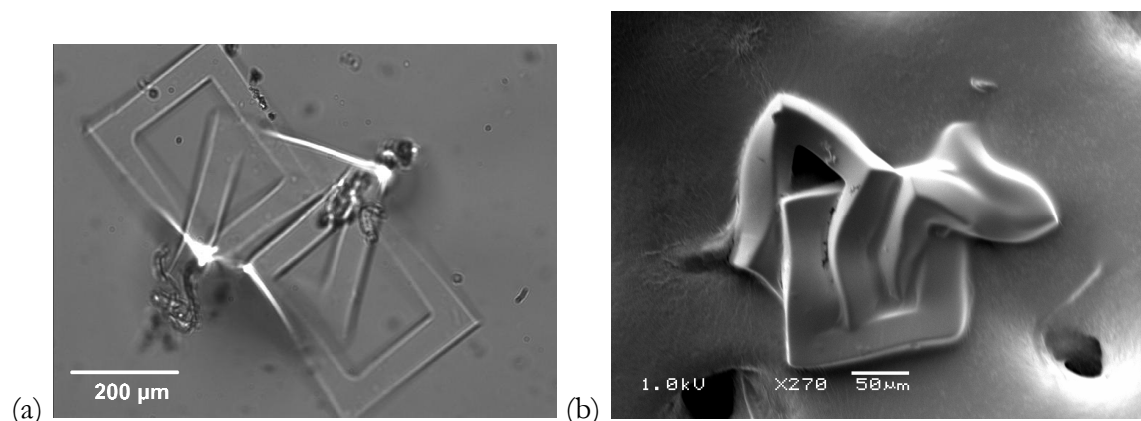


Figure 5 | A set of three interlocked rings was written using a scanning confocal microscope and 2-photon photoinitiator. The rings were then freed from the surrounding media by immersion in furfuryl alcohol. An optical micrograph shows the rings swollen in the solvent. After solvent removal the rings return to their original size as shown in the SEM micrograph (b).

REFERENCES

- (1) Duffy, D. C.; McDonald, J. C.; Schueller, O. J. A.; Whitesides, G. M. *Anal. Chem.* **1998**, *70*, 4974-4984.
- (2) Burckel, D. B.; Wendt, J. R.; Ten Eyck, G. A.; Ginn, J. C.; Ellis, A. R.; Brener, I.; Sinclair, M. B. *Adv. Mater.* **2011**, *22*, 5053-5057.
- (3) Khademhosseini, A.; Langer, R. *Biomaterials* **2007**, *28*, 5087-5092.
- (4) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767-773.
- (5) Neckers, D. C. *Polym. Eng. Sci.* **1992**, *32*, 1481-1489.
- (6) Young, J. S.; Fox, S. R.; Anseth, K. S. *J. Manuf. Sci. Eng.-Trans. ASME* **1999**, *121*, 474-477.
- (7) Ito, H. In *Microlithography - Molecular Imprinting*; Springer-Verlag Berlin: Berlin, 2005; Vol. 172, p 37-245.
- (8) Cheng, J. Y.; Rettner, C. T.; Sanders, D. P.; Kim, H. C.; Hinsberg, W. D. *Adv. Mater.* **2008**, *20*, 3155-3158.
- (9) Fischer, J.; von Freymann, G.; Wegener, M. *Adv. Mater.*, *22*, 3578-3582.
- (10) Scott, T. F.; Kowalski, B. A.; Sullivan, A. C.; Bowman, C. N.; McLeod, R. R. *Science* **2009**, *324*, 913-917.

- (11) Hakey, M. C.; Holmes, S. J.; Horak, D. V.; Katnani, A. D.; Patel, N. M.; Rabidoux, P. A. Frequency doubling hybrid photoresist having negative and positive tone USPTO 6114082 2000.
- (12) Roffey, C. *Photogeneration of Reactive Species for UV Curing*, John Wiley and Sons: West Suffex, 1997.
- (13) Ito, H.; Willson, C. G. *Polym. Eng. Sci.* **1983**, *23*, 1012-1018.
- (14) Lee, S.; Jen, K.; Willson, C. G.; Byers, J.; Zimmerman, P.; Turro, N. J. *J. Micro-Nanolithogr. MEMS MOEMS* **2009**, *8*, 11.
- (15) Stewart, M. D.; Tran, H. V.; Schmid, G. M.; Stachowiak, T. B.; Becker, D. J.; Willson, C. G. *J. Vac. Sci. Technol. B* **2002**, *20*, 2946-2952.
- (16) Krysak, M.; Ober, C. K. *PMSE Preprints* **2010**.
- (17) Engle, L. P.; Wagener, K. B. *J. Macromol. Sci. R. M C.* **1993**, *C33*, 239-257.
- (18) Kloxin, C. J.; Scott, T. F.; Adzima, B. J.; Bowman, C. N. *Macromolecules* **2010**, *43*, 2643-2653.
- (19) Adzima, B. J.; Aguirre, H. A.; Kloxin, C. J.; Scott, T. F.; Bowman, C. N. *Macromolecules* **2008**, *41*, 9112-9117.
- (20) Jones, M. W.; Mantovani, G.; Ryan, S. M.; Wang, X. X.; Brayden, D. J.; Haddleton, D. M. *Chem. Commun.* **2009**, 5272-5274.
- (21) Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. *Chem. Soc. Rev.*, *39*, 1355-1387.
- (22) Gandini, A.; Belgacem, M. N. *Prog. Polym. Sci.* **1997**, *22*, 1203-1379.
- (23) Ikuta, K.; Hirowatari, K. In *Micro Electro Mechanical Systems, 1993, MEMS '93, Proceedings An Investigation of Micro Structures, Sensors, Actuators, Machines and Systems. IEEE*. 1993, p 42-47.
- (24) Kawata, S.; Sun, H. B.; Tanaka, T.; Takada, K. *Nature* **2001**, *412*, 697-698.
- (25) Zhou, W.; Kuebler, S. M.; Braun, K. L.; Yu, T.; Cammack, J. K.; Ober, C. K.; Perry, J. W.; Marder, S. R. *Science* **2002**, *296*, 1106-1109.

CHAPTER VI: Spatial and temporal control of the alkyne–azide cycloaddition by photoinitiated Cu(II) reduction*

Abstract

The Click reaction paradigm is centered on development and implementation of reactions that are simple to perform while being robust and providing exquisite control of the reaction and its products. Arguably the most prolific and powerful of these reactions, the copper catalyzed alkyne–azide reaction (CuAAC), is highly efficient and ubiquitous in an ever increasing number of synthetic methodologies and applications, including bioconjugation, labeling, surface functionalization, dendrimer synthesis, polymer synthesis, and polymer modification. Unfortunately, since the Cu(I) catalyst is typically generated by chemical reduction of Cu(II) to Cu(I), or directly added, temporal and spatial control of the CuAAC reaction is not readily achieved. Herein, we demonstrate catalysis of the CuAAC reaction via the photochemical reduction of Cu(II) to Cu(I), affording comprehensive spatial and temporal control of the CuAAC reaction using standard photolithographic techniques. Results reveal this technique's diverse capability in small molecule synthesis, patterned material fabrication, and patterned chemical modification.

The diverse implementation of the CuAAC reaction owes to its simplicity, high yield, fast reaction kinetics, orthogonal reactivity, and tolerance of a wide variety of solvent conditions¹. As such, the CuAAC reaction is valuable across a vast library of materials applications^{2,3,4,5, 6} and chemical modifications^{7,8,9,10}. However, the conventional generation of the catalytic Cu(I) species lacks spatial and temporal control. While this deficit may seem trivial from a purely synthetic point of view, spatial control is necessitated in the creation of numerous functional materials^{11,12} such as inks, coatings, adhesives, metamaterials, contact lenses, dental materials, and photoresists, and is employed in techniques such as parallel protein synthesis¹³, cell encapsulation¹⁴, tissue engineering¹⁵, and 3D prototyping^{16,17}.

* Published in *Nature Chemistry*, **2011**, 3, 258-261. Experimental information available in Appendix D.

Temporal control enables workers to initiate a reaction on demand, as is critical when materials must be spin coated, or otherwise prepared after mixing of the components, but before a reaction occurs. The ability to spatially and temporally control the CuAAC reaction would extend the CuAAC reaction capabilities, improve its ease of use, and increase the number of materials that are readily patterned.

The critical need for complete spatial control of the CuAAC reaction is demonstrated by the extent to which researchers have gone to facilitate partial control of this reaction. Dip-pen lithography, with a Cu(I) inked tip or a copper tip^{18,19}, has been used to trace a pattern on the substrate, and catalyze the CuAAC reaction between a functionalized surface, and the alternate click reagent in the bulk. This technique has produced features as small as 50 nm, and micron scale features require one half second to complete. Similarly, microcontact printing utilizes an elastomeric stamp inked with a solution of reagent to promote spatial control^{20,2}. Here, the catalytic Cu(I) is either included in the solution, or generated from a copper metal layer coating the surface of the stamp. The stamp is brought into contact with a functionalized surface for 15 minutes to an hour. Features on the order of tens of microns are readily fabricated using this technique. Electroclic chemistry utilizes an electric potential applied across a pair of electrodes^{21,22}. At the negative electrode Cu(II) is reduced to Cu(I) and the CuAAC reaction is subsequently catalyzed where features as small as 10 microns have been produced. These techniques are not without their drawbacks. Microcontact printing utilizes inexpensive elastomeric stamps than can rapidly reproduce images. However, the master the stamps must be fabricated by another technique that is capable of directly writing the master. Electroclic chemistry shares this drawback. Dip-pen lithography is capable of directly writing high fidelity images, but is accordingly ill-suited to

the reproduction of large images and features. Alternatively, photolithography utilizes masked or focused light to irradiate a specific area, and induce chemical reactions that change the solubility of the photosensitive material. An image is then developed by immersion in a solvent. Photolithography can both directly write images and reproduces images, even utilizing masks produced by inkjet printers²³. Unlike all of the current techniques utilized for patterning the CuAAC reaction, photolithography is also used to produce three-dimensional images and reactions^{16,17}, to write images within a material⁴ and to functionalize a material anywhere throughout the material.

Upon irradiation, photochemical reactions occur either by direct excitation of chromophoric species, as in the case of [2+2] cycloadditions, or by the generation of an active species that initiates multiple reactions, as typical of photopolymerizations. Photochemical 1,3-cycloadditions are symmetry forbidden²⁴ and the photopatterning of azides and alkynes has been limited to the photochemical decarbonylation of propenones to dibenzocyclooctynes, which subsequently undergo the thermal 1,3-dipolar cycloaddition (copper-free azide—alkyne click reaction)²⁵. Despite the success of this innovative approach for labeling cells²⁵ and functionalizing surfaces²⁶, it is limited by the complexity and scarcity of materials possessing the requisite cyclopropenone functional group, the synthesis of which is non-trivial. Furthermore, this mechanism requires large irradiation doses to obtain high conversions as each absorbed photon leads to a maximum of one bimolecular coupling event. In contrast, unprotected, reactive azides are readily synthesized from acyl halides, and typical photoinitiated polymerizations follow a chain reaction mechanism, where a single absorbed photon leads to a reaction cascade that ultimately consumes many reactant molecules per absorbed photon.

While the 1,3-dipolar cycloaddition reaction is not influenced by conventional photogenerated active species, such as carbocations and radicals, the reaction rate is increased approximately 10^7 times by catalytic amounts of Cu(I)²⁷. This catalytic behavior permits the photochemical generation of Cu(I) to be utilized in a manner analogous to generation of radical or carbocation species in traditional photopolymerization processes, and would enable spatial and temporal control of the CuAAC reaction. Further, photochemical generation of Cu(0) from Cu(II) was previously demonstrated in the synthesis of three dimensional nanoparticles by photoinduced radical generation, where the radicals reduce Cu(II) to Cu(0)²⁸. Here, we demonstrate that the Cu(I) transiently generated in the course of such a process is able to catalyze the Huisgen 1,3-dipolar cycloaddition, enabling a photoinducible azide–alkyne cycloaddition (pCuAAC) reaction (**Figure 1a**).

UV irradiation of an aqueous solution of monofunctional azide and alkyne species (1-hexyne (**1**) ethyl azidoacetate (**2**)) in the presence of a cleavage-type photoinitiator (Irgacure 819 (**3**)) and copper sulfate pentahydrate results in the generation of radicals that subsequently reduce Cu(II) to Cu(I) (structures are shown in **Figure 1b**). ¹H-NMR spectroscopy reveals complete conversion (98% yield) of azide and alkyne functional groups and production of the expected triazole species without side products (see Supplementary information). The use of TiO₂ as a radical source produced similar results, but due to the heterogeneous nature of TiO₂ the system was not readily amenable to further experimental analysis. The performance of the CuAAC reaction depends strongly on the amplified character of this process, as each photoinitiated radical leads to Cu(I) species that subsequently catalyze many reactions. Kinetic aspects of the reaction were explored by monitoring the concentration of ethyl azidoacetate via Fourier transform infrared

spectroscopy (FTIR). These experiments showed a maximum rate 9×10^{-2} mM/s, which falls within the range of the two sodium ascorbate and copper sulfate systems measured by Kasuga *et al.*²⁹. Control experiments, where the light, initiator, and copper were absent, indicate that each component is necessary and thus support our proposed mechanism (**Figure 2**). Off-stoichiometric experiments further verified the absence of side reactions such as Eglinton coupling.

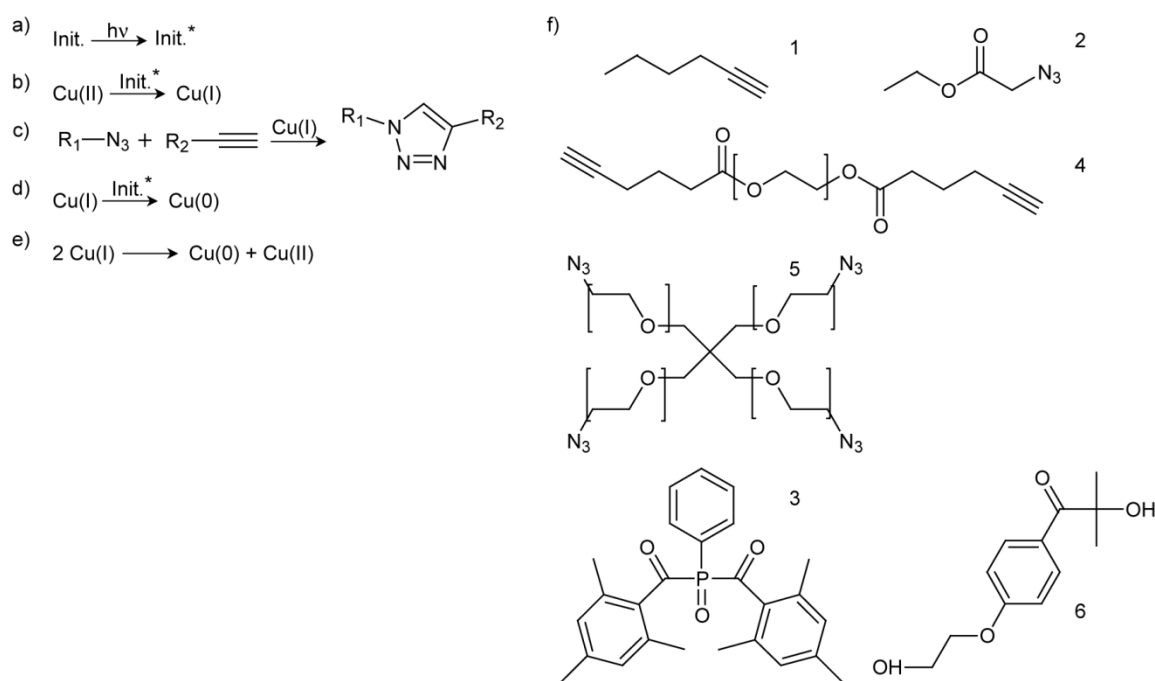


Figure 1 | General scheme for a photo-catalyzed CuAAC reaction. a) A photoinitiator is first used to generate radicals, b), which reduce Cu(II) to Cu(I). c) The transiently generated Cu(I) then catalyzes the 1,3-dipolar cycloaddition, c) before possibly being reduced to copper metal. e) Disproportionation is another potential fate of for Cu(I). Reactions of Cu(I) and oxygen are also possible (not shown). f) 1-Hexyne (1), ethyl azidoacetate (2), and Irgacure 819 (3) were used in the ¹H-NMR and FTIR experiments, while a 3K PEG-dialkyne (4), a 10K PEG-tetraazide (5), and Irgacure 2959 (6) were used for hydrogel synthesis.

The persistence of catalytic Cu(I) was explored by monitoring the reaction behavior following irradiation cessation, i.e., turning off the light, and prior to complete reactant consumption, revealing that once initiated, the reaction persists for extended times in the

dark (Figure 2). The continued reaction suggests that Cu(I) is not rapidly consumed during the dark reaction (i.e., after the irradiation is ceased), suggesting that the disproportionation of Cu(I) to Cu(II) and Cu(0) occurs over a timescale longer than that of the CuAAC reaction (as radicals are no longer available for reduction). This persistent behavior of Cu(I) enables complete reaction to be achieved with a minimal amount of required irradiation. For example, a sample irradiated for five minutes, reaches 20% conversion during irradiation, but still proceeds to 80% conversion after 160 minutes in the dark. Accordingly, in a continuously irradiated sample each photon absorbed results in the reaction of approximately 20 azide and alkynes, while a sample irradiated for five minutes produces at least 130 reaction-events per absorbed photon.

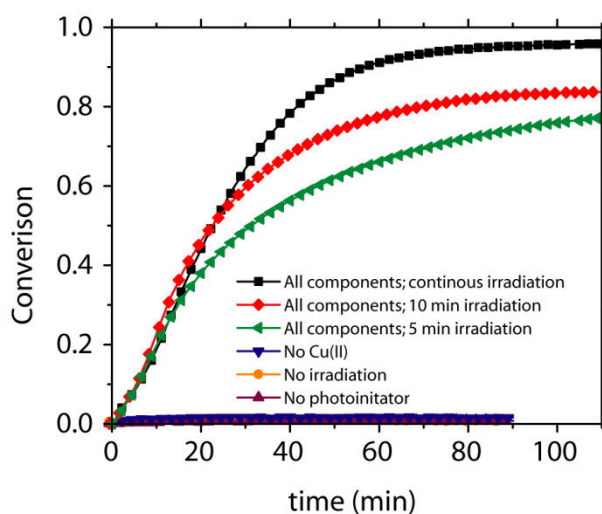


Figure 2 | Photo-CuAAC reaction kinetics. The complete conversion of the azide species is shown to occur in approximately 60 minutes for a DMF solution with 200 mM 1-hexyne (1), 200 mM ethyl azidoacetate (2), 10 mM copper sulfate, and 10 mM Irgacure 819 (3) irradiated with 10 mW/cm² 400-500 nm light. Also shown is the azide conversion for mixtures lacking Cu(II), irradiation, or photoinitiator. No significant reaction is noted for any of these control samples and all three lines overlay. Conversion is also shown when irradiation was ceased after five or ten minutes during the course of the reaction.

While temporal control of material forming reactions increases their ease of use, much of the interest in the CuAAC reaction is associated with its high conversion and functional group tolerance, promoting efficient orthogonal synthesis as well as the facile modification of materials, such as surfaces and polymers³⁰. The spatial control enabled by photopolymerization should extend the capability of the CuAAC reaction to creating patterned devices, materials and structures. Hence, we explored the synthesis and *in situ* modification of hydrogels, an important class of polymers that show promise as tissue mimics¹⁴, as well as alkyne functionalized silica surfaces. Multifunctional alkyne (**4**) and azide (**5**) functionalized polyethylene glycol (PEG) monomers were readily synthesized (see Supplementary Information) and irradiated in the presence of copper sulfate and photoinitiator (Irgacure 2959 (**6**)), yielding hydrogels that were formed in less than four minutes (as determined by rheometry, see Supplemental Information). The time to gel is comparable with gels formed by similar concentrations of Cu(II) and reduced via sodium ascorbate, and is easily controlled by varying the light intensity. As a consequence of the reduced functional group concentration, the ratio of Cu(II) to functional groups is much higher, and the reaction appears to proceed faster. Uniquely, this photopolymerization proceeds by a step growth mechanism, an attribute of photopolymerizations that is currently shared only with the thiol-ene and thiol-yne photopolymerization reactions³¹. Compared to chain growth polymerizations, this mechanism allows for delayed and readily predicted gel-point conversions. The nearly ideal hydrogels formed by the CuAAC reaction have been shown to possess improved mechanical properties compared to networks formed by radical crosslinking of diacrylates³². Further, it has been shown that the cytotoxic Cu(I) from the CuAAC reaction can be removed by ethylenediaminetetraacetic acid (EDTA)³².

The spatial resolution of a photolithographic process is either limited by the ability of the optics to project the desired image, or the capability of the photoinduced process to reproduce the image. The persistence of Cu(I) in the previous experiments suggests that the diffusivity of Cu(I) may be an important consideration, and taking the diffusivity of Cu(I) to be on the order of $10^{-5} \text{ cm}^2/\text{s}$ a characteristic distance of hundreds of micrometers is calculated for relevant experimental timescales³³. However, patterning experiments readily produced 35 micron wide (4.2 micron depth) features that were only 5 μm wider than the mask (see **Figure 3**). This illustrative result suggests that translational diffusion of Cu(I) is greatly limited by the nature of the reaction. Three potential explanations for this observation are: i) the binding of Cu(I) to the alkyne functionalized monomer, during the course of the CuAAC reaction results in diffusion being dictated by the dynamics of the telechelic polymer rather than Cu(I); ii) the ligandization of the Cu(I) with the triazole product results in a similar decrease in diffusion of Cu(I); iii) Cu (I) is rapidly consumed once it diffuses out of the irradiated area, likely via reactions with oxygen³⁴. The exact explanation remains an open question at this time. If indeed oxidation of Cu(I) is responsible for the resolution of the system, then oxygen plays a much different role in these systems than it does in other click reactions, such as thiol-ene and thiol-yne reactions. Perhaps, pattern resolution could be improved by the intentional addition of an oxidizer that would decrease the diffusion of Cu(I) outside of the irradiated area. Regardless, the resolution of this process is suitable for numerous surface and 3D material patterning applications such as the construction of hydrogel based microreactors³⁵.

Post-synthetic modification of hydrogels was also successfully demonstrated (**Figure 4**). Gels were synthesized by the thiol-yne reaction with a stoichiometric excess of alkynes.

A solution of photoinitiator, copper sulfate, and a functionalized fluorophore was then swollen into the gel. Upon irradiation, the pCuAAC reaction between the functionalized fluorophore and the pendant alkynes in the polymer network produces a fluorescent pattern within spatially defined regions of the gel. It was determined that 25 μm features could readily be formed and discerned with only 50 seconds of irradiation. The ability to selectively pattern hydrogels has been exploited to promote cell adhesion through RGD peptides, and the fabrication of high-performance organic electronic devices^{4,36}.

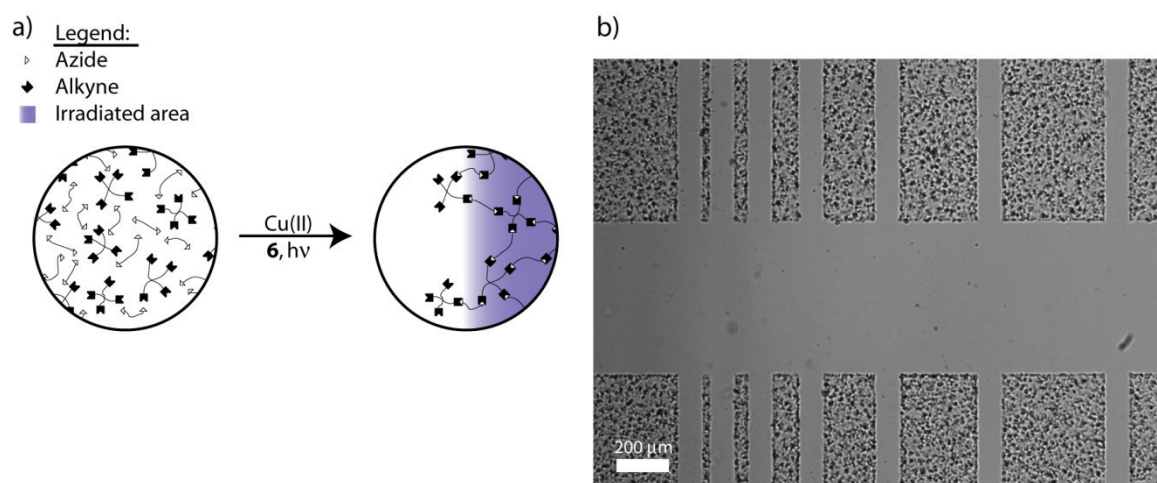


Figure 3 | Hydrogel formation patterned by photo-CuAAC reaction. a) Hydrogels are by formed irradiating a 3K PEG dialkyne (4) and a 10K PEG tetraazide (5) in the presence of a Irgacure 2959 (6) and copper sulfate using masked light. The gels form only in the irradiated area. b) The inset brightfield image show one such dehydrated gel, approximately 4 μm thick. The photomask used consists of 25, 50, 100, 200, 300, and 400 μm bars separated by 100 μm spaces.

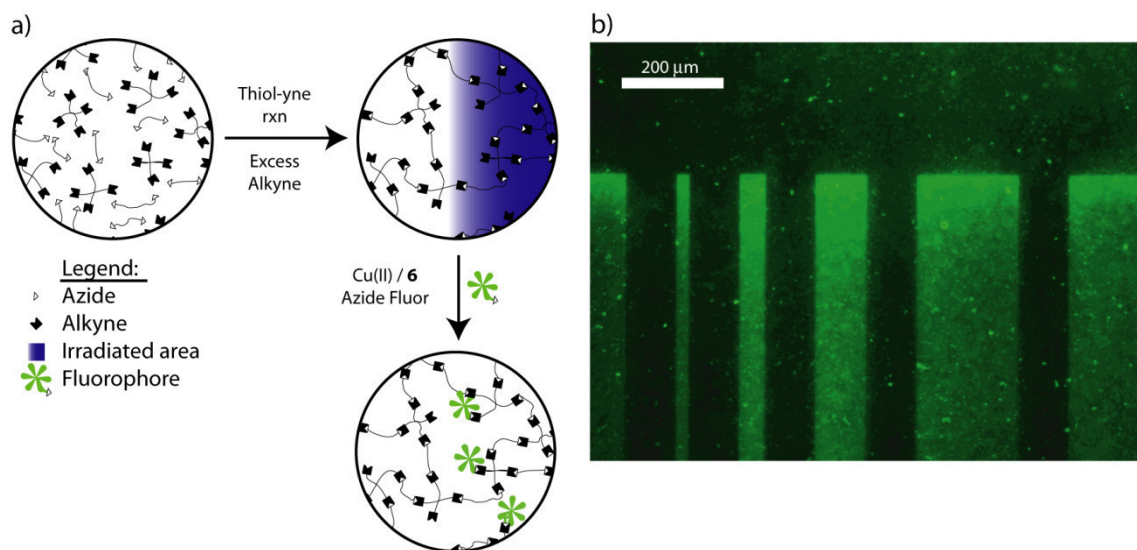


Figure 4 | Fluorescent patterning of a hydrogel by the photo-CuAAC reaction. a) The *in situ* patterning of a hydrogel (inserted photo) was achieved by first forming an alkyne rich gel via the thiol-yne click reaction of a 10K tetrathiol and 3K dialkyne. A solution of photoinitiator, copper sulfate, and an azide labeled fluorophore was swollen into the gel. Irradiation with a photomask (same mask as Figure 3) resulted in the generation of Cu(I) in the irradiated areas and the subsequent pCuAAC reaction between the pendant alkyne groups and azide functionalized fluorophore. b) After removal of the unreacted fluorophore, widefield microscopy reveals the patterned of the fluorophore.

The photochemical generation of chemical species that locally reduce Cu(II) to Cu(I) for catalysis of the CuAAC reaction was studied by a combination of ^1H -NMR spectroscopy, FTIR spectroscopy, and dynamic mechanical analysis, while confocal and optical microscopies confirm the fidelity of the patterned features produced using this technique. This approach is readily adaptable to both aqueous and non-aqueous systems, with the likely limitation being the copper salt solubility. Moreover, a variety of radical generators can be employed. TiO_2 and cleavage type photoinitiators were demonstrated herein, and the abstraction type photoinitiators frequently used in copper nanoparticle synthesis and should work equally well²⁸. Additionally, the uncanny resemblance of this system to reverse atom transfer radical polymerizations (reverse-ATRP³⁷) suggests that systems could be designed to form persistent radicals. Not only would this allow for simultaneous click reactions and

living polymerization, but some ATRP polymerizations are capable of utilizing mere ppm levels of copper, suggesting perhaps that this approach could enable a dramatic reduction in the copper concentration. Perhaps this reduction could permit the CuAAC reaction to be utilized in biological systems as the irradiation conditions and initiators used are cytocompatible.³⁸ In conclusion, this approach to catalysis of the CuAAC reaction is broadly applicable, improving the implementation, robustness and control of the CuAAC reaction.

REFERENCES

- (1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Edit.* **2001**, *40*, 2004-2021.
- (2) Spruell, J. M.; Sheriff, B. A.; Rozkiewicz, D. I.; Dichtel, W. R.; Rohde, R. D.; Reinhoudt, D. N.; Stoddart, J. F.; Heath, J. R. *Angew. Chem. Int. Edit.* **2008**, *47*, 9927-9932.
- (3) Peng, W.; Alina, K. F.; Anne, K. N.; Craig, J. H.; Arnulf, S.; Brigitte, V.; Jeffrey, P.; Jean, M. J. F.; Sharpless, K. B.; Valery, V. F. *Angew. Chem. Int. Edit.* **2004**, *43*, 3928-3932.
- (4) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. *Nature Mater.* **2009**, *8*, 659-664.
- (5) Matyjaszewski, K.; Tsarevsky, N. V. *Nature Chem.* **2009**, *1*, 276-288.
- (6) Iha, R. K.; Wooley, K. L.; Nystrom, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620-5686.
- (7) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193.
- (8) El-Sagheer, A. H.; Brown, T., *39*, 1388-1405.
- (9) Macpherson, L. J.; Dubin, A. E.; Evans, M. J.; Marr, F.; Schultz, P. G.; Cravatt, B. F.; Patapoutian, A. *Nature* **2007**, *445*, 541-545.
- (10) Cohen, M. S.; Hadjivassiliou, H.; Taunton, J. *Nature Chem. Biol.* **2007**, *3*, 156-160.
- (11) Bowman, C. N.; Kloxin, C. J. *AIChE J.* **2008**, *54*, 2775-2795.
- (12) Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int. Edit.* **2010**, *49*, 1540-1573.
- (13) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767-773.
- (14) Koh, W.-G.; Revzin, A.; Pishko, M. V. *Langmuir* **2002**, *18*, 2459-2462.
- (15) Martens, P. J.; Bryant, S. J.; Anseth, K. S. *Biomacromolecules* **2003**, *4*, 283-292.
- (16) Neckers, D. C. *Polym. Eng. Sci.* **1992**, *32*, 1481-1489.
- (17) Young, J. S.; Fox, S. R.; Anseth, K. S. *J. Manuf. Sci. Eng.-Trans. ASME* **1999**, *121*, 474-477.
- (18) Long, D. A.; Unal, K.; Pratt, R. C.; Malkoch, M.; Frommer, J. *Adv. Mater.* **2007**, *19*, 4471-4473.
- (19) Paxton, W. F.; Spruell, J. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 6692-6694.
- (20) Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. *Angew. Chem. Int. Edit.* **2006**, *45*, 5292-5296.

- (21) Devaraj, N. K.; Dinolfo, P. H.; Chidsey, C. E. D.; Collman, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 1794-1795.
- (22) Hansen, T. S.; Daugaard, A. E.; Hvilsted, S.; Larsen, N. B. *Adv. Mater.* **2009**, *21*, 4483-4486.
- (23) Qin, D.; Xia, Y. N.; Whitesides, G. M. *Adv. Mater.* **1996**, *8*, 917-919.
- (24) Padwa, A. *Angew. Chem. Int. Edit. Engl.* **1976**, *15*, 123-136.
- (25) Poloukhine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G.-J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769-15776.
- (26) Orski, S. V.; Poloukhine, A. A.; Arumugam, S.; Mao, L.; Popik, V. V.; Locklin, J. J. *J. Am. Chem. Soc.* **2010**, *132*, 11024-11026.
- (27) Meldal, M. *Macromol. Rapid Commun.* **2008**, *29*, 1016-1051.
- (28) Sakamoto, M.; Tachikawa, T.; Fujitsuka, M.; Majima, T. *Chem. Mater.* **2008**, *20*, 2060-2062.
- (29) Kasuga, Y.; Ito, M.; Onoda, W.; Nakamura, Y.; Inokuma, S.; Matsuda, T.; Nishimura, J. *Heterocycles* **2009**, *78*, 983-997.
- (30) Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J. *Macromol. Rapid Commun.* **2008**, *29*, 1052-1072.
- (31) Fairbanks, B. D.; Scott, T. F.; Kloxin, C. J.; Anseth, K. S.; Bowman, C. N. *Macromolecules* **2009**, *42*, 211-217.
- (32) Malkoch, M.; Vestberg, R.; Gupta, N.; Mespouille, L.; Dubois, P.; Mason, A. F.; Hedrick, J. L.; Liao, Q.; Frank, C. W.; Kingsbury, K.; Hawker, C. J. *Chem. Commun.* **2006**, 2774-2776.
- (33) Ribeiro, A. C. F.; Estes, M. A.; Lobo, V. M. M.; Valente, A. J. M.; Simoes, S. M. N.; Sobral, A. J. F. N.; Burrows, H. D. *J. Chem. Eng. Data* **2005**, *50*, 1986-1990.
- (34) Litter, M. I. *Appl. Catal. B-Environ.* **1999**, *23*, 89-114.
- (35) Zhan, W.; Seong, G. H.; Crooks, R. M. *Anal. Chem.* **2002**, *74*, 4647-4652.
- (36) Ofir, Y.; Moran, I. W.; Subramani, C.; Carter, K., R.; Rotello, V., M. *Adv. Mater.* **2010**, *22*, 3608-3614.
- (37) Wang, J.-S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7572-7573.
- (38) Kloxin, A. M.; Kasko, A. M.; Salinas, C. N.; Anseth, K. S. *Science* **2009**, *324*, 59-63.

CHAPTER VII: Mechanism of the photo-mediated copper catalyzed azide–alkyne cycloaddition*

Abstract

The photo-mediated catalysis of the copper catalyzed azide–alkyne cycloaddition (CuAAC) reaction using a photoinitiator was studied using infrared spectroscopy and initial rate experiments. It was found the CuAAC reaction is the rate determining step, and the undesirable side reactions of Cu(I), such as disproportionation, further reduction by radicals, and reactions with oxygen are largely avoided, likely due to ligand interactions. The lack of these reactions, and the protection of Cu(I) by ligands also explains both the propensity for dark reaction and high fidelity spatial control of the reaction. These results demonstrate that the photo mediated catalysis of the CuAAC reaction has all of the advantages of using sodium ascorbate to reduce Cu(II), while enabling spatiotemporal control of the reaction.

While the 1,3-dipolar cycloaddition is a straightforward “no mechanism” reaction,¹ its popular variant, the copper catalyzed azide–alkyne cycloaddition (CuAAC), exhibits reaction kinetics that suggests a more complex mechanism.^{2,3} The Cu(I) catalyst is typically generated *in situ* by the reduction of Cu(II)⁴ or by comproportionation of Cu(II)/Cu(0),⁵ although the direct addition of Cu(I) salts is also employed.⁶ Sodium ascorbate is the most common reductant; however, the photochemical generation of reductants^{7,8} or use of light sensitive Cu(II) complexes is also possible.⁹ Our recent report demonstrating the spatial control of radical mediated reduction of Cu(II) produced two seemingly contradictory findings.⁸ While the reaction exhibited a significant dark reaction, that is the CuAAC reaction continued after irradiation was ceased, masked images were reproduced with high fidelity despite the potential for Cu(I) to diffuse into the masked area. Here, through a series of initial rate experiments a more

*Submitted to the Journal of the America Chemical Society. Experimental informaiton available in Appendix E.

thorough understanding of the mechanisms involved in the photo-mediated catalysis of the CuAAC reaction is developed and discussed with its implications.

The CuAAC reaction mechanism is understood as involving three general steps: (I) the Cu(I)-acetylide formation, (II) the formal cycloaddition, and (III) catalyst regeneration (see **Figure 1**).^{3,5} Under saturated conditions, where catalyst turnover is not required, the CuAAC reaction shows first order dependence on both azide and alkyne concentrations, consistent with an elementary bimolecular reaction.² In contrast, the kinetics are highly dependent on any ligands, buffer, salts, and substrates present when catalytic concentrations of Cu(I) are utilized.³ This behaviour has been interpreted as the consequence of a diverse family of copper coordination complexes that are formed *in situ*.³ In general, these copper species are highly reactive as evidenced by the consistent copper catalysis of the reaction for a large variety of terminal alkynes, but the reactivity of these species varies subtly to influence which step is rate-limiting.

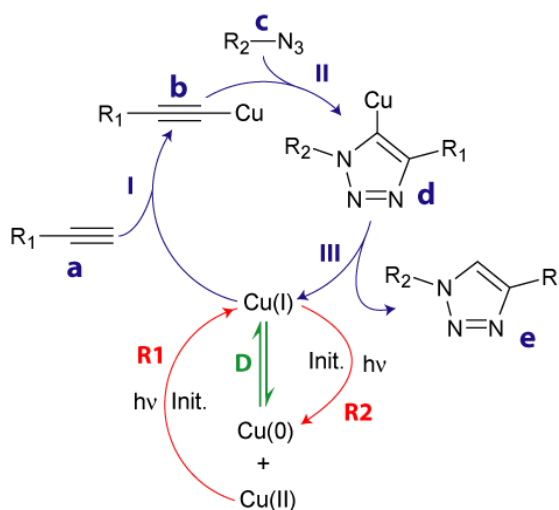


FIGURE 1 | The copper catalyzed azide–alkyne reaction is shown to occur in three steps. The alkyne (**a**) reacts with Cu(I) to form the copper-acetylide (**b**). This species then reacts with the azide (**c**) to form the cycloaddition product (**d**). The catalytic cycle is completed when Cu(I) is regenerated and the triazole product (**e**) formed. In the radical mediated process Cu(I) is generated by reduction of Cu(II) (reaction **R1**). Once generated, Cu(I) can potentially disproportionate into Cu(II) and Cu(0) (reaction **D**), or it could be expected to be further reduced to copper metal by radical reaction (reaction **R2**). Any ligands present are omitted for clarity.

Cu(I) is typically generated using sodium ascorbate as a reductant, which is used in large excess (10:1) to compensate for oxidation and disproportionation of Cu(I).^{5,10} As such, nearly quantitative reduction of Cu(II) is assumed to occur. It is perhaps surprising, given the CuAAC reaction's susceptibility to other species, that the ascorbate anion appears to have no effect on the reaction kinetics.³ While the radical mediated reduction of Cu(II) to copper metal has been observed for nearly 100 years,^{11,12} it has recently attracted renewed interest for both removal of hazardous wastes¹³ and generation of copper nanoparticles.¹⁴ Due to Cu(II)/Cu(I)'s half reaction (reduction) potential of 0.16 V, a variety of organic radicals are capable of reducing it, e.g. ketyl, phosphinoyl, and semi-pinacol radicals. The reaction is typically described as the sequential reduction of Cu(II) to Cu(I) and subsequently to copper metal (reactions **R1** and **R2**, respectively in **Figure 1**).^{12,15} Besides further reduction to copper metal, Cu(I) is both air sensitive and prone to disproportionation (reaction **D** in **Figure 1**).¹⁶ It would be expected that all three of these reactions could play a very complicated role in the photo-mediated catalysis of the CuAAC reaction, as shown in **Figure 1**.

While a variety of radicals are capable of reducing Cu(II), it is worth noting that organic azides can photochemically decompose to nitrene when irradiated with UV light below 400 nm.¹⁷ We found decomposition to be slow relative to the CuAAC reaction when using a 365 nm light source; however, by utilizing a visible light photoinitiator decomposition is entirely avoided. As such, we utilized a visible light source (400-500 nm) and a visible light photoinitiator, phosphine oxide phenyl bis(2,4,6-trimethyl benzoyl) (Irgacure 819, Ciba), to generate copper-reducing radicals. The phosphinoyl radicals generated via photolysis are expected to participate in electron transfer reactions with Cu(II).¹⁸

The CuAAC reaction was monitored using Fourier transform infrared (FTIR) spectroscopy, which allows for *in situ* measurement of azide and alkyne concentrations. Initial rate experiments performed with ethylazidoacetate and 1-dodecyne at catalytic concentrations of copper(II) and photoinitiator (ca. 20 to 1 molar ratios) verified the overall reaction rate to be nearly independent of both azide and alkyne concentrations (**Figure 2**). The independence of the reaction rate on the azide and alkyne concentration is consistent with that observed for benzylazide and phenylacetylene,² and is believed to be the general case for the CuAAC reaction in the absence of added accelerating ligands.³ The independence of the reaction rate on alkyne and azide concentrations would tentatively imply that the regeneration of the Cu(I) is typically the rate-limiting step (reaction **III** in **Figure 1**). This behavior then suggests that if the generation of Cu(I) is rapid, as in the case of reduction by sodium ascorbate, that the CuAAC reaction mechanism will not be influenced by the method used to reduce Cu(II).

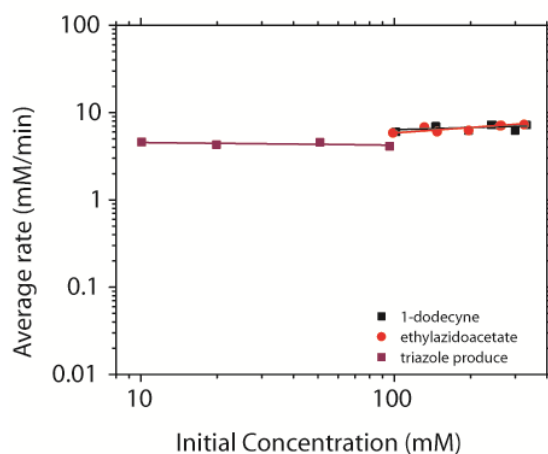


FIGURE 2 | The dependence of the reaction rate on the initial concentrations of 1-dodecyne, ethylazidoacetate, and triazole product reveals that the rate is approximately independent of all three (the slopes are 0.08 ± 0.07 , 0.16 ± 0.07 , and -0.03 ± 0.03 , respectively). The concentration of the non-varying component is 200 mM for all experiments. The photoinitiator and copper sulphate concentrations were both 10 mM, and the irradiation intensity was 20 mW/cm² for all experiments.

The reaction rate dependence on irradiation intensity is nearly zero-order (0.097 ± 0.02) at irradiation intensities greater than approximately 0.3 mW/cm^2 , as shown in **Figure 3**. The irradiation intensity is proportional to the photolysis rate, and therefore the rate at which radicals are generated. Consequently, the independence of the reaction rate on the light intensity implies that the generation of radicals is fast relative to the rate limiting step. As in the case of reduction by sodium ascorbate, the cycloaddition appears to be the rate-limiting step. This outcome is not surprising as the half-life of I819 at 20 mW/cm^2 is approximately 36 seconds. Comparatively, over the first 36 seconds less than two percent of the azide is consumed by the CuAAC reaction. When the timescales of photolysis and the CuAAC reaction become comparable, it is expected that the reaction rate will no longer be independent of the light intensity. In Figure 3 it is observed that the scaling value of the light intensity does indeed increase at irradiation intensities less than 0.3 mW/cm^2 , which corresponds to when the half-life of the photoinitiator is calculated to be of the same order as that of the CuAAC reaction.

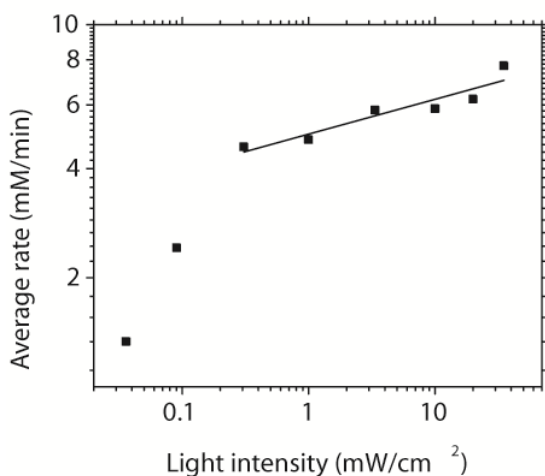


FIGURE 3 | The effect of irradiation on the CuAAC reaction rate is shown. For irradiation intensities greater than 0.5 mW/cm^2 the effect of light intensity on the reaction rate is negligible with a scaling constant equal to 0.097 ± 0.02 while for lower light intensities, the scaling exponent was found to be 1.5. The azide and alkyne concentration were 200 mM each, and the photoinitiator and copper sulphate concentrations were both 10 mM for all experiments.

Figure 4 shows that the kinetics of samples with equimolar concentrations of photoinitiator and Cu(II) prepared under ambient conditions possesses a similar reaction rate to those sparged with argon or oxygen. When the ratio of photoinitiator to Cu(II) is reduced, oxygen is then seen to significantly retard the CuAAC reaction. Oxygen is highly reactive towards phosphinoyl and benzoyl radicals,¹⁸ and the resulting peroxy radicals are incapable of reducing Cu(II).¹⁹ In contrast, equimolar mixtures of Cu(II) and photoinitiator do not exhibit an induction period. The lack of inhibition is explained by the excess of radicals from the photoinitiator which ensures complete consumption of Cu(II), even though a fraction of the radicals are scavenged by oxygen. Unlike some systems utilizing Noorish type II photoinitiators the excess radicals eliminate the need for rigorous purging of oxygen.⁷ Importantly, the data also indicates that oxygen does not irreversibly consume Cu(I). If oxygen did irreversibly consume Cu(I) then the reaction rates of all the equimolar cases would not be similar. Whether Cu(I) reactions with oxygen are prevented by ligand coordination or effectively reversed by the excess of radicals is unclear from this data alone.

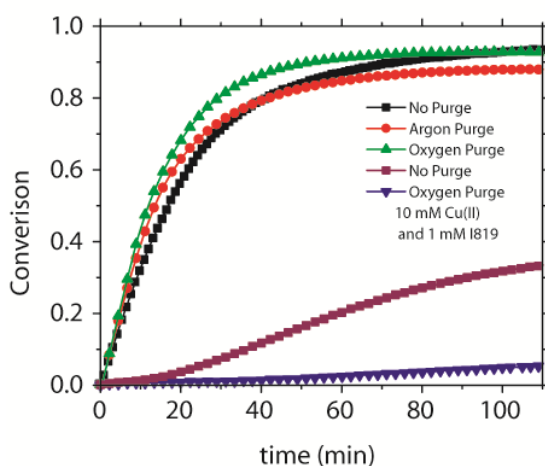


FIGURE 4 | When the concentration of photoinitiator and Cu(II) are both 10 mM, sparging with oxygen is seen to have no effect. When the concentration of photoinitiator is reduced to 1 mM, radical scavenging by oxygen significantly retards the CuAAC reaction. The azide and alkyne concentration were each 200 mM, and the irradiation intensity was 20 mW/cm² for all experiments.

The dependence of the reaction rate on copper and photoinitiator appears significantly more complicated. When the photoinitiator concentration is held constant at 10 mM the reaction rate shows an abrupt change in scaling at an initial Cu(II) concentration of 15 mM (**Figure 5**). Above the threshold value of 15 mM of Cu(II), the reaction rate is independent of the initial Cu(II) concentration. The concentration of Cu(I) resulting from the reduction of Cu(II) could either be limited by the amount of photoinitiator available to reduce Cu(II), or from the resulting disproportionation/comproportionation equilibrium. The independence of the reaction rate from the initial Cu(II) concentration implies that while disproportionation of Cu(I) is highly thermodynamically favorable,²⁰ and typically rapid,²¹ it is not occurring in this system. If disproportionation were occurring, the initial addition of excess Cu(II) would shift the equilibrium to produce more Cu(I) and the reaction rate would increase. Ligands that bind Cu(I) can protect it from disproportionation by shifting the equilibrium from favoring disproportionation ($\log K_{\text{Disp}} = 4.26$)²⁰ to comproportionation ($\log K_{\text{Disp}} = -2.20$).²² In this system whether the ligands responsible for this behaviour are the triazole products, which are known to protect Cu(I),¹⁰ or the reactants themselves is unclear. The lack of an inhibition time and the absence of autocatalysis, could suggest that the protecting ligand is present at the beginning of the reaction, implying the alkyne reactant is the protecting agent. However, as the triazole concentration is greater than that of Cu(I) after 5% conversion the resolution of these experiments may not be sufficient to detect a slight inhibition while the protecting ligand is formed.

Likewise, when the initial Cu(II) concentration is held constant at 10 mM, the reaction rate shows an abrupt change in scaling at a photoinitiator concentration of 5mM. Above this threshold concentration of photoinitiator, the reaction rate is independent of photoinitiator concentration. If the reduction of Cu(I) to copper metal

were occurring, it would be expected that adding more photoinitiator would result in more radicals and less Cu(I). As the CuAAC reaction rate typically shows a second order dependence on Cu(I) concentration,^{2,3} it would be expected that increasing the initial photoinitiator concentration would reduce the CuAAC reaction rate. The independence of the CuAAC reaction rate implies that the reduction of Cu(I) to copper metal is not occurring to a significant extent under these conditions in this system. This behavior is somewhat surprising as radical reduction has previously been used to synthesize copper nanoparticles.¹⁴ However, the alkyne or triazole ligands appear to protect Cu(I) from each of these three side reactions: oxidation by dissolved oxygen, disproportionation, and further reduction by radicals. Indeed the only time we have noted the formation of copper metal is when working with very dilute hydrogels where the concentration of Cu(II) was nearly equimolar with the reactants.

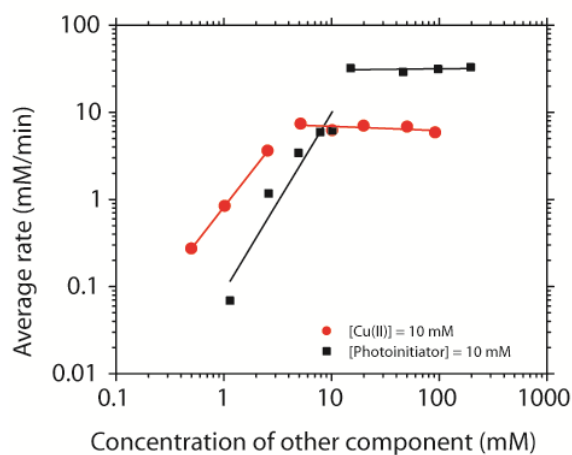


FIGURE 5 | The average reaction rate versus the initial concentrations of Cu(II) and photoinitiator (red circles and black squares, respectively), revealing two distinct regimes. When Cu(II) is in excess, Cu(II) shows a scaling constant of 0.01 ± 0.03 and the photoinitiator scales with an exponent of 1.58 ± 0.004 . When the photoinitiator is in excess, the Cu(II) shows a scaling constant of 2.0 ± 0.3 , and the photoinitiator scales with an exponent of -0.05 ± 0.04 .

In both the case of Cu(II) and the photoinitiator the threshold behavior appears to result solely from a change in the limiting reagent. The threshold values suggest that each molecule of I819 results in the reduction of 1.5 to 2 molecules of Cu(I). As I819 can produce two benzoyl and two phosphinoyl radicals this would suggest that either one of the radicals is ineffective in reducing Cu(II), or that many of the radicals are scavenged by other reactions.

Below the threshold initial Cu(II) concentration of 15 mM, the reaction rate displays a second order dependence on the initial concentration of Cu(II). In the absence of disproportionation and reduction of Cu(I) to copper metal, it would be expected that all of the Cu(II) would be reduced to Cu(I) by the excess radicals that are generated. Indeed, the scaling constant is measured to be 2.0 ± 0.3 , consistent with previous measurements.^{2,3,9} Below the threshold photoinitiator concentration of 5 mM the reaction rate shows an order of 1.58 ± 0.01 . When Cu(II) is in excess, it would be expected that the amount of Cu(II) reduced to Cu(I) would be proportional to the initial photoinitiator concentration, which would result in a second order dependence of the CuAAC reaction rate on the photoinitiator concentration. The scaling exponent of 1.58 instead of 2.0 implies that as the photoinitiator concentration is increased, unproductive radical reactions such as primary radical recombination, i.e., radical-radical termination, become more prevalent. This value is similar to the scaling exponent of 1.5 that the light intensity appears to approach at its lower extreme (Figure 3). It is expected that both the light intensity and initial radical concentration should have similar scaling constants.

These results suggest that the photo-mediated CuAAC reaction is controlled not by the rate of generation of Cu(I), but rather the amount of Cu(II) initially present. Like sodium ascorbate this process is fast relative to the CuAAC reaction under typical

conditions. When used in a polymerization reaction, this attribute would make the photo-mediated CuAAC reaction quite different from the typical radical photopolymerization where the rate of polymerization depends on the rate at which the active species are generated. Further, we have shown results that suggest oxidation by dissolved oxygen, disproportionation, and reduction of Cu(I) by radicals are all suppressed in these systems. This result likely occurs because of coordination with Cu(I) coordination with either the alkyne or triazole ligands that are present. The persistent nature of Cu(I) explains the dark cure reaction noted in a previous publication, while coordination reactions which result in the diffusion of Cu(I) being dictated by the species it is bound to, explain the high fidelity of the patterning of the CuAAC reaction as previously noted.⁸ Like recent work by Soriano *et al.* where the cytotoxicity of the CuAAC reaction was reduced by the choice of appropriate ligands, this work suggests that understanding the role of ligands in the CuAAC reaction is important not only for understanding the reaction itself, but ultimately for engineering practical systems.²³

REFERENCES

- (1) Huisgen, R. *Angew. Chem.-Int. Edit. Engl* **1963**, *2*, 633-645.
- (2) Rodionov, V. O.; V. Fokin, V., V.; Finn, M. G. *Angew. Chem.-Int. Edit.* **2005**, *44*, 2210-2215.
- (3) Rodionov, V. O.; Presolski, S. I.; Diaz, D. D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705-12712.
- (4) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.-Int. Edit.* **2002**, *41*, 2596-2599.
- (5) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Amer. Chem. Soc.* **2005**, *127*, 210-216.
- (6) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
- (7) Ritter, S. C.; Konig, B. *Chem. Commun.* **2006**, 4694-4696.
- (8) Adzima, B. J.; Tao, Y.; Kloxin, C. J.; DeForest, C. A.; Anseth, K. S.; Bowman, C. N. *Nat. Chem.* **2011**, *3*, 258-261.
- (9) Tasdelen, M. A.; Yagci, Y. *Tetrahedron Lett.* **2010**, *51*, 6945-6947.
- (10) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853-2855.
- (11) Benntt, C. W. *J. Phys. Chem.* **1912**, *16*, 782-785.
- (12) Kateda, K.; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 268.
- (13) Litter, M. I. *Appl. Catal. B-Environ.* **1999**, *23*, 89-114.

- (14) Sakamoto, M.; Tachikawa, T.; Fujitsuka, M.; Majima, T. *Chem. Mater.* **2008**, *20*, 2060-2062.
- (15) Sakamoto, M.; Fujitsuka, M.; Majima, T. *J. Photochem. Photobiol. C-Photochem. Rev.* **2009**, *10*, 33-56.
- (16) Simmons, M. G.; Merrill, C. L.; Wilson, L. J.; Bottomley, L. A.; Kadish, K. M. *J. Chem. Soc.-Dalton Trans.* **1980**, 1827-1837.
- (17) Roffey, C. *Photogeneration of Reactive Species for UV Curing*, John Wiley and Sons: West Suffex, 1997.
- (18) Jockusch, S.; Turro, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 11773-11777.
- (19) Buettner, G. R.; Jurkiewicz, B. A. *Radiat. Res.* **1996**, *145*, 532-541.
- (20) Tsarevsky, N. V.; Braunecker, W. A.; Matyjaszewski, K. *J. Organomet. Chem.* **2007**, *692*, 3212-3222.
- (21) Gagne, R. R.; Allison, J. L.; Gall, R. S.; Koval, C. A. *J. Am. Chem. Soc.* **1977**, *99*, 7170-7178.
- (22) Matyjaszewski, K.; Tsarevsky, N. V.; Braunecker, W. A.; Dong, H.; Huang, J.; Jakubowski, W.; Kwak, Y.; Nicolay, R.; Tang, W.; Yoon, J. A. *Macromolecules* **2007**, *40*, 7795-7806.
- (23) Soriano del Amo, D.; Wang, W.; Jiang, H.; Besanceney, C.; Yan, A. C.; Levy, M.; Liu, Y.; Marlow, F. L.; Wu, P. *J. Am. Chem. Soc.* **2010**, *132*, 16893-16899.

CHAPTER VIII: Conclusions and future directions

Cycloadditions reactions possess several desirable attributes for the synthesis of polymeric materials: tolerance of both oxygen and water allowing for their use in regular atmospheric conditions, high yields under appropriate conditions, and a tolerance of other functional groups allowing subsequent reactions to be carried out. This thesis explored two specific reactions for polymer synthesis: the Diels–Alder reaction and the copper-catalyzed Azide-Alkyne cycloaddition (CuAAC reaction). The unique reversibility of the Diels–Alder reaction was employed to create several unique materials including a thermally reversible covalent adaptable network, an electromagnetic field responsive polymer composite, and a negative tone photoresist. Concurrently, the photochemical generation of copper(I) was explored as a method for catalyzing the CuAAC reaction. The ability to spatially control the CuAAC reaction and the mechanisms that enabled spatial control of the reaction were examined.

The Diels–Alder Reaction

The initial direction of this thesis was the development of a crosslinked polymer formed by the Diels–Alder reaction. While the current literature suggests a variety of approaches,¹⁻⁸ it was found that the Michael addition of furfuryl mercaptan to commercially available multifunctional acrylates provides a facile route to synthesize multifunctional

furans. Maleic anhydride and amines readily condense to form maleamic acids that can be closed to yield maleimides by a variety of mechanisms.⁹⁻¹¹ However, 1,1'-(methylenedi-4,1-phenylene) bismaleimide is commercially available and was used for the majority of this thesis. When combined, these two monomers produced a glassy polymer that did not *readily* dissolve in solvents.

The resulting material was carefully studied using FTIR spectroscopy to determine the reaction rate and equilibrium conversion over a broad temperature range. The equilibrium conversion of the furan and maleimide varied from 87% at 45°C to 24% at 155°C, demonstrating significant depolymerization via the retro-Diels–Alder reaction. Rheometric measurements and application of the Winters–Chambon criterion showed the gel point to occur at 92 °C, corresponding to 71% conversion, consistent with the Flory–Stockmayer equation. Rheometric experiments also revealed a relaxation process occurring near the calculated rate of bond cleavage in the material. This material presented the unique opportunity to measure scaling of the viscosity and storage modulus near the gel point. Such measurements are inherently difficult because most polymerizations only proceed in the forward direction and cannot be precisely quenched. The reported values deviated significantly from current models but were comparable to many other experimental systems.

The ability of the material to depolymerize to a liquid allows the material to be readily reformed and reshaped. This behavior differs from most thermosets formed by irreversible covalent bonds that break only during material fracture or destructive decomposition. Once a crack is formed, either by a fabrication defect, mechanical deformation, or material fatigue, the material's strength and overall mechanical performance

rapidly deteriorates. The ability to depolymerise allows the material to heal fractures and other defects by allowing material to flow into the crack and form new bonds upon cooling. While this outcome can be accomplished in a conventional oven, autoclave, or on a hotplate, methods for selectively heating materials near thermally sensitive substrates and where the material may not be directly accessible are desirable. Due to high temperature side reactions (well beyond the sol-to-gel transition temperature), a controlled heating mechanism is needed. These requirements lead to an exploration of polymer and magnetic particle composites. When a ferromagnetic material is placed in an alternating magnetic field, heating occurs via rearrangement of the magnetic domains. Known as hysteresis heating, this phenomenon ceases when the material reaches the Curie temperature and becomes paramagnetic. It was found that by adding a material with an appropriate Curie temperature to the polymer network an inherently self-limiting heating and healing process was created. This process enabled the material to retain its native properties over ten cycles of fracture and repair, demonstrating the utility of these reversible polymer networks for creating self-healing materials.

The ability of a reversibly crosslinked polymer network to depolymerize allows it to function as a photoresist. Photoresists are used in many modern technologies including microfluidic devices,¹² metamaterials,¹³ artificial tissues,¹⁴ parallel protein synthesis techniques,¹⁵ 3D prototyping,^{16,17} and perhaps most prominently, microchip fabrication.¹⁸ In these applications a photosensitive material is irradiated and undergoes a chemical reaction resulting in a solubility change. The soluble portion of the resist is then dissolved away and the image developed. Accordingly, irreversibly crosslinked polymers can only function as positive tone resists where the material is degraded by irradiation. However, it was

demonstrated that otherwise thermoreversible polymer networks formed by the Diels–Alder reaction can be selectively rendered irreversible by photochemical reactions. These networks were subsequently developed by carrying out the retro-Diels–Alder reaction to remove unwanted material. This “photofixation” approach presents a number of advantages. Diffusion of the active species is reduced by the crosslinked network. Thin films can be prepared without the use of a solvent as the starting materials are small molecules. Furthermore, in micro-stereolithographic applications the use of a solid state photoresist allows the fabrication of arbitrary shapes, as opposed to conventional liquid resists where overhanging features are not readily fabricated.

Future Directions

The photofixation process warrants a more detailed exploration. This approach is easily adaptable to a number of so called diffraction unlimited techniques where multiple visible and near UV laser sources are used to generate sub-50 nanometer sized spots.^{19,20} These techniques could prove or disprove the hypothesis that improved resolution does result from using a crosslinked photoresist.

Furthermore, the use of photofixation resists in nano-imprint lithography could prove useful. Conventional nanoimprint lithography utilizes either plastic materials that are embossed by a stamp, or liquid polymers that polymerize within the confines of a stamp and retain the pattern when removed.²¹ Photofixation resists would be able function in both modes. As such, patterns containing both reversibly and irreversibly crosslinked areas could be prepared. Such materials could be useful in micro and nano mechanical systems where a

patterned device would be created and then portions of the device could be selectively modified or removed at a later date while other features are permanently retained.

It is also conceivable that similar materials could be prepared by creating local variations in the concentration of irreversible crosslinks using multiple exposures. Areas that received no irradiation would develop at the lowest temperatures. Areas with a moderate concentration of irreversible crosslinks could then be later developed at higher temperatures. Finally, the regions with the highest concentrations of crosslinks would be developed at the most forcing conditions. Depending on the developing conditions used, multiple patterns could be developed from a single resist.

Furthermore, the photofixation process could be used to selectively incorporate molecules in a polymer scaffold. Such processes are used to selectively modify the cellular environment in tissue engineering applications.²² Cysteine containing polypeptides could easily replace the thiols currently used in the process.

The development of methods to systematically tune the reactivity of these reversible Diels–Alder systems is perhaps the area with the greatest possible impact. While the gel-point temperature can be varied by changes to monomer functionality and reactive group concentration in accordance with equation 5 (chapter I), the kinetics of the reaction are dependent on the particular functional groups chosen, and to some extent the solvent or local chemical environment. The 2-substituted furans and aryl/alkyl maleimides used in this thesis require several hours to reach equilibrium at room temperature. Furthermore, the half-life of the resulting adducts is on the order of days. As such, while materials can be

made that have gel-point temperatures near room temperature, the transition between gel and sol are incredibly slow. This behavior was illustrated when an attempt to make hydrogels with a 30°C gel point temperature resulted in materials that only showed signs of depolymerization after 6 months (albeit the aqueous environment played a role in slowing the retro-reaction).²³ It would be desirable for other applications that reactivity be reduced such that plasticity stemming from bond rearrangement only occurs at elevated temperatures.

Wudl and coworkers have developed cyclopentadiene based systems that show promise for high temperature systems.²⁴ Furthermore, Lehn and coworkers have developed several systems with reasonable room temperature kinetics based on fulvene and tricyano acrylate moieties.^{25,26} The stability of this system to ambient environmental conditions is not clear, but these materials warrant further examination.

A somewhat cynical observation is that more than 50 years of, albeit limited, exploration of reversible covalent systems has only produced one pair of reactants (furan and maleimide) with robust tolerance of environmental conditions. Further, the furan and maleimide system does not appear to be amenable to subtle tweaking of reactivity.²⁷ It may therefore be advantageous to pursue non-covalent interactions²⁸⁻³¹ such as hydrogen bonding and pi-pi stacking which have shown considerable promise as well as being the foundation of all terrestrial life.

The copper-catalyzed azide–alkyne cycloaddition

The copper catalyzed alkyne–azide reaction (CuAAC), is highly efficient and ubiquitous in an ever increasing number of synthetic methodologies and applications, including bioconjugation, labeling, surface functionalization, dendrimer synthesis, polymer synthesis, and polymer modification.³² Unfortunately, since the Cu(I) catalyst is typically generated by chemical reduction of Cu(II) to Cu(I), or directly added, temporal and spatial control of the CuAAC reaction is not readily achieved. The photochemical catalysis of the CuAAC reaction via the radical mediated reduction of Cu(II) was examined as a method of fabricating cycloaddition polymers. Standard photoinitiators were shown to be capable of reducing Cu(II) to Cu(I) and catalyzing the reaction. This approach was demonstrated to provide comprehensive spatial and temporal control of the CuAAC reaction using standard photolithographic techniques. Both the patterning of hydrogel formation and the *in situ* labeling of swollen hydrogels with fluorescent dyes were demonstrated.

One surprising result of the preliminary experiments was that even though Cu(I) showed persistent behavior, that is the reaction continued even after irradiation was ceased, Cu(I) did not appear to readily diffuse out of the irradiated area even in swollen hydrogels. Initial rate experiments revealed that undesirable side reactions of Cu(I) such as disproportionation, reduction of Cu(I) by radicals, and the reaction of Cu(I) with oxygen were suppressed. The most probable explanation is that Cu(I) strongly interacts with the ligands present in the system (both the alkyne reactants and triazole products) preventing these side reactions from occurring. The ligand interactions also explain the high fidelity of patterning. In these systems the Cu(I) interacts strongly enough with the macromolecular species present that its diffusion becomes controlled by the polymer dynamics.

Future directions of the CuAAC reaction

While the CuAAC reaction has enjoyed success in a number of areas, one of its chief limitations is the cytotoxicity of the copper species employed. Several groups have developed alkyne species that readily undergo the uncatalyzed Huisgen cycloaddition.³³⁻³⁵ However, these species are synthetically taxing to prepare, making their universal implementation questionable.³⁶ Sorino *et al.* developed ligands that bind Cu(I) strongly enough to protect it from cellular interactions, significantly increasing the biocompatibility of the process. Pursuing the development of protocols that either utilize reduced Cu(I) concentrations or that prevent cells from interacting with Cu(I) may prove more fruitful than the pursuit of alkynes that undergo the Huisgen reaction at room temperature.

Atom transfer radical polymerization (ATRP) is controlled radical polymerization technique used for the synthesis of low polydispersity polymers and for grafting polymers from functionalized surfaces.³⁷ In its most basic form it utilizes the reversible deactivation of propagating radicals via the reduction of a transition metal complex, typically copper. Equilibrium favors the deactivated state, and consequently most growing chains are in a deactivated state, which results in a controlled polymerization. The similarity between these systems, and the systems examined in this thesis for catalyzing the CuAAC reaction is striking. Indeed, other workers have developed methods for catalyzing the CuAAC reaction based on ATRP systems,³⁸ and explored simultaneous CuAAC and ATRP reactions.³⁹ The kinetic experiments in chapter VII show no sign of an equilibrium radical reaction. However, developing such a system may allow the reduction of the required copper

concentration. ATRP techniques have been developed where copper concentration on the order of parts per million are employed.⁴⁰

Finally, the development of polymerization reactions using the CuAAC reaction is a relatively unexplored area, despite the use of the reaction for many other purposes.⁴¹ The triazole adducts formed by the reaction are thermally and chemically stable⁴² and may produce materials with superior mechanical properties. Azide-olefin resists were extensively used in the microelectronics industry in the 1970s, a re-examination of that literature may suggest azide monomers safe for routine use.⁴³

Final remarks

While the pursuit of difficult synthetic chemistry has its place⁴⁴ and cannot always be avoided, its value as a goal in and of itself is questionable.^{42,45} This is as true in the field of material science as it is of pharmaceutical chemistry where the philosophy of click chemistry emerged. When material properties are the ultimate goal, very similar results can be produced from highly divergent approaches. For example synthetic polymers, mercury-silver amalgams, and nacre⁴⁶ have all been successfully utilized in dental restorations.

This thesis generally utilized well established reactions: organo-silanes were employed for generation of functionalized surfaces; the Michael addition was used for small molecule synthesis; and the Diels–Alder and CuAAC reactions formed the main body of the work. The ability to fall back on a significant body of research considerably aided both the development and understanding of the systems explored in thesis. Seldom was it necessary to resort to large numbers of experiments to locate the “Goldilocks regime” where reactions would function reliably. The Diels–Alder and CuAAC reactions are well suited to such an

approach and demonstrate that cycloadditions are well-understood, efficient, and modular reactions, and that these attributes enable the facile synthesis of polymeric materials with unique properties.

REFERENCES

- (1) Craven, J. M. Cross-linked Thermally Reversible Polymers Produced from Condensation Polymers with Pendant Furan Groups Cross-linked with Maleimides USPTO 3435003 1966.
- (2) Canary, S. A.; Stevens, M. P. *J. Polym. Sci. Part A* **1992**, *30*, 1755-1760.
- (3) Laita, H.; Boufi, S.; Gandini, A. *Eur. Polym. J.* **1997**, *33*, 1203-1211.
- (4) Gheneim, R.; Perez-Berumen, C.; Gandini, A. *Macromolecules* **2002**, *35*, 7246-7253.
- (5) Chen, X. X.; Dam, M. A.; Ono, K.; Mal, A.; Shen, H. B.; Nutt, S. R.; Sheran, K.; Wudl, F. *Science* **2002**, *295*, 1698-1702.
- (6) Chen, X. X.; Wudl, F.; Mal, A. K.; Shen, H. B.; Nutt, S. R. *Macromolecules* **2003**, *36*, 1802-1807.
- (7) Goiti, E.; Heatley, F.; Huglin, M. B.; Rego, J. M. *Eur. Polym. J.* **2004**, *40*, 1451-1460.
- (8) Liu, Y. L.; Hsieh, C. Y. *J. Polym. Sci. Pol. Chem.* **2006**, *44*, 905-913.
- (9) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652-2654.
- (10) Ondrus, V.; Fisera, L.; Bradac, V. *Arkivoc* **2001**, *2*, 8.
- (11) de Figueiredo, R. M.; Oczipka, P.; Frohlich, R.; Christmann, M. *Synthesis-Stuttgart* **2008**, 1316-1318.
- (12) Duffy, D. C.; McDonald, J. C.; Schueller, O. J. A.; Whitesides, G. M. *Anal. Chem.* **1998**, *70*, 4974-4984.
- (13) Burckel, D. B.; Wendt, J. R.; Ten Eyck, G. A.; Ginn, J. C.; Ellis, A. R.; Brener, I.; Sinclair, M. B. *Adv. Mater.* **2011**, *22*, 5053-5057.
- (14) Khademhosseini, A.; Langer, R. *Biomaterials* **2007**, *28*, 5087-5092.
- (15) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767-773.
- (16) Neckers, D. C. *Polym. Eng. Sci.* **1992**, *32*, 1481-1489.
- (17) Young, J. S.; Fox, S. R.; Anseth, K. S. *J. Manuf. Sci. Eng.-Trans. ASME* **1999**, *121*, 474-477.
- (18) Ito, H. In *Microlithography - Molecular Imprinting*; Springer-Verlag Berlin: Berlin, 2005; Vol. 172, p 37-245.
- (19) Fischer, J.; von Freymann, G.; Wegener, M. *Adv. Mater.*, *22*, 3578-3582.
- (20) Scott, T. F.; Kowalski, B. A.; Sullivan, A. C.; Bowman, C. N.; McLeod, R. R. *Science* **2009**, *324*, 913-917.
- (21) Guo, L. J. *Adv. Mater.* **2007**, *19*, 495-513.
- (22) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. *Nature Mater.* **2009**, *8*, 659-664.
- (23) Adzima, B. J.; Wagner, E.; Kloxin, C.; Bowman, C. N. *unpublished results*.
- (24) Murphy, E. B.; Bolanos, E.; Schaffner-Hamann, C.; Wudl, F.; Nutt, S. R.; Auad, M. L. *Macromolecules* **2008**, *41*, 5203-5209.
- (25) Ono, T.; Fujii, S.; Nobori, T.; Lehn, J. M. *Chem. Commun.* **2007**, 46-48.
- (26) Reutenauer, P.; Boul, P. J.; Lehn, J. M. *Eur. J. Org. Chem.* **2009**, 1691-1697.

- (27) Koehler, K.; Durackova, A.; Kloxin, C.; Bowman, C. N. *in preparation*.
- (28) Cordier, P.; Tournilhac, F.; Soulie-Ziakovic, C.; Leibler, L. *Nature* **2008**, *451*, 977-980.
- (29) Noro, A.; Matsushita, Y.; Lodge, T. P. *Macromolecules* **2008**, *41*, 5839-5844.
- (30) Noro, A.; Matsushita, Y.; Lodge, T. P. *Macromolecules* **2009**.
- (31) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem.-Int. Edit.* **2002**, *41*, 898-952.
- (32) Meldal, M. *Macromol. Rapid Commun.* **2008**, *29*, 1016-1051.
- (33) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 16793-16797.
- (34) Poloukhine, A. A.; Mbua, N. E.; Wolfert, M. A.; Boons, G.-J.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769-15776.
- (35) Orski, S. V.; Poloukhine, A. A.; Arumugam, S.; Mao, L.; Popik, V. V.; Locklin, J. J. *Am. Chem. Soc.* **2010**, *132*, 11024-11026.
- (36) Soriano del Amo, D.; Wang, W.; Jiang, H.; Besanceney, C.; Yan, A. C.; Levy, M.; Liu, Y.; Marlow, F. L.; Wu, P. *J. Am. Chem. Soc.* **2010**, *132*, 16893-16899.
- (37) Patten, T. E.; Matyjaszewski, K. *Adv. Mater.* **1998**, *10*, 901-915.
- (38) Tasdelen, M. A.; Yagci, Y. *Tetrahedron Lett.* **2010**, *51*, 6945-6947.
- (39) Xu, L. Q.; Yao, F.; Fu, G. D.; Shen, L. *Macromolecules* **2009**, *42*, 6385-6392.
- (40) Jakubowski, W.; Min, K.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 39-45.
- (41) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Macromolecules*, *43*, 8693-8702.
- (42) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Edit.* **2001**, *40*, 2004-2021.
- (43) Roffey, C. *Photogeneration of Reactive Species for UV Curing*; John Wiley and Sons: West Suffex, 1997.
- (44) Kingston, D. G. I. *Chem. Commun.* **2001**, 867-880.
- (45) Service, R. F. *Science* **1999**, *285*, 184-187.
- (46) Westbrook, P.; Marin, F. *Nature* **1998**, *392*, 861-862.

REFERENCES

- Adolf, D., J. E. Martin, et al. (1990). "Evolution of structure and viscoelasticity in an epoxy near the sol-gel transition." Macromolecules **23**(2): 527-531.
- Adzima, B. J., H. A. Aguirre, et al. (2008). "Rheological and Chemical Analysis of Reverse Gelation in a Covalently Cross-Linked Diels-Alder Polymer Network." Macromolecules **41**(23): 9112-9117.
- Adzima, B. J., Y. Tao, et al. (2011). "Spatial and temporal control of the alkyne-azide cycloaddition by photoinitiated Cu(II) reduction." Nature Chemistry **3**: 258–261.
- Ahmed, T. J., D. Stavrov, et al. (2006). "Induction welding of thermoplastic composites - An overview." Composites Part a-Applied Science and Manufacturing **37**(10): 1638-1651.
- Ajayaghosh, A. and S. J. George (2001). "First Phenylenevinylene Based Organogels: Self-Assembled Nanostructures via Cooperative Hydrogen Bonding and π -Stacking." Journal of the American Chemical Society **123**(21): 5148-5149.
- Anseth, K. S., S. M. Newman, et al. (1995). Polymeric dental composites: Properties and reaction behavior of multimethacrylate dental restorations. Biopolymers **Li. 122**: 177-217.
- Barner-Kowollik, C. and A. J. Inglis (2009). "Has Click Chemistry Lead to a Paradigm Shift in Polymer Material Design?" Macromolecular Chemistry and Physics **210**(12): 987-992.
- Baskin, J. M., J. A. Prescher, et al. (2007). "Copper-free click chemistry for dynamic in vivo imaging." Proceedings of the National Academy of Sciences of the United States of America **104**(43): 16793-16797.
- Benntt, C. W. (1912). "Photochemical reduction of copper sulphate." Journal of Physical Chemistry **16**(9): 782-785.

- Bergman, S. D. and F. Wudl (2008). "Mendable polymers." Journal of Materials Chemistry **18**(1): 41-62.
- Billmeyer (1984). Textbook of Polymer Science, John Wiley and Sons.
- Binder, W. H. and R. Sachsenhofer (2007). "'Click' chemistry in polymer and materials science." Macromolecular Rapid Communications **28**(1): 15-54.
- Boul, P. J., P. Reutenauer, et al. (2005). "Reversible Diels-Alder reactions for the generation of dynamic combinatorial libraries." Organic Letters **7**(1): 15-18.
- Bowman, C. N. and C. J. Kloxin (2008). "Toward an Enhanced Understanding and Implementation of Photopolymerization Reactions." Aiche Journal **54**(11): 2775-2795.
- Bozorth, R. M. (1978). Ferromagnetism. Piscataway, NJ, IEEE Press.
- Buettner, G. R. and B. A. Jurkiewicz (1996). "Catalytic metals, ascorbate and free radicals: Combinations to avoid." Radiation Research **145**(5): 532-541.
- Burckel, D. B., J. R. Wendt, et al. (2011). "Micrometer-Scale Cubic Unit Cell 3D Metamaterial Layers." Advanced Materials **22**(44): 5053-5057.
- Canary, S. A. and M. P. Stevens (1992). "Thermally reversible crosslinking of polystyrene via the furan-maleimide Diels-Alder reaction." Journal of Polymer Science Part A: Polymer Chemistry **30**(8): 1755-1760.
- Carruthers, W. (1990). Cycloaddition Reactions in Organic Synthesis. Elmsford, Pergamon Press.
- Chan, T. R., R. Hilgraf, et al. (2004). "Polytriazoles as copper(I)-stabilizing ligands in catalysis." Organic Letters **6**(17): 2853-2855.
- Chang, B. T. A., D. A. Dubois, et al. (1999). CARIVERSE resin: a thermally reversible network polymer for electronic applications. Electronic Components and Technology Conference, 1999. 1999 Proceedings. 49th.
- Chang, J. Y., S. K. Do, et al. (2001). "A sol-gel reaction of vinyl polymers based on thermally reversible urea linkages." Polymer **42**(18): 7589-7594.
- Chen, R. T., B. W. Muir, et al. (2010). "Fabrication of asymmetric "Janus" particles via plasma polymerization." Chemical Communications **46**(28): 5121-5123.

- Chen, X. X., M. A. Dam, et al. (2002). "A thermally re-mendable cross-linked polymeric material." Science **295**(5560): 1698-1702.
- Chen, X. X., F. Wudl, et al. (2003). "New thermally remendable highly cross-linked polymeric materials." Macromolecules **36**(6): 1802-1807.
- Cheng, J. Y., C. T. Rettner, et al. (2008). "Dense self-assembly on sparse chemical patterns: Rectifying and multiplying lithographic patterns using block copolymers." Advanced Materials **20**(16): 3155-3158.
- Chiou, B. S., R. J. English, et al. (1996). "Rheology and photo-cross-linking of thiol-ene polymers." Macromolecules **29**(16): 5368-5374.
- Chujo, Y., K. Sada, et al. (1990). "A novel nonionic hydrogel from 2-methyl-2-oxaline.4. Reversible gelation of polyoxazolines by means of Diels-Alder reaction." Macromolecules **23**(10): 2636-2641.
- Chung, C. M., Y. S. Roh, et al. (2004). "Crack healing in polymeric materials via photochemical [2+2] cycloaddition." Chemistry of Materials **16**(21): 3982-3984.
- Cohen, M. S., H. Hadjivassiliou, et al. (2007). "A clickable inhibitor reveals context-dependent autoactivation of p90 RSK." Nature Chemical Biology **3**(3): 156-160.
- Cordier, P., F. Tournilhac, et al. (2008). "Self-healing and thermoreversible rubber from supramolecular assembly." Nature **451**(7181): 977-980.
- Corten, C. C. and M. W. Urban (2009). "Repairing Polymers Using Oscillating Magnetic Field." Advanced Materials **21**(48): 5011-5015.
- Craven, J. M. (1966). Cross-linked Thermally Reversible Polymers Produced from Condensation Polymers with Pendant Furan Groups Cross-linked with Maleimides. USPTO. US, E.I. du Pont de Nemours and Company.
- Dag, A., H. Durmaz, et al. "An easy way to the preparation of multi-miktoarm star block copolymers via sequential double click reactions." Polymer Chemistry **1**(5): 621-623.
- de Figueiredo, R. M., P. Oczipka, et al. (2008). "Synthesis of 4-maleimidobutyric acid and related maleimides." Synthesis-Stuttgart(8): 1316-1318.
- de Gennes, P. G. (1976). "On a relation between percolation theory and the elasticity of gels." Le Journal de Physique-Letters **37**.
- de Gennes, P. G. (1979). Scaling Concepts in Polymer Physics.

- Decker, C. (2002). "Kinetic study and new applications of UV radiation curing." Macromolecular Rapid Communications **23**(18): 1067-1093.
- DeForest, C. A., B. D. Polizzotti, et al. (2009). "Sequential click reactions for synthesizing and patterning three-dimensional cell microenvironments." Nature Materials **8**(8): 659-664.
- Deng, G., C. Tang, et al. "Covalent Cross-Linked Polymer Gels with Reversible Solâ''Gel Transition and Self-Healing Properties." Macromolecules.
- Devaraj, N. K., P. H. Dinolfo, et al. (2006). "Selective Functionalization of Independently Addressed Microelectrodes by Electrochemical Activation and Deactivation of a Coupling Catalyst." Journal of the American Chemical Society **128**(6): 1794-1795.
- Devreux, F., J. P. Boilot, et al. (1993). "Crossover from scalar to vectorial percolation in silica gelation." Physical Review E **47**(4): 2689-2694.
- Dewar, M. J. S. and A. B. Pierini (1984). "Mechanism of the Diels-Alder reaction - studies of maleic-anhydride to furan and methyl furans." Journal of the American Chemical Society **106**(1): 203-208.
- Diels, O. and K. Alder (1928). "Synthesen in der hydroaromatischen Reihe." Liebig. Ann. Chem. **460**: 98.
- Duffy, D. C., J. C. McDonald, et al. (1998). "Rapid prototyping of microfluidic systems in poly(dimethylsiloxane)." Analytical Chemistry **70**(23): 4974-4984.
- Durand, D., M. Delsanti, et al. (1987). "Frequency dependence of viscoelastic properties of branched polymers near gelation threshold " Europhysics Letters **3**(3): 297-301.
- El-Sagheer, A. H. and T. Brown "Click chemistry with DNA." Chemical Society Reviews **39**(4): 1388-1405.
- Enami, Y., C. T. Derose, et al. (2007). "Hybrid polymer/sol-gel waveguide modulators with exceptionally large electro-optic coefficients." Nature Photonics **1**(3): 180-185.
- Engle, L. P. and K. B. Wagener (1993). "A review of thermally controlled covalent bond formation in polymer chemistry
" Journal of Macromolecular Science-Reviews in Macromolecular Chemistry and Physics **C33**(3): 239-257.
- Enns, J. B. and J. K. Gillham (1983). "Time temperature transformation (T³T) cure diagram - modeling the cure behavior of thermosets." Journal of Applied Polymer Science **28**(8): 2567-2591.

- Fairbanks, B. D., T. F. Scott, et al. (2009). "Thiol-Yne Photopolymerizations: Novel Mechanism, Kinetics, and Step-Growth Formation of Highly Cross-Linked Networks." Macromolecules **42**(1): 211-217.
- Ferry, J. D. (1980). Viscoelastic Properties of Polymers, John Wiley and Sons.
- Fischer, J., G. von Freymann, et al. "The Materials Challenge in Diffraction-Unlimited Direct-Laser-Writing Optical Lithography." Advanced Materials **22**(32): 3578-3582.
- Flory, P. J. (1941). "Molecular Size Distribution in Three Dimensional Polymers. I. Gelation." J. Am. Chem. Soc. **63**(11): 3083-3090.
- Flory, P. J. (1941). "Molecular Size Distribution in Three Dimensional Polymers. II. Trifunctional Branching Units." J. Am. Chem. Soc. **63**(11): 3091-3096.
- Flory, P. J. (1941). "Molecular Size Distribution in Three Dimensional Polymers. III. Tetrafunctional Branching Units." J. Am. Chem. Soc. **63**(11): 3096-3100.
- Flory, P. J. (1953). Principles of Polymer Chemistry. Ithaca, Cornell University Press.
- Fodor, S. P. A., J. L. Read, et al. (1991). "Light-directed, spatially addressable parallel chemical synthesis." Science **251**(4995): 767-773.
- Fringuelli, F. and A. Taticchi (2002). The Diels-Alder Reaction: Selected Practical Methods.
- Gagne, R. R., J. L. Allison, et al. (1977). "Models for copper-containing proteins - structure of novel 5-coordinate copper(I) complexes." Journal of the American Chemical Society **99**(22): 7170-7178.
- Gandini, A. and M. N. Belgacem (1997). "Furans in polymer chemistry." Progress in Polymer Science **22**(6): 1203-1379.
- Gheneim, R., C. Perez-Berumen, et al. (2002). "Diels-Alder reactions with novel polymeric dienes and dienophiles: Synthesis of reversibly cross-linked elastomers." Macromolecules **35**(19): 7246-7253.
- Goiti, E., F. Heatley, et al. (2004). "Kinetic aspects of the Diels-Alder reaction between poly(styrene-co-furfuryl methacrylate) and bismaleimide." European Polymer Journal **40**(7): 1451-1460.
- Gousse, C. and A. Gandini (1999). "Diels-Alder polymerization of difurans with bismaleimides." Polymer International **48**(8): 723-731.

- Gousse, C., A. Gandini, et al. (1998). "Application of the Diels-Alder reaction to polymers bearing furan moieties. 2. Diels-Alder and retro-Diels-Alder reactions involving furan rings in some styrene copolymers." Macromolecules **31**(2): 314-321.
- Guo, L., R. H. Colby, et al. (2003). "Physical gelation of gelatin studied with rheo-optics." Macromolecules **36**(26): 10009-10020.
- Guo, L. J. (2007). "Nanoimprint lithography: Methods and material requirements." Advanced Materials **19**(4): 495-513.
- Haakey, M. C., S. J. Holmes, et al. (2000). Frequency doubling hybrid photoresist having negative and positive tone. USPTO. US, International Business Machines Corporation.
- Hansen, T. S., A. E. Dugaard, et al. (2009). "Spatially Selective Functionalization of Conducting Polymers by "Electroclick" Chemistry." Advanced Materials **21**(44): 4483-4486.
- Heath, W. H., F. Palmieri, et al. (2008). "Degradable cross-linkers and strippable imaging materials for step-and-flash imprint lithography." Macromolecules **41**(3): 719-726.
- Higaki, Y., H. Otsuka, et al. (2006). "A thermodynamic polymer cross-linking system based on radically exchangeable covalent bonds." Macromolecules **39**(6): 2121-2125.
- Himo, F., T. Lovell, et al. (2005). "Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates." Journal of the American Chemical Society **127**(1): 210-216.
- Hodgson, D. F. and E. J. Amis (1991). "Dynamic viscoelasticity during sol-gel reactions." Journal of Non-Crystalline Solids **131**: 913-920.
- Hopewell, J. L., D. J. T. Hill, et al. (1998). "Electron spin resonance study of the homopolymerization of aromatic bismaleimides." Polymer **39**(23): 5601-5607.
- Hoyle, C. E. and C. N. Bowman (2010). "Thiol-Ene Click Chemistry." Angewandte Chemie-International Edition **49**(9): 1540-1573.
- Hoyle, C. E., T. Y. Lee, et al. (2004). "Thiol-enes: Chemistry of the past with promise for the future." Journal of Polymer Science Part a-Polymer Chemistry **42**(21): 5301-5338.
- Hoyle, C. E., A. B. Lowe, et al. "Thiol-click chemistry: a multifaceted toolbox for small molecule and polymer synthesis." Chemical Society Reviews **39**(4): 1355-1387.

- Huisgen, R. (1963). "1,3-Dipolar Cycloadditions. Past and Future." Angewandte Chemie International Edition in English **2**(10): 565-598.
- Huisgen, R. (1963). "Kinetics and Mechanism of 1,3-Dipolar Cycloadditions." Angewandte Chemie International Edition in English **2**(11): 633-645.
- Iha, R. K., K. L. Wooley, et al. (2009). "Applications of Orthogonal "Click" Chemistries in the Synthesis of Functional Soft Materials." Chemical Reviews **109**(11): 5620-5686.
- Ikuta, K. and K. Hirowatari (1993). Real three dimensional micro fabrication using stereo lithography and metal molding. Micro Electro Mechanical Systems, 1993, MEMS '93, Proceedings An Investigation of Micro Structures, Sensors, Actuators, Machines and Systems. IEEE.
- Imai, Y., H. Itoh, et al. (2000). "Thermally reversible IPN organic-inorganic polymer hybrids utilizing the Diels-Alder reaction." Macromolecules **33**(12): 4343-4346.
- Inoue, K., M. Yamashiro, et al. (2005). "Rewritable shape-memory polylactic acid fabricated by thermo-reversible cross-linking based on the Diels-Alder reaction." Kobunshi Ronbunshu **62**(6): 261-267.
- Israelachvili, J. (2002). Intermolecular and Surface Forces. London, Academic Press.
- Ito, H. (2005). Chemical amplification resists for microlithography. Microlithography - Molecular Imprinting. Berlin, Springer-Verlag Berlin. **172**: 37-245.
- Ito, H. and C. G. Willson (1983). "CHEMICAL AMPLIFICATION IN THE DESIGN OF DRY DEVELOPING RESIST MATERIALS." Polymer Engineering and Science **23**(18): 1012-1018.
- Iyer, S. R. and P. K. Wong (1998). Anisotropic conductive adhesives compositions USPTO. US, Shell Oil Company, Houston Tx.
- Iyer, S. R. and P. K. Wong (1999). Die attach adhesive compositions USPTO. US, Shell Oil Company.
- Jakubowski, W., K. Min, et al. (2006). "Activators regenerated by electron transfer for atom transfer radical polymerization of styrene." Macromolecules **39**(1): 39-45.
- Jen, K.-Y., J. Luo, et al. (2008). Thermally reversibly crosslinkable polymer as cladding for electro-optic devices. USPTO. US, University of Washington.

- Jockusch, S. and N. J. Turro (1998). "Phosphinoyl radicals: Structure and reactivity. A laser flash photolysis and time-resolved ESR investigation." Journal of the American Chemical Society **120**(45): 11773-11777.
- Johnson, J. A., M. G. Finn, et al. (2008). "Construction of linear polymers, dendrimers, networks, and other polymeric architectures by copper-catalyzed azide-alkyne cycloaddition "Click" chemistry." Macromolecular Rapid Communications **29**(12-13): 1052-1072.
- Jones, G. O. and K. N. Houk (2008). "Predictions of substituent effects in thermal azide 1,3-dipolar cycloadditions: Implications for dynamic combinatorial (reversible) and click (irreversible) chemistry." Journal of Organic Chemistry **73**(4): 1333-1342.
- Jones, M. W., G. Mantovani, et al. (2009). "Phosphine-mediated one-pot thiol-ene "click" approach to polymer-protein conjugates." Chemical Communications(35): 5272-5274.
- Jurczak, J., A. L. Kawczynski, et al. (1985). "Stability of cycloadducts obtained by high-pressure Diels-Alder reaction between 3,4-dimethoxyfuran and 1,4-benzoquinones - kinetic-studies of retro-Diels -Alder reaction." Journal of Organic Chemistry **50**(7): 1106-1107.
- Kamplain, J. W. and C. W. Bielawski (2006). "Dynamic covalent polymers based upon carbene dimerization." Chemical Communications(16): 1727-1729.
- Kasuga, Y., M. Ito, et al. (2009). "Kinetic Study on Huisgen Reaction Catalyzed by Copper (1): Triazol Formation from Water-Soluble Alkyne and Alkyl Azide " Heterocycles **78**(4): 983-997.
- Kateda, K. and Y. Iwakura (1968). "Reduction of cupric ion to zero valent metal by benzophenone ketyl radical." Bulletin of the Chemical Society of Japan **41**(1): 268.
- Kawata, S., H. B. Sun, et al. (2001). "Finer features for functional microdevices - Micromachines can be created with higher resolution using two-photon absorption." Nature **412**(6848): 697-698.
- Khademhosseini, A. and R. Langer (2007). "Microengineered hydrogels for tissue engineering." Biomaterials **28**(34): 5087-5092.
- Kim, T. D., J. Luo, et al. (2006). "Ultralarge and Thermally Stable Electro-optic Activities from Diels-Alder Crosslinkable Polymers Containing Binary Chromophore Systems." Advanced Materials **18**(22): 3038-3042.

- Kingston, D. G. I. (2001). "Taxol, a molecule for all seasons." Chemical Communications(10): 867-880.
- Kittel, C. (1996). Introduction to Solid State Physics. New York, John Wiley and Sons, Inc.
- Kloosterboer, J. G. (1988). "Network formation by chain-crosslinking photopolymerization and its application in electronics." Advances in Polymer Science **84**: 1-61.
- Kloxin, A. M., A. M. Kasko, et al. (2009). "Photodegradable Hydrogels for Dynamic Tuning of Physical and Chemical Properties." Science **324**(5923): 59-63.
- Kloxin, C. J., T. F. Scott, et al. (2010). "Covalent Adaptable Networks (CANs): A Unique Paradigm in Cross-Linked Polymers." Macromolecules **43**(6): 2643-2653.
- Koehler, K., A. Durackova, et al. "Kinetic and thermodynamic measurements for the facile property prediction of Diels-Alder based materials." *In preparation*
- Koh, W.-G., A. Revzin, et al. (2002). "Poly(ethylene glycol) Hydrogel Microstructures Encapsulating Living Cells." Langmuir **18**(7): 2459-2462.
- Kolb, H. C., M. G. Finn, et al. (2001). "Click chemistry: Diverse chemical function from a few good reactions." Angewandte Chemie-International Edition **40**(11): 2004-2021.
- Krysak, M. and C. K. Ober (2010). "Photoacid generator-attached molecular glass photoresists." PMSE Preprints.
- Lairez, D., M. Adam, et al. (1992). "Rheological behavior of an epoxy amine system near the gel point." Macromolecules **25**(1): 286-289.
- Lairez, D., M. Adam, et al. (1992). "Do local motions influence rheological properties near the gelation threshold." Progress in Colloid and Polymer Science **90**: 37-42.
- Laita, H., S. Boufi, et al. (1997). "The application of the Diels-Alder reaction to polymers bearing furan moieties .1. Reactions with maleimides." European Polymer Journal **33**(8): 1203-1211.
- LeBaron, P. C., Z. Wang, et al. (1999). "Polymer-layered silicate nanocomposites: an overview." Applied Clay Science **15**(1-2): 11-29.
- Lee, S., K. Jen, et al. (2009). "Materials modeling and development for use in double-exposure lithography applications." Journal of Micro-Nanolithography Mems and Moems **8**(1): 11.

- Lendlein, A., H. Y. Jiang, et al. (2005). "Light-induced shape-memory polymers." Nature **434**(7035): 879-882.
- Litter, M. I. (1999). "Heterogeneous photocatalysis - Transition metal ions in photocatalytic systems." Applied Catalysis B-Environmental **23**(2-3): 89-114.
- Liu, Y. L. and Y. W. Chen (2007). "Thermally reversible cross-linked polyamides with high toughness and self-repairing ability from maleimide- and furan-functionalized aromatic polyamides." Macromolecular Chemistry and Physics **208**(2): 224-232.
- Liu, Y. L. and C. Y. Hsieh (2006). "Crosslinked epoxy materials exhibiting thermal remendability and removability from multifunctional maleimide and furan compounds." Journal of Polymer Science Part a-Polymer Chemistry **44**(2): 905-913.
- Long, B. K., B. K. Keitz, et al. (2007). "Materials for step and flash imprint lithography (S-FIL (R))." Journal of Materials Chemistry **17**(34): 3575-3580.
- Long, D. A., K. Unal, et al. (2007). "Localized "Click" chemistry through dip-pen nanolithography." Advanced Materials **19**(24): 4471-4473.
- Lu, H., J. W. Stansbury, et al. (2004). "Towards the elucidation of shrinkage stress development and relaxation in dental composites." Dental Materials **20**(10): 979-986.
- Luo, L. and C. D. Frisbie (2010). "Length-Dependent Conductance of Conjugated Molecular Wires Synthesized by Stepwise Click Chemistry." Journal of the American Chemical Society **132**(26): 8854-8855.
- Lusignan, C. P., T. H. Mourey, et al. (1995). "Viscoelasticity of randomly branched polymers in the critical percolation class." Physical Review E **52**(6): 6271-6280.
- Lusignan, C. P., T. H. Mourey, et al. (1999). "Viscoelasticity of randomly branched polymers in the vulcanization class." Physical Review E **60**(5): 5657-5669.
- Macpherson, L. J., A. E. Dubin, et al. (2007). "Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines." Nature **445**(7127): 541-545.
- Maier, G. (1996). "Polymers by 1,3-dipolar cycloaddition reactions: the "criss-cross" cycloaddition." Macromolecular Chemistry and Physics **197**(10): 3067-3090.
- Malkoch, M., R. Vestberg, et al. (2006). "Synthesis of well-defined hydrogel networks using Click chemistry." Chemical Communications(26): 2774-2776.
- March, J. (1992). Advanced Organic Chemistry.

- Martens, P. J., S. J. Bryant, et al. (2003). "Tailoring the Degradation of Hydrogels Formed from Multivinyl Poly(ethylene glycol) and Poly(vinyl alcohol) Macromers for Cartilage Tissue Engineering." Biomacromolecules **4**(2): 283-292.
- Matyjaszewski, K. and N. V. Tsarevsky (2009). "Nanostructured functional materials prepared by atom transfer radical polymerization." Nature Chemistry **1**(4): 276-288.
- Matyjaszewski, K., N. V. Tsarevsky, et al. (2007). "Role of Cu-0 in controlled/"living" radical polymerization." Macromolecules **40**(22): 7795-7806.
- McElhanon, J. R., E. M. Russick, et al. (2002). "Removable foams based on an epoxy resin incorporating reversible Diels-Alder adducts." Journal of Applied Polymer Science **85**(7): 1496-1502.
- McNaught, A. D. and A. Wilkinson (1997). IUPAC. Compendium of Chemical Terminology. Oxford, Blackwell Scientific Publications.
- Meldal, M. (2008). "Polymer "Clicking" by CuAAC reactions." Macromolecular Rapid Communications **29**(12-13): 1016-1051.
- Michon, C., G. Cuvelier, et al. (1993). "Concentration-dependence of the critical viscoelastic properties of gelatin at the gel point." Rheologica Acta **32**(1): 94-103.
- Miyagawa, T., M. Shimizu, et al. (2005). "Six-membered cyclic carbonate having styrene moiety as a chemically recyclable monomer. Construction of novel cross-linking-decross-linking system of network polymers." Macromolecules **38**(19): 7944-7949.
- Murphy, E. B., E. Bolanos, et al. (2008). "Synthesis and Characterization of a Single-Component Thermally Remendable Polymer Network: Staudinger and Stille Revisited." Macromolecules **41**(14): 5203-5209.
- Neckers, D. C. (1992). "Architecture with photopolymerization." Polymer Engineering and Science **32**(20): 1481-1489.
- Nijenhuis, K. t. (1997). "Thermoreversible networks - Viscoelastic properties and structure of gels." Advances in Polymer Science **130**: 1+.
- Noro, A., Y. Matsushita, et al. (2008). "Thermoreversible supramacromolecular ion gels via hydrogen bonding." Macromolecules **41**(15): 5839-5844.
- Noro, A., Y. Matsushita, et al. (2009). "Gelation Mechanism of Thermoreversible Supramacromolecular Ion Gels via Hydrogen Bonding." Macromolecules.
- Odian, G. (1991). Principles of Polymerization. New York, John Wiley and Sons, Inc.

- Ofir, Y., I. W. Moran, et al. (2010). "Nanoimprint Lithography for Functional Three-Dimensional Patterns." Advanced Materials **22**(32): 3608-3614.
- Ondrus, V., L. Fisera, et al. (2001). "On the use of water as a solvent - simple and short one-step synthesis of maleimides." Arkivoc **2**: 8.
- Ono, T., S. Fujii, et al. (2007). "Soft-to-hard transformation of the mechanical properties of dynamic covalent polymers through component incorporation." Chemical Communications(1): 46-48.
- Ono, T., T. Nobori, et al. (2005). "Dynamic polymer blends - component recombination between neat dynamic covalent polymers at room temperature." Chemical Communications(12): 1522-1524.
- Orski, S. V., A. A. Poloukhine, et al. (2010). "High Density Orthogonal Surface Immobilization via Photoactivated Copper-Free Click Chemistry." Journal of the American Chemical Society **132**(32): 11024-11026.
- Oshima, A., K. Abe, et al. (1976). "United States Patent No. 3978178."
- Padwa, A. (1976). "Intramolecular 1,3-dipolar Cycloaddition Reactions." Angewandte Chemie-International Edition in English **15**(3): 123-136.
- Paine, A. J., G. K. Hamer, et al. (1998). Phase change ink compositions, Xerox Corporation.
- Park, J. S., K. Takahashi, et al. (2008). "Towards Development of a Self-Healing Composite using a Mendable Polymer and Resistive Heating." Journal of Composite Materials **42**(26): 2869-2881.
- Patten, T. E. and K. Matyjaszewski (1998). "Atom transfer radical polymerization and the synthesis of polymeric materials." Advanced Materials **10**(12): 901-915.
- Paxton, W. F., J. M. Spruell, et al. (2009). "Heterogeneous Catalysis of a Copper-Coated Atomic Force Microscopy Tip for Direct-Write Click Chemistry." Journal of the American Chemical Society **131**(19): 6692-6694.
- Pazos, J. (1975). Polymers Coupled by Nitroso Groups USPTO. US.
- Peng, W., K. F. Alina, et al. (2004). "Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligation of Azides and Alkynes." Angewandte Chemie International Edition **43**(30): 3928-3932.

- Poloukhine, A. A., N. E. Mbu, et al. (2009). "Selective Labeling of Living Cells by a Photo-Triggered Click Reaction." Journal of the American Chemical Society **131**(43): 15769-15776.
- Qin, A., J. W. Y. Lam, et al. "Click Polymerization: Progresses, Challenges, and Opportunities." Macromolecules **43**(21): 8693-8702.
- Qin, D., Y. N. Xia, et al. (1996). "Rapid prototyping of complex structures with feature sizes larger than 20 μ m." Advanced Materials **8**(11): 917-919.
- Quemener, D., T. P. Davis, et al. (2006). "RAFT and click chemistry: A versatile approach to well-defined block copolymers." Chemical Communications(48): 5051-5053.
- Reddy, P. Y., S. Kondo, et al. (1997). "Lewis acid and hexamethyldisilazane-promoted efficient synthesis of N-alkyl- and N-arylimide derivatives." Journal of Organic Chemistry **62**(8): 2652-2654.
- Reutenauer, P., P. J. Boul, et al. (2009). "Dynamic Diels-Alder Reactions of 9,10-Dimethylantracene: Reversible Adduct Formation, Dynamic Exchange Processes and Thermal Fluorescence Modulation." European Journal of Organic Chemistry(11): 1691-1697.
- Ribeiro, A. C. F., M. A. Esteso, et al. (2005). "Diffusion Coefficients of Copper Chloride in Aqueous Solutions at 298.15 K and 310.15 K." Journal of Chemical & Engineering Data **50**(6): 1986-1990.
- Ritter, S. C. and B. Konig (2006). "Signal amplification and transduction by photo-activated catalysis." Chemical Communications(45): 4694-4696.
- Rodionov, V. O., S. I. Presolski, et al. (2007). "Ligand-accelerated Cu-catalyzed azide-alkyne cycloaddition: A mechanistic report." Journal of the American Chemical Society **129**(42): 12705-12712.
- Rodionov, V. O., V. V. Fokin, V., et al. (2005). "Mechanism of the Ligand-Free Cu(1)-Catalyzed Azide-Alkyne Cycloaddition Reaction." Angewandte Chemie International Edition **44**(15): 2210-2215.
- Roffey, C. (1997). Photogeneration of Reactive Species for UV Curing. West Suffex, John Wiley and Sons.
- Rostovtsev, V. V., L. G. Green, et al. (2002). "A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes." Angewandte Chemie-International Edition **41**(14): 2596-2599.

- Rowan, S. J., S. J. Cantrill, et al. (2002). "Dynamic covalent chemistry." Angewandte Chemie-International Edition **41**(6): 898-952.
- Rozkiewicz, D. I., D. Janczewski, et al. (2006). "'Click' chemistry by microcontact printing." Angewandte Chemie-International Edition **45**(32): 5292-5296.
- Rubenstein, M., R. H. Colby, et al., Eds. (1989). Dynamic Scaling for Polymer Gelation. Space-Time Organization in Macromolecular Fluids. Berlin, Springer-Verlag.
- Rulisek, L., P. Sebek, et al. (2005). "An experimental and theoretical study of stereoselectivity of furan-maleic anhydride and furan-maleimide Diels-Alder reactions." Journal of Organic Chemistry **70**(16): 6295-6302.
- Sakamoto, M., M. Fujistuka, et al. (2009). "Light as a construction tool of metal nanoparticles: Synthesis and mechanism." Journal of Photochemistry and Photobiology C-Photochemistry Reviews **10**(1): 33-56.
- Sakamoto, M., T. Tachikawa, et al. (2008). "Three-Dimensional Writing of Copper Nanoparticles in a Polymer Matrix with Two-Color Laser Beams." Chemistry of Materials **20**(6): 2060-2062.
- Sanyal, A. "Diels-Alder Cycloaddition-Cycloreversion: A Powerful Combo in Materials Design." Macromolecular Chemistry and Physics **211**(13): 1417-1425.
- Scanlan, J. C. and H. H. Winter (1991). "Composition dependence of the viscoelasticity of end-linked poly(dimethylsiloxane) at the gel point." Macromolecules **24**(1): 47-54.
- Schoch, J., M. Wiessler, et al. (2010). "Post-Synthetic Modification of DNA by Inverse-Electron-Demand Diels Alder Reaction." Journal of the American Chemical Society **132**(26): 8846-8847.
- Scott, T. F., B. A. Kowalski, et al. (2009). "Two-Color Single-Photon Photoinitiation and Photoinhibition for Subdiffraction Photolithography." Science **324**(5929): 913-917.
- Scott, T. F., A. D. Schneider, et al. (2005). "Photoinduced plasticity in cross-linked polymers." Science **308**(5728): 1615-1617.
- Sershen, S. R., G. A. Mensing, et al. (2005). "Independent optical control of microfluidic valves formed from optomechanically responsive nanocomposite hydrogels." Advanced Materials **17**(11): 1366-1368.
- Service, R. F. (1999). "Race for Molecular Summits." Science **285**(5425): 184-187.

- Shi, Z., S. Hau, et al. (2007). "Highly Efficient Diels-Alder Crosslinkable Electro-Optic Dendrimers for Electric-Field Sensors." Advanced Functional Materials **17**(14): 2557-2563.
- Simmons, M. G., C. L. Merrill, et al. (1980). "The (bis-2,6-[1-(2-imidazol-4-ylethylimino)ethyl]pyridine)copper(i) cation - a synthetic cu-1 oxygen carrier in solution as a potential model for oxyhemocyanin." Journal of the Chemical Society-Dalton Transactions(10): 1827-1837.
- Small, J. H., D. A. Loy, et al. (2001). Method of making thermally removable polymeric encapsulants. USPTO, Sandia Corporation.
- Soriano del Amo, D., W. Wang, et al. (2010). "Biocompatible Copper(I) Catalysts for in Vivo Imaging of Glycans." Journal of the American Chemical Society **132**(47): 16893-16899.
- Spruell, J. M., B. A. Sheriff, et al. (2008). "Heterogeneous Catalysis through Microcontact Printing." Angewandte Chemie-International Edition **47**(51): 9927-9932.
- Stern, M. D. and A. V. Tobolsky (1946). "Stress - time - temperature relations in polysulfide rubbers." Journal of Applied Physics **17**(5): 406-406.
- Stewart, M. D., H. V. Tran, et al. (2002). "Acid catalyst mobility in resist resins." Journal of Vacuum Science & Technology B **20**(6): 2946-2952.
- Stockmayer, W. H. (1943). "Theory of Molecular Size Distribution and Gel Formation in Branched-Chain Polymers." The Journal of Chemical Physics **11**(2): 45-55.
- Stockmayer, W. H. (1944). "Theory of Molecular Size Distribution and Gel Formation in Branched Polymers II. General Cross Linking." The Journal of Chemical Physics **12**(4): 125-131.
- Sumerlin, B. S. and A. P. Vogt (2009). "Macromolecular Engineering through Click Chemistry and Other Efficient Transformations." Macromolecules.
- Suwanwatana, W., S. Yarlagadda, et al. (2006). "Influence of particle size on hysteresis heating behavior of nickel particulate polymer films." Composites Science and Technology **66**(15): 2825-2836.
- Szalai, M. L., D. V. McGrath, et al. (2007). "Dendrimers based on thermally reversible furan-maleimide Diels-Alder adducts." Macromolecules **40**(4): 818-823.
- Tasdelen, M. A. and Y. Yagci (2010). "Light-induced copper(I)-catalyzed click chemistry." Tetrahedron Letters **51**(52): 6945-6947.

- Tian, Q., Y. C. Yuan, et al. (2009). "A thermally remendable epoxy resin." Journal of Materials Chemistry **19**(9): 1289-1296.
- Toohey, K. S., N. R. Sottos, et al. (2007). "Self-healing materials with microvascular networks." Nature Materials **6**(8): 581-585.
- Tornøe, C. W., C. Christensen, et al. (2002). "Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides." The Journal of Organic Chemistry **67**(9): 3057-3064.
- Tsarevsky, N. V., W. A. Braunecker, et al. (2007). "Electron transfer reactions relevant to atom transfer radical polymerization." Journal of Organometallic Chemistry **692**(15): 3212-3222.
- Urabe, H., K. Wakasa, et al. (1990). "Application of multifunctional base monomer to dental composite resins." Journal of Materials Science-Materials in Medicine **1**(3): 163-170.
- Wagener, K. B. and L. P. Engle (1991). "Thermally reversible polymer linkages .3. Covalently cross-linked poly(azlactone)." Macromolecules **24**(26): 6809-6815.
- Wagener, K. B. and M. A. Murla (1989). Thermally reversible urethanes. American Chemical Society, Polymer Preprints, Division of Polymer Chemistry, ACS. **30**: 287-288.
- Wang, J.-S. and K. Matyjaszewski (1995). "'Living"/Controlled Radical Polymerization. Transition-Metal-Catalyzed Atom Transfer Radical Polymerization in the Presence of a Conventional Radical Initiator." Macromolecules **28**(22): 7572-7573.
- Wang, Q., T. R. Chan, et al. (2003). "Bioconjugation by Copper(I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition." Journal of the American Chemical Society **125**(11): 3192-3193.
- Westbroek, P. and F. Marin (1998). "A marriage of bone and nacre." Nature **392**(6679): 861-862.
- White, S. R., N. R. Sottos, et al. (2001). "Autonomic healing of polymer composites." Nature **409**(6822): 794-797.
- Winter, H. H. (1987). "Can the Gel Point of a Cross-linking Polymer be Detected by the G'-G" Crossover." Polymer Engineering and Science **27**(22): 1698-1702.
- Wool, R. P. (2008). "Self-healing materials: a review." Soft Matter **4**(3): 400-418.

- Xu, L. Q., F. Yao, et al. (2009). "Simultaneous "Click Chemistry" and Atom Transfer Radical Emulsion Polymerization and Prepared Well-Defined Cross-Linked Nanoparticles." Macromolecules **42**(17): 6385-6392.
- Young, J. S., S. R. Fox, et al. (1999). "A novel device for producing three-dimensional objects." Journal of Manufacturing Science and Engineering-Transactions of the Asme **121**(3): 474-477.
- Yurke, B., D. C. Lin, et al. (2006). Use of DNA nanodevices in modulating the mechanical properties of polyacrylamide gels. DNA Computing. **3892**: 417-426.
- Zhan, W., G. H. Seong, et al. (2002). "Hydrogel-Based Microreactors as a Functional Component of Microfluidic Systems." Analytical Chemistry **74**(18): 4647-4652.
- Zhang, Y., A. A. Broekhuis, et al. (2009). "Thermally Self-Healing Polymeric Materials: The Next Step to Recycling Thermoset Polymers?" Macromolecules **42**(6): 1906-1912.
- Zhou, W., S. M. Kuebler, et al. (2002). "An Efficient Two-Photon-Generated Photoacid Applied to Positive-Tone 3D Microfabrication." Science **296**(5570): 1106-1109.

APPENDIX A: Supplement to the Rheological and chemical analysis of reverse gelation in a Diels—Alder polymer network

REACTION MODEL

For the non-diffusion controlled regime a simple model assuming a second order reaction for the forward reaction and first order behavior for the retro-reaction can be expected to describe the cure kinetics. The rate of consumption of furan, or maleimide, $d[F]/dt$ is then given as,

$$\frac{d[F]}{dt} = -k_f[F][M] + k_r[A], \quad (\text{S-1})$$

where k_f and k_r are the forward and reverse rate constants, respectively and $[F]$, $[M]$, and $[A]$ the concentrations of furan, maleimide, and the adduct, respectively. Assuming a stoichiometric mixture of furan and maleimide and applying the definition of conversion, $[F] = F_0(1-x)$, gives

$$\frac{dx}{dt} = k_f F_0 (1-x)^2 - k_r x, \quad (\text{S-2})$$

this can be rearranged to yield,

$$\int dt = \int \frac{dx}{k_f F_0 (1-x)^2 - k_r x}. \quad (\text{S-3})$$

The forward and reverse rate coefficients can be related through the equilibrium constant, $K = k_f / k_r$, and integration of eq. (S-3) gives the complex form,

$$t = \frac{2}{i \cdot k_r \sqrt{4KF_0 + 1}} \left[\arctan \left(\frac{2KF_0(x-1)-1}{i \cdot \sqrt{4KF_0 + 1}} \right) + \arctan \left(\frac{(2KF_0 + 1)}{i \cdot \sqrt{4KF_0 + 1}} \right) \right], \quad (\text{S-4})$$

which through the identity,

$$\arctan(y) = \frac{i}{2} \left[\ln \left(\frac{1-i \cdot y}{1+i \cdot y} \right) \right], \quad (\text{S-5})$$

the imaginary number, i , can be eliminated to give,

$$t = \frac{1}{k_r \sqrt{4KF_0 + 1}} \ln \left(\frac{\left[1 - \frac{2KF_0(x-1)-1}{\sqrt{4KF_0 + 1}} \right] \left[1 - \frac{2KF_0 + 1}{\sqrt{4KF_0 + 1}} \right]}{\left[1 + \frac{2KF_0(x-1)-1}{\sqrt{4KF_0 + 1}} \right] \left[1 + \frac{2KF_0 + 1}{\sqrt{4KF_0 + 1}} \right]} \right). \quad (\text{S-6})$$

A regression of the isothermal cure data from Figure 1(a) to eq. (S-6) allows the rate constant, k_r , to be determined in the temperature range from 25 to 80°C, as shown in Figure S-1. An extrapolation of the equilibrium constant to 25°C is necessary, as diffusion prevents measurement of that value. To avoid deviation from the effects of diffusion the data was fit only to 50% conversion, although past 50% conversion the fit behaves well for the 45, 60, and 80°C curves. However, as expected the fit of the 25°C cure shows deviation.

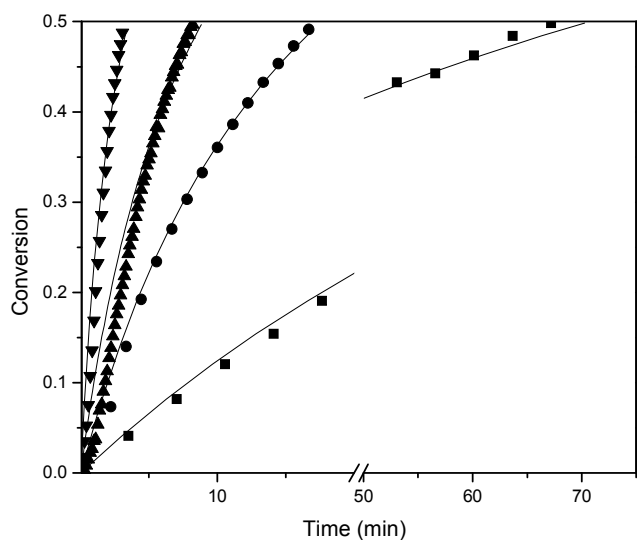


Figure S-1. Plot of the conversion versus time, lines represent fits to eq. (S-6). Isothermal cures were measured at 25 (■), 45 (●), 60 (▲), and 80 (▼)°C.

EXPERIMENTAL INFORMATION

Materials

Pentaerythritol propoxylate triacrylate (PPTA), 1,1'-(methylenedi-4,1-phenylene) bismaleimide (DPBM), furfuryl mercaptan, triethyl amine, and dichloromethane were obtained from Sigma-Aldrich and used without further preparation.

Synthesis of pentaerythritol propoxylate tris(3-(furfurylthiol)propionate) (PPTF).

To a mixture of 10.0 g (0.019 mol) of PPTA and 7.1 g (0.063 mol) of furfuryl mercaptan, a catalytic amount of triethyl amine was added, heated to 40°C, and allowed to react for 24 hours while stirring. The triethylamine and residual furfuryl mercaptan were removed under vacuum (0.2 mm Hg) at 45°C. Absence of peaks in the ¹H-NMR spectrum of the product due to residual acrylate (6.35, 6.06, and 5.82 ppm) or thiol (1.91 ppm) confirmed complete reaction and subsequent purification of PPTF.

Polymer Synthesis.

Polymer samples were prepared by combining PPTF and DPBM at a 1:1 furan to maleimide ratio. The material was briefly heated (less than 5 minutes) to $\sim 155^{\circ}\text{C}$ to melt the DPBM, and mixed until homogeneous. Upon cooling, a glassy yellow solid, insoluble in common organic solvents, was formed. The solid material visibly reverted to a liquid upon heating to $\sim 110^{\circ}\text{C}$.

FTIR Spectroscopy

Spectroscopic studies were performed with a Nicolet Magna 750 series II Fourier-transform infrared (FTIR) spectrometer equipped with a MCT detector and a horizontal transmission temperature-controlled stage (accurate to 0.1°C). Samples for IR spectroscopy were produced by casting a thin film of a freshly prepared solution of PPTF and DPBM in dichloromethane (at a 1:1 furan to maleimide functional group stoichiometric ratio) onto a NaCl crystal and rapidly evaporating the solvent under vacuum. Typically, less than three minutes elapsed between mixing and the initial spectra collection. Reaction during the sample preparation was assumed to be negligible as the DA reaction between furan and maleimide proceeds slowly at ambient temperature. The number of scans per spectrum (between 16 and 512) was adjusted based on the reaction rate. Conversion of the furan and maleimide functionalities was evaluated by monitoring the evolution of the furan peak area, centered at 1010 cm^{-1} , and the maleimide peak area, centered at 690 cm^{-1} .^{1,2}

Rheometry

Rheological measurements were performed using an ARES rheometer (TA Instruments), configured with a parallel-plate geometry. The lower fixture incorporated a Peltier plate, providing temperature control, while the upper fixture was equipped with a poly(*p*-phenylene sulfide) (PPS) plate to minimize the temperature gradient across the sample. The polymeric material was heated on the Peltier plate at 115°C, liquefying the material and enabling intimate contact with both plates. Above and below the gel-point temperature, strain sweeps were conducted from 0.1 to 10 rad/s to verify the material was in the linear viscoelastic regime. Viscosity experiments were conducted over a strain rate ramp from 1.0 to 500 1/s to verify the material was strain rate independent.

REFERENCES

- (1) Decker, C.; Bianchi, C.; Jonsson, S. *Polymer* **2004**, *45*, 5803-5811.
- (2) Tarducci, C.; Badyal, J. P. S.; Brewer, S. A.; Willis, C. *Chemical Communications* **2005**, 406-408.

APPENDIX B: Externally triggered healing of a thermoreversible covalent network via self-limited hysteresis heating

EXPERIMENTAL INFORMATION

Polymer synthesis.

Pentaerythritol propoxylate tris(3-(furfurylthiol)propionate) (PPTF) was synthesized via the Michael-addition of furfuryl mercaptan and pentaerythritol propoxylate triacrylate, Appendix A for further details. Deionized water and denatured ethanol were added to chromium IV oxide (CrO_2) particles (Magtrieve®) in the ratio of 200 g DI H_2O : 200 g alcohol: 1 g chromium IV oxide powder and the mixture was sonicated using a SharperTek Ultrasound Cell Crusher for 10 minutes at 20 Watts power. PPTF was then added to the mixture and the alcohol and water were removed *in vacuo*. The mixture was then added to a stoichiometric equivalent of 1,1'-(methylenedi-4,1-phenylene) bismaleimide (DPBM, Sigma Aldrich, no further purification) and heated to 150 °C for 30 minutes (above the melt temperature of DPBM). Upon cooling a glossy black solid was formed.

Temperature measurements.

All experiments were carried out in a Taylor-Winfield 7.5 kW Ther-Monic generator, using a 3-turn solenoid coil (113 turns per meter). One gram samples of polymer were formed in a glass scintillation vial, which was revolved in the coil at ~8 rpm to insure uniform radial exposure to the RF field. An Omega Engineering OS552-V1-6 pyrometer

was used to measure the sample temperature. Field strengths were calculated from the coil current.

Mechanical testing and healing.

The flexural modulus was measured for 2x4x25 mm bars in an MTS 858 Minibionix II, using a 100 N load cell. The geometry of the testing apparatus was consistent with standard ASTM D 790M. An actuator velocity of 10 mm per minute was used to insure brittle fracture of the material. Samples were cast in molds formed from crosslinked PDMS (Sylgard 184) coated with Rainex®, to further decrease adhesion of the polymer to the mold. All samples were initially cast in a laboratory oven. After fracture, the samples were returned to the mold and then revolved in the coil at field strength of 14.2 mT for 300 seconds. The samples were allowed to cool for 12-20 hours to permit full curing of the material before mechanical testing.

APPENDIX C: Photofixation lithography in Diels-Alder Networks

REACTION KINETICS OF ALTERNATIVE FORMULATIONS

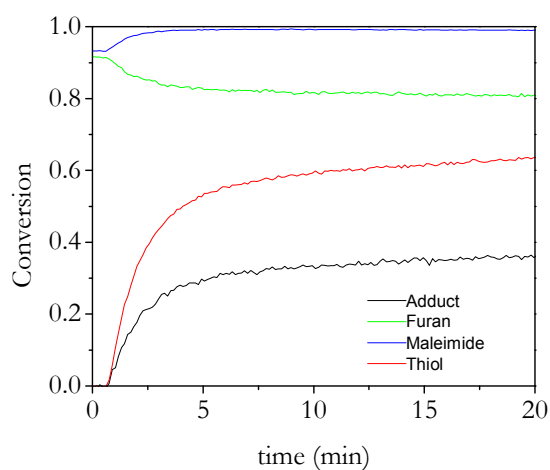


FIGURE S1 | IR experiments using 1,1'-(methylenedi-4,1-phenylene) bismaleimide and pentaerythritol tetrakis 3-mercaptopropionate instead of (5) and (6) showed similar behavior to those shown in Figure 3; however, the thiol behavior could be observed in these systems. These materials were later abandoned due to the difficulty in preparing thin films containing 1,1'-(methylenedi-4,1-phenylene) bismaleimide.

EXPERIMENTAL INFORMATION

Materials

All materials were used without further preparation unless indicated otherwise below.

The synthesis of pentaerythritol propoxylate tris(3-(furfurylthiol)propionate) is described in Appendix A.

Synthesis of exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (8)

Furan (65.6 g, Sigma-Aldrich) was first purified by short pass distillation, and then combined with maleic anhydride (89.6 g, FLUKA). The maleic anhydride was then dissolved in 90 ml of anhydrous THF. After approximately 4 hours a white precipitate formed. The reaction was allowed to continue overnight. The supernatant liquid was removed, and the remaining material was dried *in vacuo* and used without further preparation.

Synthesis of 1,13-Bismaleimido-4,7,10-trioxatridecane

The procedure was adapted from [1] with a furan protected maleic anhydride (8). THF was dried using sodium and benzophenone under reflux. All other compounds were extensively dried under vacuum. 19.0 g of (9) was added to 450 ml of dry THF under nitrogen. To this solution, 12.0 g of 4,7,19-trioxa-1,13-tridecanediamine (Fluka) dissolved in 100 ml of THF was added dropwise. After 1 hour a cloudy solution formed. ZnBr (25.8 g, Fluka) was added under nitrogen, followed by the dropwise addition of hexamethyldisilazane (28 g, Sigma-Aldrich). After the complete addition of the hexamethyldisilazane all of the material in the flask dissolved. A white precipitate then formed after approximately 1 hour.

The reaction mixture was then washed three times with 150 ml of 0.5 M HCl. The aqueous layer was then extracted with three washes of diethyl ether. The combined organic extracts were then washed with saturated sodium bicarbonate, and reduced *in vacuo* at 120°C for 4 hours. After purification, the crude product was purified using a silica gel column (100% ethyl acetate) to yield a white solid (62% yield). ¹H NMR (CDCl₃): δ 1.87 (4H, p), 3.47 (4H, t), 3.54-3.64 (m, 12), 6.69 (4H, s).

Polymer Synthesis.

A 0.225 wt. percent solution of hydrochloric acid (Sigma-Aldrich) in (6) was prepared. This solution was then combined with (4), (5), and (7), such that furan, maleimide, and thiol functional groups were equimolar and (7) was 1% of the total mass. Bulk solid samples were prepared by heating the material at 80°C. The resulting solid material readily reverted to a liquid upon heating.

Slides were spin coated using a Speedline Technologies Model P6700 at an initial speed of 1000 rpm for 10 seconds and then a final speed of 4000 rpm for 30 seconds (ramp times were 20 seconds for all steps). Thin films were prepared by the addition of a 10 wt% equivalent of PEG 100 K (Sigma-Aldrich), and a 50 wt% equivalent of a solution of 0.5% TWEEN 20(Sigma-Aldrich) in toluene(Sigma-Aldrich). Films cast by the latter methods were on the order of 10 microns in thickness while those produced by the later were less than 1 micron thick. In both cases, slides were baked at 80°C for 8 hours after coating.

The gels were exposed for 200 seconds in an OAI Hybraalign series 200 Mask Alignment system using a Photronics chrome mask. The light intensity of the i-line was approximately 9 mW/cm². After exposure, the gels were immediately immersed in furfuryl alcohol (70°C) to develop the image.

3D patterning was obtained via two-photon techniques, where the regions of interest (x-y control) within the gel were selectively exposed to pulsed laser light ($\lambda = 740$ nm, power = 670 mW/mm², scan speed = 1.27 msec/mm²) at 1 mm z-plane increments on a 710 LSM NLO confocal microscope stage (Carl Zeiss) equipped with a 20x/0.8 Plan-Apochromat objective (NA = 1.0, Carl Zeiss).

FTIR Spectroscopy

Spectroscopic studies were performed with a Nicolet Magna 750 series II Fourier-transform infrared (FTIR) spectrometer equipped with a MCT detector and a horizontal temperature-controlled stage (accurate to 0.1°C). Samples for IR spectroscopy were produced by casting a thin film of the reactants in dichloromethane onto a NaCl crystal and rapidly evaporating the solvent under vacuum. In a typically run, less than three minutes elapsed between mixing and the initial spectra collection. Reaction during the sample preparation was assumed negligible as the Diels–Alder reaction between furan and maleimide proceeds slowly at ambient temperature. The number of scans per spectrum (between 16 and 512) was adjusted based on the reaction rate. Conversion of the furan and maleimide functionalities was evaluated by monitoring the evolution of the furan peak area, centered at 1010 cm⁻¹, and the maleimide peak area, centered at 690 cm⁻¹.^{2,3}

REFERENCES

- (1) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652-2654.
- (2) Decker, C.; Bianchi, C.; Jonsson, S. *Polymer* **2004**, *45*, 5803-5811.
- (3) Tarducci, C.; Badyal, J. P. S.; Brewer, S. A.; Willis, C. *Chem. Commun.* **2005**, 406-408.

APPENDIX D: Spatial and temporal control of the azide-alkyne cycloaddition by photoinitiated Cu(II) reduction

Materials

The following compounds 1-hexyne (Sigma Aldrich), methanol (Sigma Aldrich), Alexo Fluor 488 5-carboxamide-(6-azidohexanyl), bis(triethylamine salt) 5-isomer(Invitrogen), copper sulfate pentahydrate (Sigma Aldrich), Irgacure 819 (Bis(2,4,6-trimethylbenzoyl)-phenylphosphineoxide, Ciba), Irgacure 2959 (1-[4-(2-Hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propane-1-one, Ciba), and PEG 100K (Polysciences) were used without further purification. PEG 10K tetraazide was synthesized following previously published procedures¹.

Ethyl azidoacetate (~25% in ethanol, Sigma Aldrich) was mixed with dimethylformamide and then reduced *in vacuo*. The ultimate ethyl azideacetate concentration was determined by ¹H-NMR.

Synthesis of PEG 3K dialkyne

4-pentynoic acid (1.64 g, 16.7 mmol, Fluka) was added to N,N'-dicyclohexylcarbodiimide (3.44 g, 16.7 mmol, Sigma), dissolved in minimal DCM, and stirred overnight under argon. The 4-pentynoic anhydride product was filtered, concentrated, and added to a solution containing vacuum dried poly(ethylene glycol) (5g, 1.67 mmol, Mn ~

3000, Fluka), pyridine (1.34 mL, 16.7 mmol, Sigma), 4-dimethylaminopyridine (200 mg, 1.67 mmol, Sigma) in minimal DCM, and stirred overnight under argon. The crude product was concentrated, precipitated in diethyl ether, dissolved in deionized water, dialysed for two days, and lyophilized to give the desired product at 95% yield. ^1H NMR (CDCl_3): ^1H NMR (CDCl_3): δ 1.99 (2H, t, 2 x $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$), 2.49-2.61 (8H, m, 2 x $\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$), 3.60-3.70 (m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.26 (4H, t, 2 x $\text{OCH}_2\text{CH}_2\text{OOC}$)

Photo-CuAAC reaction of ethyl azidoacetate and 1-hexyne

Ethyl azidoacetate (20 mM), 1-hexyne (20 mM), CuSO_4 (10 mM), I2959 (10 mM), and methanol were combined in a 20 ml scintillation vial and stirred rapidly at room temperature. The sample was then irradiated for 50 minutes using $10\text{ mW}/\text{cm}^2$ from an Acticure 4000 lamp using a 365 nm bandgap filter. The resulting mixture was extracted with dichloromethane and 5% aqueous ammonium hydroxide. The organic layer was separated, dried over MgSO_4 , filtered, and evaporated to give triazole product at 98% yield. ^1H -NMR(CDCl_3): 0.93 (3H t), 1.29 (3H t), 1.42 (2H m), 1.67 (2H m), 2.74 (2H t), 4.25 (2H q), 5.12 (2H s), 7.42 (1H s). X denotes residual dichloromethane in **Figure S1**.

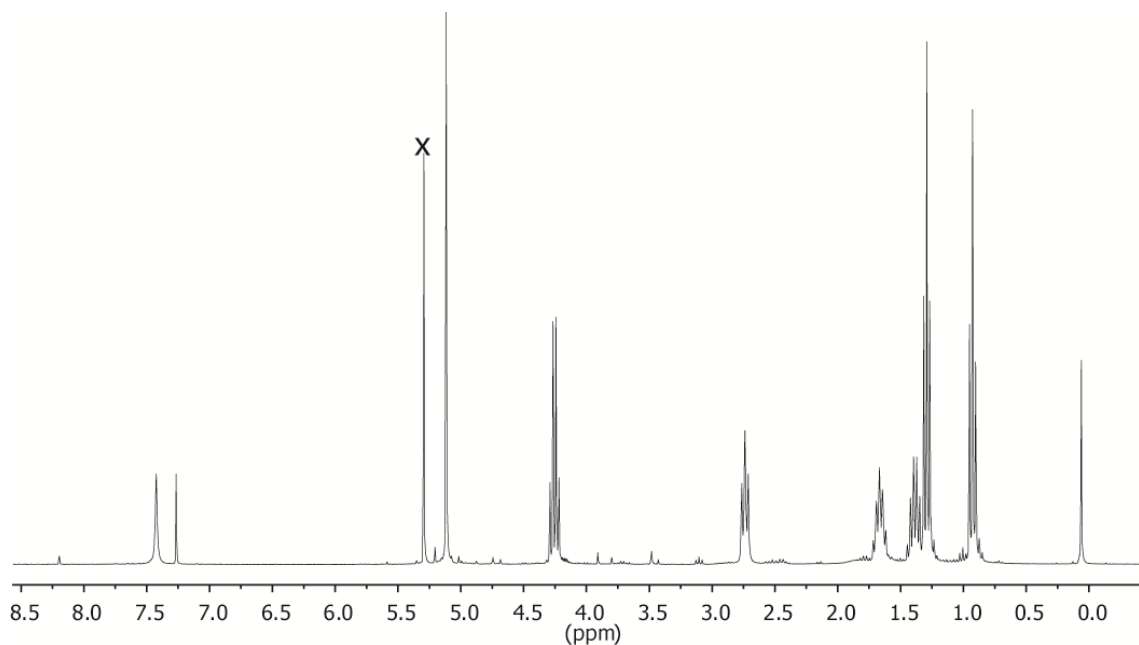


Figure S1 | ^1H -NMR of triazole product

Fourier Transform Infrared (FTIR) Spectroscopy

A Nicolet Magna-IR 750 Series II FTIR spectrometer, outfitted with a horizontal transmission stage, was used in conjunction with a variable pathlength liquid cell with calcium difluoride windows (International Crystal Laboratories). A pathlength of 50 μm was used for all experiments enabling greater than 90% transmission of light. The samples were irradiated by an EXFO Acticure high pressure mercury vapor short arc lamp equipped with a 400-500 nm bandgap filter. Light intensities were measured using an International Light IL1400A radiometer equipped with a GaAsP detector and a quartz diffuser.

In a typical experiment, a solution of dimethylformamide (DMF) with 200 mM ethyl azidoacetate, 200 mM 1-hexyne, 10 mM copper sulfate pentahydrate, and 10 mM I819 was injected into the liquid cell. Irgacure 819 was chosen as the photosensitive radical generator for its absorbance at 405 nm. Irradiation was commenced between five and ten minutes.

Approximately 1.8 scans per minute were performed. This delay time enabled the initial peak areas to be determined, which are used to calculate conversion (discussed below).

The IR spectrum of ethylazidoacetate and DMF solutions clearly show the expected asymmetric azide vibration at 2109 cm^{-1} that is convoluted with the DMF peaks nearby². In the region between 2213 and 1900 cm^{-1} the contribution of the azide group can be calculated by subtracting the DMF spectrum from the solutions spectrum. When plotted against concentration (**Figure S2**), the peak area shows linear behavior that gives an extinction coefficient (ϵ) of $1.51 \pm 0.03\text{ M}^{-1}\text{ }\mu\text{m}^{-1}$. Although, an alkyne peak is observed in that range, its extinction coefficient is two orders of magnitude less than the azide.

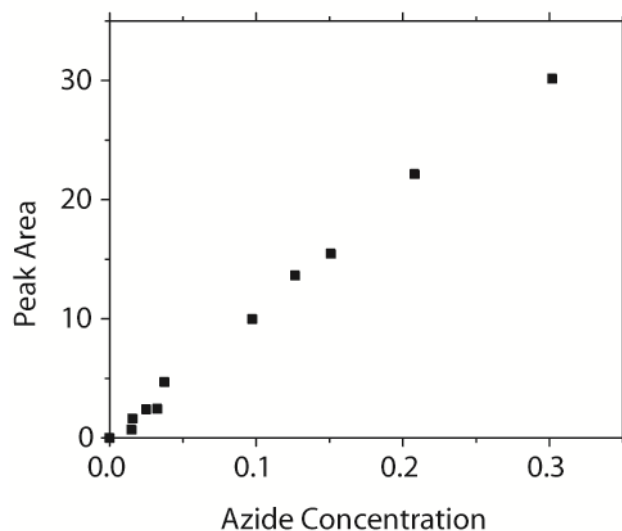


Figure S2 | Extinction coefficient of ethyl azidoacetate in dimethylformamide.

To analyze the reaction the initial conversion was calculated using the extinction coefficient, pathlength (l), initial concentration (c_0), initial peak area ($A(t_0)$), and area ($A(t)$), as shown in equation 1.

$$X = 1 - \frac{A(t) - [A(t_0) - \epsilon l c_0]}{\epsilon l c_0} \quad (1).$$

Rheometry

Direct monitoring of the extent of reaction in hydrogels is often difficult owing to both the dilute nature of the reactants and the formation of an incipient gel. In such systems, dynamic mechanical analysis (DMA) has emerged as a useful technique for measuring the time evolution of the mechanical properties and as an indirect measure of the extent of reaction^{3,1}. While such measurements do not provide detailed kinetic information, the emergence of a plateau modulus demonstrates the formation of a crosslinked solid and the gelation time enables determination of sufficient exposure times for both polymerizations and *in situ* patterning.

In these experiments a 36 mM solution of Irgacure 2959 and copper sulfate pentahydrate was prepared with DI water and combined with a stoichiometric mixture of 3K molecular weight PEG dialkyne and 10K molecular weight PEG tetraazide so that the polymers comprised 13.5% of the total mass, and an azide and alkyne concentration of 40 mM. A TA Ares rheometer with a parallel plate geometry employing a 20 mm quartz plate was used in all experiments. An EXFO Ultracure high pressure mercury vapor arc lamp with a 365 nm bandpass filter was used for irradiation. A constant strain of 10% and a frequency of 10 rad/s were used. The gap was less than 250 μ m for all experiments, allowing

for approximately 90 % transmission of light. Post-polymerization strain sweeps showed strains of 0.5 to 10 % to be in the linear region at the applied frequency. Post-polymerization frequency sweeps showed a constant modulus over time for the entire frequency range considered (1-100 rad/s). The gel point was taken to be the emergence of a storage modulus an order of magnitude above the noise (see **Figure S3**). All of these values yield identical scaling constants of -0.72 ± 0.3 for a log-log plot of gelation time versus light intensity result (see **Figure S4**). More rigorous criteria could not be applied due to the rapid time for gelation and non-linear behavior at higher strains. However, such experiments were sufficient to interpolate exposure times for various light intensities.

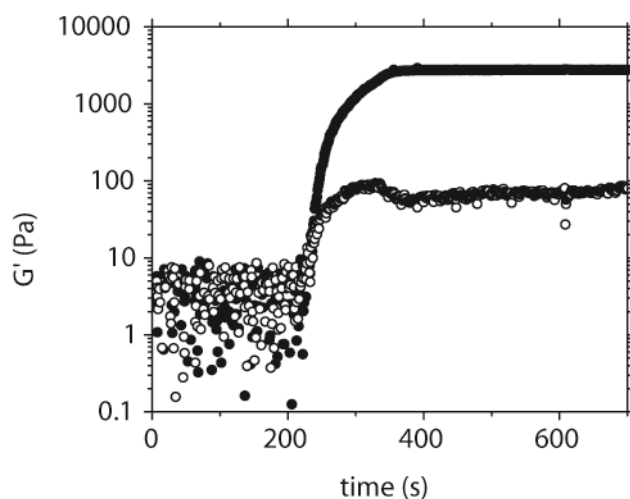


Figure S4 | The evolution of the storage (●) and loss moduli (○) during the photocuring of a 10K tetraazide and 3K dialkyne functionalized PEGs at an intensity 100 mW/cm² (365 nm). The crossover of the moduli occurs near the detection of the instrument at approximately 10-20 Pa.

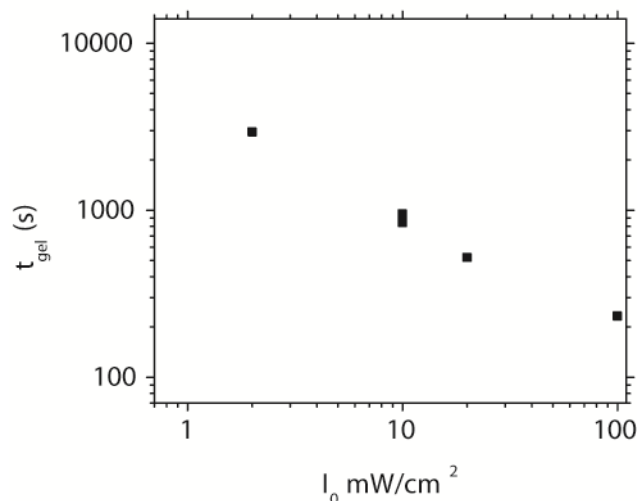


Figure S5 | Dependency of time to gel on light intensity. The time for samples to reach a storage modulus of 10 Pa, assigned as the gel-point, is shown for several intensities.

Slide functionalization

Glass micro slides (Corning) were cleaned using piranha solution, rinsed, and dried thoroughly. Subsequently, they were immersed in a (3-mercaptopropyl) trimethoxy silane, n-butyl amine, and toluene solution (70 mM of the silane and amine) for approximately 4-12 hours. After rinsing in toluene, the slides were then immersed in a solution of 120 mM propargyl acrylate and 40 mM triethylamine for 4-12 hours.

The contact angle of a pendant water droplet on the surface of the slides functionalized with (3-mercaptopropyl) trimethoxy silane was found to be $58.3 \pm 0.8^\circ$. The contact angle of the slides that were further treated with propargyl acrylate was found to be $55.3 \pm 1.0^\circ$. Gels formed on the surface of both thiol and acrylate functionalized slides were found to adhere to the surface and could only be removed with a razor blade. Gels formed on native glass were easily removed after rinsing with water. This suggested that the gels

were covalently bound to the surface via either the CuAAC reaction or radical mediated thiol-alkyne reaction rather than through physical interactions.

Gel Patterning

A solution was prepared in identical proportions to those used in the photo-rheology experiments. PEG 100K was added so that the final solution was 10% PEG 100K by mass. The addition of the linear polymer enabled the liquid to be readily spin coated on an alkyne functionalized glass slide. Slides were spin coated using a Speedline Technologies Model P6700 at an initial speed of 750 rpm for 30 seconds and then a final speed of 4000 rpm for 60 seconds (ramp times were 20, 10, and 5 seconds). The gels were then exposed for 500 seconds in an OAI Hybraalign series 200 Mask Alignment system using a Photronics chrome mask. The light intensity was 35 mW/cm². After exposure, the gels were immediately immersed in DI water to develop the pattern.

In Situ Gel Patterning

A 13.5 wt% PEG solution of 10K PEG tetrathiol and 3K PEG diazide (thiol to yne ratio = 0.95) was prepared with 0.8% wt. (36 mM) I2959. To increase the viscosity of the mixture and enable spin casting of the solution, PEG 100K was added such that the final formulation was 10% PEG 100K by mass. This mixture was then spin coated on slides functionalized with thiol groups using the same procedure as for the patterned gels (see previous section) and irradiated for 50 s. The slides were subsequently immersed in DI water for approximately 30 minutes.

A solution of 36 mM I2959, 36 mM copper sulfate pentahydrate, and 0.4 mM Alexo Fluor 488 5-carboxamide-(6-azidoheptyl), bis(triethylamine salt) was then swollen into the gel for 30 minutes before the samples were irradiated for 50 s. Afterwards the gels were soaked in DI water for several minutes to remove residual fluorophore.

REFERENCES

- (1) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. *Nature Materials* **2009**, *8*, 659-664.
- (2) Lieber, E.; Rao, C. N. R.; Chao, T. S.; Hoffman, C. W. W. *Analytical Chemistry* **1957**, *29*, 916-918.
- (3) Polizzotti, B. D.; Fairbanks, B. D.; Anseth, K. S. *Biomacromolecules* **2008**, *9*, 1084-1087.

APPENDIX E: Mechanism of the photo-mediated copper-catalyzed azide—alkyne cycloaddition

Materials

All of the following compounds 1-dodecyne (Sigma Aldrich), dimethylformamide (ACS or Biological grade, Sigma Aldrich), copper sulfate pentahydrate (Sigma Aldrich), Irgacure 819 (Bis(2,4,6-trimethylbenzoyl)-phenylphosphineoxide, Ciba), were used without further purification.

Experiments were carried out as in Appendix D. Samples that were noted as being sparged had either ultra high purity argon or oxygen bubbled through them for 15 minutes.