Photocleavable Junctions in Complex Polymer Architectures and Photoetchable Thermoplastics

Elizabeth Surles Sterner

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PHOTOCLEAVABLE JUNCTIONS IN COMPLEX POLYMER ARCHITECTURES AND PHOTOETCHABLE THERMOPLASTICS

A Dissertation Presented

by

ELIZABETH SURLES STERNER

Submitted to the Graduate School of the
University of Massachusetts Amherst
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2014

Polymer Science and Engineering
PHOTOCLEAVABLE JUNCTIONS IN COMPLEX POLYMER ARCHITECTURES AND PHOTOETCHABLE THERMOPLASTICS

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Polymer Science and Engineering
DEDICATION

This dissertation is dedicated to my many friends at UMass and elsewhere, for providing new perspectives and much-needed downtime.

It is also dedicated to my family, who have become quite good at smiling and nodding, and who have always respected my enthusiasm and my professional goals, even if they didn’t always understand them.

But most of all, this dissertation is dedicated to my husband Jon, without whom life would be much more difficult and much less interesting, and whose unflagging support ensured I remembered to eat and sleep.
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ABSTRACT

PHOTOCLEAVABLE JUNCTIONS IN COMPLEX POLYMER ARCHITECTURES AND PHOTOETCHABLE THERMOPLASTICS

FEBRUARY 2014

ELIZABETH SURLES STERNER
Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor E. Bryan Coughlin

Polymer materials have become important tools in nanomanufacturing due to their facile processing and ready attainment of the necessary feature sizes. The development of cleavable junctions has led to advances in the production of polymer nanotemplates. Photocleavage strategies have come to the forefront of the field because photons, as a cleavage stimulus, do not have the mass-transport limitations of chemical methods, and provide for targeted two- and three-dimensional feature control. This dissertation presents a method for producing photocleavable materials by one-pot copper-catalyzed azide-alkyne “click” chemistry (CuAAC), activator regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP) and activated ester substitution methods that have each block labeled with a fluorescent dye, enabling exploration of the polymer physics of these systems by correlation fluorescence spectroscopy. It also introduces a novel photocleavable linker, the o-nitrobenzyl-1,2,3-triazole, its behavior on photocleavage, and a facile method for the production of the o-nitrobenzyl azides necessary for their synthesis. The synthesis and properties of a bulk photodegradable polytriazole are reported, as are proof of concept experiments demonstrating its potential as a directly photoetchable material.
SYMBOLES, ABBREVIATIONS AND ACRONYMS

δ – NMR chemical shift in ppm

°C – degrees Celsius

Δ – Dispersity, expressed as M_W/M_N

μg – Microgram

μmol – Micromole

AFM – Atomic Force Microscopy

ATR-FTIR – Attenuated Total Reflectance FTIR

ATRP – Atom Transfer Radical Polymerization

ARGET ATRP – Activator Regenerated by Electron Transfer ATRP

BDCP – Bis(1,4-dichlorophenyl)phosphate

BIB – α-Bromoisobutryl bromide

Boc – Butoxycarbamoyl group

13C NMR - Carbon-13 Nuclear Magnetic Resonance Spectroscopy

CFS – Correlation Fluorescence Spectroscopy

CuAAC – Copper-catalyzed Azide/Alkyne Cycloaddition

Da – Dalton, defined as 1 g/mol molecular weight

DBU – 1,8-Diazabicycloundec-7-ene

DMAP – 4-Dimethylaminopyridine

DMSO - Dimethylsulfoxide

DMF – N,N’-Dimethylformamide

DPPA – Diphenylphosphoryl azide

DSC – Differential Scanning Calorimetry
DTT – Dithiothreitol
EBIB – Ethyl-2-bromo-isobutyryl bromide
EI-MS – Electron Impact Mass Spectrometry
Equiv. – Molar equivalents
ESI-MS – Electrospray Ionization Mass Spectroscopy
EtOAc – Ethyl acetate
EtOH – Ethanol
FTIR – Fourier Transform Infrared Spectroscopy
GC-MS – Gas Chromatography-Mass Spectroscopy
GPC – Gel Permeation Chromatography
1H NMR – Proton Nuclear Magnetic Resonance Spectroscopy
hv – Use in polymer names to indicate presence of a photocleavable junction, or in chemical equations to indicate light as a reagent
HEMA – 5-Hydroxyethyl methacrylate
Hex – Hexanes
HMTETA – 1,1,4,7,10,10-Hexamethyltriethylenetetramine
In vacuo – Under reduced pressure/vacuum
M+ - Molecular ion
MAIZ – Mono-ATRP initiator azide
Mass spec – Mass spectrometry
MeOH – Methanol
mmol – Millimole
Mol% - Equivalent of reagent expressed as percentage of reference reagent moles
MN – Number-average molecular weight
MOM – Methoxymethyl ether protecting group
MOMCl – Chloromethyl methyl ether
M.P. – Melting point
MW – Weight-average molecular weight
m/z – Mass per unit charge, used in mass spectrometry
NBD – 4-Nitro-7-piperazin-1-yl)-2,1,3-benzoxadiazole
NIPAM – N-isopropyl acrylamide
NMR – Nuclear Magnetic Resonance Spectroscopy
ONB – o-Nitrobenzyl
ONBTz – o-Nitrobenzyl-1,2,3-triazole
PAAm – Polyacrylamide
PEO – Poly(ethylene oxide)
PHEMA – Poly(5-hydroxyethyl methacrylate)
pHNB – 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde
PFPMA – Pentafluorophenyl methacrylate
pMAI - 2-Nitro-5-(prop-2-yn-1-yloxy)benzyl 2-bromo-2-methylpropanoate
PNIPAM – Poly(N-isopropyl acrylamide)
pONBz – 2-nitro-5-(Prop-2-yn-1-yloxy)benzyl azide
ppm – Parts per million
ppt – Parts per thousand
PS – Polystyrene
PTz - Polytriazole
RBF – One-neck Round Bottom Flask
RI – Refractive index
SN2 – Substitution by Nucleophilic Attack
TEA - Triethylamine
TEM – Transmission Electron Microscopy
Tert. - Tertiary
TGA – Thermogravimetric Analysis
THF – Tetrahydrofuran
Tg – Glass transition temperature
TLC – Thin Layer Chromatography
TMS – Trimethylsilyl ether protecting group
TPP – Triphenylphosphine
TPPO – Triphenylphosphine oxide
UV – Ultraviolet
UV-Vis – Ultraviolet-Visible Light Absorption Spectroscopy
v:v – Volume:Volume ratio
XPS – X-ray Photoelectron Spectroscopy
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CHAPTER 1
INTRODUCTION

1.1. General Background and Motivation

Polymers have many applications in the field of nanopatterned and responsive materials. Due to the ability of block copolymers to form amphiphilic structures such as micelles, vesicles and phase-segregated thin films, they are of particular interest as nanoscale templates for electronics, photovoltaics, and magnetic media for data storage,\textsuperscript{1} surface coatings,\textsuperscript{2} and for the encapsulation and delivery of various chemical payloads.\textsuperscript{3} Nanoporous polymer films resulting from removal of the minor phase of a cylindrical morphology can be used to prepare nanorods or nanodots of inorganic materials, generate a p-n junction for a photovoltaic cell, or serve as a nanoporous membrane for filtration.\textsuperscript{4} In other applications, control of the chemical nature of the polymer leads to surface patterning or controlled assembly/disassembly of amphiphilic structures.\textsuperscript{5}

Previously, achieving these transformations has been performed by complete degradation of one block through various means including acid, base, or UV etching.\textsuperscript{6} These techniques break numerous chemical bonds in the backbone of the minor block, creating soluble fragments that can be washed away with a selective solvent. Because many bonds must be broken, these techniques require long exposure times. Failure to allow sufficient degradation results in residual non-degraded polymer remaining in the templated structure. Many of these conditions are very harsh (i.e. high-intensity 245 nm light or immersion in concentrated HI), strictly limiting the types of materials that can be used in these templates to those sufficiently robust to survive degradation and removal of the minor block.
Rather than forcing the cleavage of many bonds throughout the backbone of the minor block, a more elegant approach is to introduce a cleavable linker between the blocks so that cleavage of a single bond is sufficient to separate them. By reducing the number of bonds that must be cleaved, we can reduce the time the material must be exposed to the cleavage conditions. By careful selection of the cleavable structure, one can use cleavage conditions that will not disturb or alter the polymer structure.

Early cleavable linker structures were designed to produce cleavage upon exposure to a specific chemical stimulus, such as a chemical agent or a photon. There are many of these cleavable junctions, including those that are acid, base, or redox sensitive. The Coughlin, Venkataraman and Russell research groups have worked in the past with a polystyrene-\textit{b}-poly(ethylene oxide) (PS-\textit{b}-PEO) system that contained an acid-cleavable trityl ether linker between the two polymer blocks (figure 1.1).  

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{PS-\textit{b}-PEO featuring the trityl ether linker.}
\end{figure}

Thin films of this material were solvent-annealed to cause long-range ordering of PEO cylinders oriented normal to the surface within the polystyrene matrix. As seen in figure 1.2A, the cylinders are hexagonally packed. After exposing these films to trifluoroacetic acid, the PEO was removed with a methanol wash. Left behind were well-ordered, nanoporous polystyrene films (figure 1.2B). Similar results have also been achieved in copolymers linked through an acid-sensitive acetal rather than a trityl ether.
Figure 1.2: A) AFM image of the annealed copolymer film (inset Fourier transform shows long-range ordering) (2 μm x 2 μm); B) TEM image of the nanoporous polystyrene film after PEO removal (1 μm x 1 μm).10

Other groups have explored the use of disulfide linkers, which are redox, rather than acid, sensitive. Thayumanavan et al. were able to produce nanoporous polystyrene films similar to those based on trityl ether chemistries from PS-b-PEO linked by a disulfide that was cleaved with dithiothreitol (DTT).11 Installation of many disulfide groups in the backbone of the polymer leads to overall degradation of the chain when exposed to DTT or glutathione, an important physiological antioxidant.12 Lastly, cleavable polymer systems have been prepared through use of electrostatic interactions between two polymers end-functionalized with a dimethyl amino group and a sulfonic acid group, respectively.13

Despite the excellent results achieved with chemical-sensitive linkers, these methods have several disadvantages. The acid required to cleave the trityl ether is harsh, and limits the types of materials that can be used in these polymer systems as these could lead to undesirable side reactions. The disulfide linker is itself chemically vulnerable, and cleavage can be triggered by contamination or oxygen exposure before the researcher intends cleavage to occur. Furthermore, both linkers are dependent on infiltration of a chemical agent into the film (acid or DTT), requiring stimulus exposure times of hours to
achieve sufficient cleavage because of diffusional limitations. Finally, the need to use a chemical agent to cause cleavage mandates changes to the material’s chemical and physical environment, especially if solvent-swelling or higher temperatures are used to overcome the diffusion limitations. These changes can lead to loss of the annealed morphology, as the material may no longer be at an equilibrium state.

The equilibrium morphology of a phase-separated system is generally discussed in terms of the relative volume fraction of the two (or more) blocks and the relevant $\chi$ parameter, as expressed in a phase diagram like that shown below in figure 1.3. Changing either the temperature or the chemical nature of either block can destabilize the phase separated morphology through effects on either the volume fraction or $\chi$ parameter. The $\chi$ parameter is an enthalpic term describing the interaction between the two blocks as well as taking into account the temperature of the system. Swelling the film with solvent to facilitate chemical agent permeation alters the volume fraction of one or both blocks, changing where the morphology is placed on the horizontal axis of the phase diagram. This can push the morphology into a different region of the diagram, altering the carefully annealed original structure. By increasing the temperature, or infiltrating a chemical, the $\chi$ parameter can be changed, which will move the morphology along the vertical axis of the phase diagram. Movement along either axis can change the morphology by putting the system in a different phase region, or destabilize it entirely by moving it into a region of the diagram where the material is inherently disordered.
Figure 1.3: Symmetrical volume fraction vs. $\chi$ parameter phase separation diagram showing morphologies for diblock copolymer systems, including spherical (S), cylindrical (C), gyroid (G) and lamellar (L) regions.\textsuperscript{14}

In order to avoid the drawbacks of using a chemical stimulus for cleavage, photocleavable linkers were investigated. Most polymer structures are not vulnerable to photochemical side reactions provided the photon’s wavelength and intensity are sufficiently mild. Photons do not suffer from the mass-transport diffusion limit of a chemical agent, leading to shorter stimulus exposure times. Infiltration of a photon into a polymer material does not require swelling the material with solvent, infiltration of a chemical agent, or changing the temperature of the system, all factors that help to preserve the thermodynamic equilibrium of the microphase separated state and therefore will help to preserve template morphology. Photocleavage is an orthogonal strategy to chemically-based methods, allowing a wider variety of functional groups to be present in the material to be cleaved as well as allowing the installation of multiple types of cleavable linkers that each respond to a different stimulus. Photocleavage of specific areas of a film or monolith
can be achieved using photomasks or 2-photon excitation, adding a further degree of control over the material.\textsuperscript{15}

A 1997 paper by Rodebaugh discusses the \textit{o}-nitrobenzyl (ONB) ester photocleavable linker (figure 1.4).\textsuperscript{16} This linker, upon irradiation with 300-365 nm light, releases a free carboxylic acid and an \textit{o}-nitrosobenzaldehyde byproduct.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{The \textit{o}-nitrobenzyl ester and its cleavage products.}
\end{figure}

In recent years, the \textit{o}-nitrobenzyl (ONB) ester has been utilized by polymer scientists for a variety of applications.\textsuperscript{17} Multiple research groups have used ONB functionalized crosslinkers and tethers to produce hydrogels for tissue scaffolding applications prepared from several different biocompatible materials that can be selectively decrosslinked both as a way to etch the gel surface, and to produce three dimensional cavities within hydrogel monoliths.\textsuperscript{15, 18} This photocleavable chemistry can also be used to release important biosignaling molecules to direct tissue growth.\textsuperscript{19} This decrosslinking can also be used to pattern portions of hydrogel with much greater swelling capability, creating gels with tailored topography and stress profiles.\textsuperscript{20}

The ONB ester can also be used as a hydrophobic protecting group for the hydrophilic carboxylic acid moiety. Using light to unmask the carboxylic acid in block copolymers converts a compatible system to a phase-separating system, or vice versa. This property has been used to make micelles that form, or degrade, on exposure to UV light,\textsuperscript{21} and has been paired with the thermoresponsive behavior of poly(N-isopropylacrylamide)
(PNIPAM) to create multi-stimulus responsive materials.\textsuperscript{22} This tunable amphiphilicity can also be applied to collapsing single chains,\textsuperscript{23} and to dendritic structures.\textsuperscript{24} This masking is also used in surface patterning applications to tune surface wettability,\textsuperscript{25} serve as a photoresist material,\textsuperscript{26} and in the preparation of microfluidic devices.\textsuperscript{27}

This dissertation consists of three general research thrusts that are all centered on the application of photocleavable junctions in functional polymer materials. The first section details efforts to prepare a dual dye-labeled photocleavable block copolymer suitable for correlation fluorescence spectroscopy (CFS) experiments investigating how photocleavage affects the disassembly of amphiphilic structures. The second and third sections focus on applications of a novel linker structure, the \textit{o}-nitrobenzyl-1,2,3-triazole (ONBTz). The second section focuses on using the ONBTz linker in click/clip complex polymer architectures, which can be assembled by CuAAC “click” chemistry, and then cleaved apart by exposure to UV light. The third project is the synthesis of a directly photoetchable thermoplastic.

1.2. Background and motivation for chapter two – dual dye-labeled materials

Two of the most prevalent applications of photocleavable block copolymers are preparing nanoporous thin films and triggered-degradation micelles. There have been many reports of these systems, but they have largely been limited to reporting the synthesis of the polymer, and the conditions needed for complete cleavage of the linker.\textsuperscript{4c, 22, 28} These systems focus on using only the photocleavable block copolymer as the material component, its assembly into the amphiphilic structure, and the effect of irradiation time on the morphological order. Little investigation into the physical mechanisms behind the behavior of these systems has been undertaken, nor on the effect of blending in non-
photocteavable, comparable copolymer. Certain reported materials display sharp order to
disorder transitions with irradiation, while others show a more gradual response. These
different reported behaviors indicate that the process of structure degradation may depend
on more factors than simple irradiation time. In order to properly design photocteavable
materials for sophisticated applications in drug delivery or device fabrication, a thorough
understanding of how these systems function is necessary.

In the case of nanoporous thin films, there are concerns regarding the complete
removal of the sacrificial block after photocteavage. Remaining material could affect the
deposition of or the morphology of the templated material after complete removal of the
template. Characterization methods such as X-ray photoelectron spectroscopy (XPS) can
provide an elemental profile of the material at different depths from the surface, but typical
measurements are limited to the 10-20 \( \mu \text{m} \) at the surface, meaning that differences in
composition at the interface between the polymer film and the substrate cannot be
interrogated. It is at the bottom of the pores that uncleaved or non-removed sacrificial
material is most likely to be found. Infrared spectroscopy techniques in attenuated total
reflectance mode suffer from a similar limitation in terms of sample penetration, while
transmission mode techniques cannot differentiate between residual sacrificial block
remaining in the pores and traces of sacrificial block remaining on the surface of the film
that has not been fully washed away.\(^{29}\)

In the case of degradable micelles, interrogation of the basic physical mechanisms
behind micellar collapse is needed. It is currently unknown what fraction of cleaved chains
is necessary to destabilize the amphiphilic structure, nor how the micellar collapse proceeds
after the system has been sufficiently destabilized. Do the chains in the insoluble micelle
core rearrange themselves during the collapse? What kinds of mobility changes occur for each block as cleavage progresses? Do cleaved corona chains become fully solubilized in the matrix solvent immediately after photocleavage, or do entanglements with other corona chains or interactions with the core sequester the cleaved chains for some period of time before collapse? Common micelle imaging techniques like cryo-transmission electron microscopy can capture images of precise moments in the cleavage and collapse of these systems, but these static images cannot provide us with dynamic data in real time. Sample preparation for electron microscopy requires methods (vitrification, fracture, staining, etc.) that may disturb dynamic morphologies, resulting in an incorrect representation of the system.

Correlation fluorescence spectroscopy (CFS) is a technique that can provide important insights into these amphiphilic systems by measuring the fluorescence of a sample as a function of time. The fluorescence intensity fluctuations are analyzed with an autocorrelation function, from which can be derived information such as diffusion coefficient, analyte concentration, hydrodynamic radii and reaction kinetics. These capabilities are powerful tools for answering questions about the physics of photocleavable amphiphilic systems.30

In order to use CFS to interrogate the dynamics of amphiphilic polymer systems, it is necessary to synthetically prepare a polymer that has the following features; two well-defined polymer blocks that are totally soluble in at least one common solvent, as well as phase-separating under the right conditions, a photocleavable junction between the two blocks, and finally each block must be labeled independently with fluorescent dyes that do not competitively absorb the photocleavage wavelength and are suitable for the excitation
sources and detectors used by our collaborators. Labeling with two dyes will allow both blocks to be tracked individually. The structure that was designed to meet these criteria can be seen in figure 1.5 below.

![Figure 1.5: Target structure for a photocleavable, dual dye-labeled block copolymer for CFS exploration of polymer physics.](image)

This polyacrylamide-$b$-poly(hydroxyethyl methacrylate) can be prepared by atom transfer radical polymerization (ATRP), a method noted for producing materials with narrow dispersity and targeted molecular weight. The green fluorophore, 4-nitro-7-(piperazin-1-yl)-2,1,3-benzoxadiazole (NBD), is introduced via reaction with a pentafluorophenyl activated ester, while the Nile Blue is introduced via polymerization into the backbone during CuAAC/activator regenerated by electron transfer (ARGET) ATRP chain extension. The characteristics and synthesis of this material are discussed in detail in chapter two of this dissertation.

1. 3. Background and motivation for chapter three – click/clip complex polymer architectures

The “click/clip” paradigm signifies a polymer material that has been assembled using a click-type chemistry such as the CuAAC reaction, and possesses a photocleavable linker that can later be used to clip apart the structure. The advantages of this paradigm include the facility of click chemistry to produce complex polymer architectures, and the
ease with which a photocleavable group can trigger disassembly in a controlled manner.\textsuperscript{17} The ONB ester linker has been used to prepare these types of polymers.\textsuperscript{33}

Copper-catalyzed 3+2 Huisgen cycloaddition of azides and alkynes (CuAAC) was first introduced in 2002 independently by Sharpless and Meldal.\textsuperscript{34} This highly robust reaction produces a 1,2,3-triazole from the 3+2 cycloaddition of an azide and an alkyne (figure 1.6). The reaction proceeds with total atom economy, reaches quantitative conversion in minutes to hours, and tolerates a staggering variety of solvents and substrates.\textsuperscript{35} Further, azides and alkynes are considered to be "spring loaded" reagents in that they are unreactive to most chemical functionalities, but react with each other swiftly under click conditions. Because of this functional group tolerance and efficiency, CuAAC click has become a crucial tool for the preparation of complex polymer architectures like stars, brushes, and block copolymers, especially from macromolecular-size components.\textsuperscript{36} This method is also used to assemble supramolecular structures, such as rotaxanes and catenanes.\textsuperscript{37}

\[
R_1-N_3 + \equiv \equiv R_2 \xrightarrow{\text{Cu catalyst}} \xrightarrow{\text{ambient conditions}} \xrightarrow{\text{minutes to hours}} R_1-N\equiv\equiv N=\equiv R_2
\]

**Figure 1.6:** CuAAC reagents and product.

To facilitate the use of click/clip materials, a photocleavable linker was designed that is synthesized by click chemistry, the o-nitrobenzyl-1,2,3-triazole (ONBTz) (figure 1.7). This linker can be used with either traditional click conditions, or in recently developed one-pot click/ATRP systems where the polymerization and the click reaction are catalyzed in tandem by the Cu(I). Introduced by the Fustin group in 2010, one-pot click/ATRP allows for the facile synthesis of complex polymer architectures like block
copolymers from small molecule and simple macromolecular components.\textsuperscript{33a} Further, the benzyl triazole is expected to have higher thermal and chemical stability than the corresponding benzyl ester that will make photocleavable junctions viable options in copolymer systems that must be used under harsher thermal and chemical conditions. Esters are known for pH sensitivity and vulnerability to water and nucleophiles,\textsuperscript{38} while the 1,2,3-triazole linker created by CuAAC click chemistry is notably stable to similar conditions.\textsuperscript{35}

\textbf{Figure 1.7:} The synthesis and structure of the ONBTz linker.

In order to use the ONBTz linker, it is necessary that \textit{o}-nitrobenzyl azides be obtained in good yield via a facile synthesis. It is convenient to start from commercially available \textit{o}-nitrobenzyl alcohols. Early attempts using Mitsunobu conditions with hydrazoic acid as the azide source produced only modest yields (\textasciitilde35\%) of product azide while requiring a highly hazardous reagent.\textsuperscript{39} Modification of this reaction led to the use of diphenyl phosphorazidate (DPPA) in conjunction with 1,8-diazabicycloundec-7-ene (DBU) to achieve the transformation, but yields for \textit{o}-nitrobenzyl substrates were very low as only the intermediate phosphates were found to form.\textsuperscript{40} The same researchers that discovered this proposed an alternative chemistry that used a more activated phosphate reagent, bis(2,4-dichlorophenyl) chlorophosphate (BDCP) and sodium azide. While yields for \textit{o}-nitrobenzyl substrates were improved, this method requires the use of a costly
phosphate reagent and is not suitable for a large-scale, high-throughput synthesis. Therefore, some time was devoted to the development of a two-step process that uses an Appel reaction to prepare an o-nitrobenzyl bromide that is transformed to an azide by straightforward S_{N}2 chemistry. This method allows for multi-gram scale batches to be prepared in a matter of days with a single column chromatography purification step and up to 80% process yields for the bromide and azide transformation steps. This method will be elaborated upon in its designated chapter.

For click/clip materials, an azide-functionalized mono-ATRP initiator (MAIZ) was synthesized that can function as both a polymerization initiator and a click substrate, thus accessing complex and photocleavable polymer architectures via one-pot preparation methods.

1.4. Background and motivation for chapter four – photodegradable polytriazoles

A major application of photoactive polymer materials is for use as photoresists in the lithographic preparation of electronics. A diagram that details the general process is found in figure 1.8 below.

**Figure 1.8:** The photolithographic process for microscale patterning featuring a positive resist.\(^{41}\)
First, a photoresist is coated on top of the active layer to be patterned. Next, a photomask is used to pattern where the resist is to become more or less soluble in the developing solvent. In the case of a positive resist, such as Novolac resin, a chemical reaction is triggered in areas exposed to the light source that causes the photoresist to become more soluble in those areas. In the case of a negative resist, such as poly(tert-Boc styrene), the photo-induced chemical reaction makes the exposed areas less soluble in the developing solvent. After exposure, the soluble areas are washed away and etch conditions are used to pattern the active layer. Areas protected by the insoluble resist are not etched, leading to a topographical pattern in the active layer that can be backfilled with another material.

There are two major challenges in the use of traditional photoresists. The first is that the photoinduced chemical reactions are dependent upon the presence of a small molecule blended into the polymer resin, for instance a sulfonium salt or diazanaphthoquinone. These small molecules must be blended in homogeneously if good pattern reproduction is to be achieved, which can be difficult if the small molecule is poorly compatible with the resin or the mixing method is inadequate. The second challenge of photoresist lithography is that the photoresist serves solely as a sacrificial layer, which can be wasteful. A directly photoetchable thermoplastic, one that contained photocleavable groups within the backbone, would address both of these challenges.

The goals in designing this directly photoetchable thermoplastic were to produce a polymer that could be easily synthesized, possess sufficient chemical, thermal, and mechanical stability to serve as a useful surface layer, and that would readily photodegrade into small, highly soluble fragments. The target structure is a polytriazole, as seen in figure
1.9. A facile synthesis has been developed for the necessary monomer for this material, and the polymer itself is prepared by click polymerization, a swift step-growth method that has recently been reported. The resulting polymer has a high aromatic content, which provides chemical, thermal and mechanical stability, and possesses a photo-cleavable ONBTz linker in every repeat unit, granting the desired photodegradation characteristics. A final benefit of this material is that photocleavage occurs at any wavelength between 300-365 nm, making it a drop-in replacement material for current standard photolithographic apparatus.

\[
\begin{align*}
\text{Figure 1.9: Target structure for a photodegradable polytriazole.}
\end{align*}
\]

1.5. Introduction Coda

The introduction of photo-cleavable linkers to polymer synthesis has allowed investigators to produce a wide variety of materials that display interesting and useful behaviors ranging from block copolymer cleavage to controlling the amphiphilicity of polymer materials. This dissertation is intended to provide tools for the exploration of the underlying physics of some of these behaviors, as well as to introduce a novel cleavable linker, the \( o \)-nitrobenzyl-1,2,3-triazole. This linker can be prepared by CuAAC chemistry, facilitating the preparation of photo-cleavable complex polymer architectures, as well as serving as the repeat unit structure in a directly photoetchable thermoplastic. The results presented here advance the understanding and applicability of controlled assembly-disassembly systems, presenting new opportunities for responsive, tailorable polymer systems.
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CHAPTER 2

DUAL-DYE LABELED MATERIALS FOR INVESTIGATING THE PHYSICS OF AMPHIPHILIC POLYMER STRUCTURES

In this section, the synthesis and characterization of a photocleavable, dye-labeled block copolymer suitable for correlation fluorescence spectroscopy (CFS) experiments is presented. This material was designed to fulfil the following criteria:

- Two well-defined polymer blocks that can form amphiphilic structures
- A photocleavable junction located between the blocks
- A fluorescent dye label in each block, enabling them to be tracked independently

Our collaborators’ CFS instrument has two excitation/emission windows available, one for a blue/UV absorbing and green emitting dye, and one for a yellow absorbing, red-emitting dye. The dyes and photocleavable linker must be selected such that there is minimal overlap of absorption and emission profiles. The target structure can be seen in figure 2.1 below.

![Target structure of dual-dye labeled, photocleavable block copolymer](image_url)

**Figure 2.1:** Target structure of dual-dye labeled, photocleavable block copolymer.

Our choice of photocleavable junction is the o-nitrobenzyl ester as it is the most common photocleavable linker in use by polymer chemists.\(^7\) This linker has a UV-Vis
profile with a $\lambda_{\text{max}}$ of 302 nm, and an onset of absorption at 370 nm. The dyes selected are the 4-nitro-7-(piperazin-1-yl)-2,1,3-benzoxadiazole (NBD) green fluorophore, with an absorbance maximum at 495 nm and an emission maximum at 520 nm, and Nile blue. Nile blue is a strongly solvatochromic dye, and it only has the desired absorption maximum (620-640 nm) and emission maximum (660-680 nm) when dissolved in alcohols or water. This limitation dictated that we select for our polymer blocks poly(5-hydroxyethyl methacrylate) (PHEMA) and polyacrylamide (PAAm). Both blocks are water soluble, but PAAm is insoluble in methanol while PHEMA remains soluble. This means that fully soluble experiments can be performed in aqueous solution, and micelle formation can be triggered by the addition of methanol. The Nile blue dye was placed in the PHEMA block because the hydroxyl groups on the polymer may maintain a chemical environment that will keep the dye’s solvatochromic absorption and emission within the desired wavelengths during solid phase experiments. Nile blue dye functionalized with a methacrylamide group was obtained so that it could simply be polymerized into the pHEMA block. The NBD fluorophore can be placed in the PAAm block through a similar method. The research group of Prof. Theato at the University of Hamburg has used the NBD fluorophore with an acrylate monomer bearing a pentafluorophenyl ester that is highly active to functionalization with amines. As the NBD dye has a piperidinyl group in its structure, it readily reacts with these activated esters to near-quantitatively functionalize them with the dye.
Table 2.1: The absorption and emission maxima of the linker and dyes in the target block copolymers.

<table>
<thead>
<tr>
<th>Chromophore</th>
<th>Abs. $\lambda_{\text{max}}$ (nm)</th>
<th>Emis. $\lambda_{\text{max}}$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nile Blue (ethanol)</td>
<td>628</td>
<td>667</td>
</tr>
<tr>
<td>Nile Blue (methanol)</td>
<td>626</td>
<td>668</td>
</tr>
<tr>
<td>Nile Blue (water)</td>
<td>635</td>
<td>674</td>
</tr>
<tr>
<td>NBD Fluorophore</td>
<td>494</td>
<td>521</td>
</tr>
<tr>
<td>ONB Linker</td>
<td>300</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Figure 2.2: Activated ester chemistry for NBD incorporation.

ARGET ATRP was selected as the polymerization method because it is a controlled radical polymerization that readily prepares well-defined block copolymers and can be performed in the aqueous and alcoholic-solvent systems that are required. ARGET is an extension of conventional copper-mediated ATRP that includes the addition of a reducing agent to generate and regenerate the activating Cu$^+$ species in situ.$^{30}$ The presence of reducing agent permits very low levels of copper loading, from the part per thousand to the part per million level,$^{43}$ as well as making the polymerization tolerant of alcohols, water and oxygen.$^{44}$ This method produces polymers with an alkyl halide endgroup, which can be converted to an azide and used in recently reported one-pot reactions that combine copper-catalyzed alkyne-azide “click” chemistry with ATRP chain extension to produce block copolymer structures.$^{32a}$ Therefore, with several well-established methods, the target dye-labeled copolymer structure can be prepared targeting a series of block lengths.
2. 1. Materials and Methods

All reagents are used as received unless otherwise noted. Ethyl-2-bromo-2-methylpropanoate, 5-hydroxy-2-nitrobenzaldehyde, sodium borohydride and tetrahydrofuran were obtained from Aldrich Chemical Co. Acrylamide, ascorbic acid, and 5-hydroxyethyl methacrylate were obtained from TCI Chemical. Copper (II) bromide, 1,1,4,7,10,10-hexamethyltriethylenetramine, and α-bromoisobutyryl bromide were obtained from Sigma Chemical Co. Anhydrous dimethylformamide, anhydrous dimethylsulfoxide, propargyl bromide (80 wt% in toluene), and triethylamine were obtained from Alfa Aesar. Sodium azide and methanol were obtained from EMD Chemical. Nile blue methacrylamide was obtained from Polysciences, Inc. Anhydrous potassium carbonate was obtained from Fluka. Ethyl acetate was obtained from Fisher Scientific. Diethyl ether was obtained from BDH Chemical. Deuterated solvents were obtained from Cambridge Isotopes. Triethylamine was distilled from CaH₂. Tetrahydrofuran was distilled from sodium/benzophenone.

¹H and ¹³C NMR were performed on a Bruker 300 MHz spectrometer. FTIR was performed on a Perkin-Elmer Spectrum 100 spectrometer with a Universal ATR sampling accessory fitted with a ZnSe diamond-laminated crystal. Mass spectrometry was performed on a JEOL-700 MStation. GPC was performed on a Knauer instrument eluted with 0.05 M LiCl in DMF using RI detection and calibrated with linear PMMA standards.
2.2. Synthesis of control and dye-labeled polymers

Scheme 2.1: Overall synthesis of dual-dye labeled block copolymer. In each block, n and y are 1-2 mol% of ATRP initiator.

Three copolymers were targeted with both blocks of equal size, approximately 5 kDa, 10 kDa and 20 kDa molecular weight, respectively. The PAAm block was synthesized first, in both labeled and unlabeled versions. Half of the obtained PAAm was then functionalized with an azide endgroup and used in one-pot click/ARGET ATRP chain extension to add the poly(5-hydroxyethyl methacrylate) (PHEMA) block. Dye-labeled PAAm was chain extended with dye-labeled PHEMA, and the unlabeled PAAm was extended with unlabeled PHEMA.
2.2.1. Synthesis of 2-Nitro-5-(prop-2-yn-1-yloxy)benzyl 2-bromo-2-methylpropanoate (pMAI)

![Reactions diagram]

**Scheme 2.2:** Synthetic scheme of pMAI.

2.2.1.1. Synthesis of 5-(prop-2-yn-1-yloxy)-2-nitrobenzaldehyde (pHNB)

1.0417 g (6.23 mmol) 5-hydroxy-2-nitrobenzaldehyde and 1.4456 g (10.5 mmol) anhydrous \( \text{K}_2\text{CO}_3 \) were dissolved in 25 mL anhydrous DMF. The solution was stirred at 60 °C for 30 minutes, then 1.5 mL (13.4 mmol) propargyl bromide (80 wt% in toluene) were added slowly by syringe. The solution was stirred at 60 °C for 1 hour. The solution was diluted with ethyl acetate and water. The organic layer was washed with water and brine, then dried over MgSO\(_4\) and the volatiles removed in vacuo. Pure pHNB was obtained as a light brown crystalline solid. 86% isolated yield. M.P.: 62-63°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) = 10.28 (s, 1H, H-C=O), 8.198 (d, 1H, H\(_{Ar}\)), 7.455 (d, 1H, H\(_{Ar}\)), 7.350 (s, 1H, H\(_{Ar}\)), 5.075 (s, 2H, -O-CH\(_2\)-C=), 3.729 (s, 1H, C=C-H). \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) = 189.88 (-C=O), 161.34 (C\(_{Ar}\)-NO\(_2\)), 142.69 (C\(_{Ar}\)-O-), 134.21 (C\(_{Ar}\)-C=O), 127.43 (C\(_{Ar}\)), 119.24 (C\(_{Ar}\)), 114.72 (C\(_{Ar}\)), 79.68 (-C=C=H), 77.70 (-CH\(_2\)-C=O-).
FTIR (ATR, cm⁻¹): 3280 m, 2120 w, 1688 s, 1583 s, 1520 s, 1232 s. Mass spec (El-MS): theoretical M⁺: 205.2 m/z, observed M⁺: 205.0 m/z.

2. 1. 2. 2. Synthesis of 5-(prop-2-yn-1-yloxy)-2-nitrobenzyl alcohol (pONB)

4.2620 g (20.8 mmol) pHNB were dissolved in 100 mL MeOH, and the flask was placed in an ice/water bath. 2.9838 g (78.9 mmol) NaBH₄ granules were added slowly. The solution was stirred at 0 °C for 1 hour. The solution was diluted with water and diethyl ether. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with 100 mL brine, the dried over MgSO₄ and the volatiles were removed in vacuo. Pure pONB was obtained as a beige, crystalline solid. 84 % isolated yield. M.P.: 133-134 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.190 (d, 1H, H₆). 7.333 (s, 1H, H₅), 6.990 (d, 1H, H₆), 5.013 (d, 2H, -O-CH₂-C≡), 4.811 (s, 2H, Ar-CH₂-OH), 2.572 (t, 1H, -C≡C-H), 2.520 (s, 1H, -O-H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 162.30 (C₆-NO₂), 141.190 (C₆-O-), 140.25 (C₆-CH₂-OH), 128.37 (C₆), 115.65 (C₆), 113.95 (C₆), 77.47 (-C≡C-H), 77.00 (-CH₂-C≡C-), 63.34 (-O-CH₂-C≡), 56.55 (Ar-CH₂-OH). FTIR (ATR, cm⁻¹): 3274 b, 3266 s, 2125 w, 1587 s, 1507 s, 1240 s. Mass spec (El-MS): theoretical M⁺: 207.2 m/z, observed M⁺: 207.06 m/z.

2. 2. 1. 2. Synthesis of 2-Nitro-5-(prop-2-yn-1-yloxy)benzyl 2-bromo-2-methylpropanoate (pMAI)

A 100 mL RBF was charged with 1.0132 g (4.89 mmol) pONB that was dissolved in 50 mL dry, freshly distilled THF. 1.0 mL (7.17 mmol) dry, freshly distilled TEA were added by syringe, followed by 0.65 mL (5.26 mmol) bromoisobutyryl bromide. The flask was stirred at room temperature for 24 hours, then transferred to a separatory funnel and diluted with ethyl acetate. The organic layer was washed twice with water and once with
brine, then dried over MgSO₄ and the volatiles removed in vacuo to yield pMAI as a clear, colorless oil. Isolated yield: 87%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.221 (d, 1H, H₃), 7.296 (s, 1H, H₄), 7.011 (d, 2H, H₅), 5.671 (s, 1H, Ar-CH₂-O-C=O), 4.793 (s, 2H, Ar-CH₂-C≡), 2.586 (s, 1H, C≡C-H), 2.005 (6H, C(CH₃)₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 170.80 (C=O), 161.68 (C₃-N=O₂), 140.15 (C₅-O-CH₂-), 135.22 (C₆-CH₂-), 127.92 (C₇), 114.41 (C₈), 113.32 (C₉), 77.204 (-CH₂-C≡C-), 76.847 (-C≡C-H), 64.41 (-O-CH₂-C≡), 56.67 (Ar-CH₂-O), 55.47 (-C(CH₃)₂Br), 30.84 ((CH₃)₂). FTIR (ATR, cm⁻¹): 3290 (m), 2125 (w), 1740 (s), 1580 (s), 1515 (s), 1250 (b). Mass spec (ESI-MS): theoretical M⁺: 377.9948 m/z, observed M⁺: 377.9932 m/z.

2.2.2. ARGET ATRP of PAAm

![Scheme 2.3: ARGET ATRP of PAAm.](image_url)

The polymerizations were performed in 20 mL scintillation vials. Vials A, B, and C were not dye labeled, while vials D, E, and F were labeled with the NBD fluorophore via activated ester chemistry. Vials A and D, B and E, and C and F targeted PAAm molecular weights of 5 kDa, 10 kDa, and 20 kDa, respectively. The example procedures shown below are for the 10 kDa unlabeled and labeled polymers.

30
Table 2.2: Composition of PAAm panel.

<table>
<thead>
<tr>
<th>Vial Label</th>
<th>Target Mn</th>
<th>Labeled (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5,000 g/mol</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>10,000 g/mol</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>20,000 g/mol</td>
<td>No</td>
</tr>
<tr>
<td>D</td>
<td>5,000 g/mol</td>
<td>Yes</td>
</tr>
<tr>
<td>E</td>
<td>10,000 g/mol</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>20,000 g/mol</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Two 20 mL scintillation vials were charged with 1.0 g (14 mmol) acrylamide and 7.3 mL DMSO. 19.7 mg (0.101 mmol) ethyl-2-bromoisobutyrate (EBIB), 1.14 mg (5.1 μmol) CuBr₂ and 5.76 mg (25.5 μmol) 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) were added from stock solutions in DMSO. To the dye-labeled vial (vial E) were also added 9.9 μL (10.2 μg, 4.04 nmol) pentafluorophenyl methacrylate (PFPMA) and 1.00 μg (4.01 nmol) NBD fluorophore. The vials were bubbled with dry N₂ for one minute. The vials were stirred at room temperature for 20 minutes, then 53.3 mg (0.303 mmol) ascorbic acid was added in 1.00 mL DMSO to initiate the polymerization. The vials were sealed and stirred at room temperature for 24 hours. The polymer was precipitated from methanol and dried. 60-80% isolated yield. ¹H NMR (DMSO-\textit{d₆}, 300 MHz): δ (ppm) = 7.186 and 6.832 (broad, 2H, backbone NH₂), 2.073 (broad, 1H, backbone CH), 1.5-1.15 (broad, 11H, backbone CH₂, three endgroup CH₃). FTIR (ATR, cm⁻¹): 3410 (broad, N-H), 1740 (s, carbonyl).

PAAm molecular weights were determined by ¹H NMR due to difficulties with performing GPC analysis. This was done by comparing the PAAm backbone CH proton resonance at 2.07 ppm to the overlapping resonances from the PAAm backbone CH₂ protons and the end-group protons from the three methyl groups at 1.10 ppm. As the CH₂ integration should be twice that of the CH, the integral difference between the two can be
attributed to the endgroup protons, allowing the ratio of endgroup to backbone protons to be calculated, leading to the number-average molecular weight, \( M_N \), of the polymer. Below is a table correlating the sample with its targeted and obtained molecular weights.

**Table 2.3:** Molecular weights obtained by \(^1\)H NMR of the PAAm blocks.

<table>
<thead>
<tr>
<th>Vial</th>
<th>Dye label (Y/N)</th>
<th>Target ( M_N ) (Da)</th>
<th>Obtained ( M_N ) (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No</td>
<td>5,000</td>
<td>4,980</td>
</tr>
<tr>
<td>B</td>
<td>No</td>
<td>10,000</td>
<td>17,300</td>
</tr>
<tr>
<td>C</td>
<td>No</td>
<td>20,000</td>
<td>25,400</td>
</tr>
<tr>
<td>D</td>
<td>Yes</td>
<td>5,000</td>
<td>7,400</td>
</tr>
<tr>
<td>E</td>
<td>Yes</td>
<td>10,000</td>
<td>14,500</td>
</tr>
<tr>
<td>F</td>
<td>Yes</td>
<td>20,000</td>
<td>26,400</td>
</tr>
</tbody>
</table>

2.2.3. Preparation of PAAm azides

![Reaction Scheme](image)

**Scheme 2.4:** Conversion of alkyl bromide to alkyl azide via \( S_N2 \) mechanism.

A 5 mL scintillation vial was charged with a stir bar, 100 mg (20 \( \mu \)mol) PAAm (polymer A, unlabeled, 5 kDa) and 16.0 mg (0.246 mmol) \( NaN_3 \). 2.0 mL DMF and 2.0 mL water were added, and the vial stirred at 50 °C for 24 hours. The polymer was precipitated from 40 mL methanol and collected by vacuum filtration. Collected yield: 55-72 % by weight.

All \(^1\)H NMR spectra were similar to those before the azide conversion. These spectra can be seen in Appendix A. The FTIR spectra, on the other hand, displayed a band associated with azides, around 2100 cm\(^{-1}\), that was not present before the bromide to azide transformation. Example spectra of PAAm F before and after azide transformation are
shown in figure 2 below. While this is not evidence of complete functionalization, high conversion is likely due to the strength of the observed azide band despite its high dilution.

![PAAm F Overlay](image)

**Figure 2.3:** Overlay of ATR-FTIR spectra before and after azide transformation, showing azide absorbance band at \( \sim 2100 \text{ cm}^{-1} \).

After the synthesis of the PAAm azides, chain extension under ARGET ATRP conditions was performed with HEMA as monomer and pMAI as clickable ATRP initiator.

2.3. ARGET ATRP Chain Extension with HEMA

![Scheme 2.5](image)

**Scheme 2.5:** General polymerization conditions for preparation of PAAm-\( h \)-PHEMA.
A 5 mL scintillation vial was charged with 1 equiv. PAAM-azide, 1 equiv. pMAI, 0.1 mol % (from a stock solution in DMSO), 5:1 HMTETA:CuBr₂ (as regarding copper content, from a stock solution in DMSO), the required amount of HEMA to achieve the target molecular weight at 50% conversion, and 0.5 mL water. In dye-labeled samples, 2 mol % (as compared to equiv. of PAAM-azide and pMAI) of Nile Blue methacrylamide were added as a stock solution in DMSO. The vials were then swirled over a heat gun until the polymer dissolved, then placed in a heating block set to 35 °C. To start the polymerization, 6 mol % ascorbic acid were added as a stock solution in DMSO, and the vial was wrapped in Al foil to protect it from light. After 2.5 hours, the vial contents were dripped into 30 mL of methanol to precipitate the polymer. The polymer was collected by vacuum filtration. Typical polymer yields were in the range of 40-80 %. Low concentrations of the dyes are required for these materials to be appropriate for the CFS measurements, meaning that 2 mol% of each block is labeled and therefore 1 chain per 2,500 should bear both dyes. This should not present issues during the experiments, as both blocks can still be tracked by their fluorescent signatures. If materials that bear both dyes in each chain are required, a stoichiometric ratio of dye to ATRP initiator can be used. Comparable materials can then be synthesized without dye and used to dilute the fluorescent material, if needed.

After precipitation, all methanol filtrates were clear and colorless, indicating that all the added Nile Blue was incorporated into the polymer. The polymers were analyzed by $^1$H NMR to determine HEMA content, the results of which can be seen below in table 2.3. The resonance at about 7 ppm from the nitrogen-bonded protons in the PAAm block were compared to the resonances between 2.5 and 1 ppm, which are from the backbone
units of both the PAAm and PHEMA blocks. Any PHEMA not conjugated to PAAm remained soluble in the methanol, and does not appear in the copolymer NMR traces. The PHEMA block masses are slightly underestimated due to the presence in the NMR traces of residual diethyl ether that was used to wash out residual methanol from the precipitated block copolymer, as well as by being diluted by any PAAm that was not azide functionalized and therefore not chain extended with PHEMA.

Table 2.4: Molecular weights of each block in the PAAm-\(h\)-PHEMA copolymer series.

<table>
<thead>
<tr>
<th>Copolymer batch</th>
<th>(M_N) PAAm (Da)</th>
<th>(M_N) PHEMA (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17,300</td>
<td>7,700</td>
</tr>
<tr>
<td>3</td>
<td>25,400</td>
<td>2,800</td>
</tr>
<tr>
<td>4</td>
<td>7,400</td>
<td>1,080</td>
</tr>
<tr>
<td>5</td>
<td>14,500</td>
<td>1,560</td>
</tr>
<tr>
<td>6</td>
<td>26,400</td>
<td>6,600</td>
</tr>
</tbody>
</table>

2.4. Photocleavage of PAAm-\(h\)-PHEMA Materials

To verify that the generated polymers were photocleavable, 1-3 mg of each block copolymer was dissolved in 0.5 mL DMSO, then placed under a 365 nm UV source (1.36 mW/cm²) for 17 hours. The samples were then diluted with 1.0 mL MeOH-\(d_4\) to precipitate any PAAm, whether cleaved or still bound. Any free PHEMA would remain soluble. For all samples, a fine white precipitate formed that was removed from the solution by filtration through a Teflon filter. The MeOH-\(d_4\) was then removed under a stream of dry nitrogen, and the sample analyzed again by \(^1\)H NMR.

In all cases, no PAAm resonances were observed, while resonances associated with the PHEMA block were still present, as can be seen in figure 2.3 below. The slight shift in the ppm value of the PHEMA resonances is attributed to incomplete removal of the MeOH-\(d_4\).
**Figure 2.4:** Comparison of PAAm-$h$-PHEMA (bottom) to the residue after UV irradiation and PAAm removal by precipitation (top) showing only PHEMA left behind.

2.5. Conclusion

To investigate fundamental questions in the polymer physics of photocleavable polymer systems, it was necessary to design a photocleavable block copolymer that had each block labeled with a fluorescent dye that would enable them to be independently tracked via correlation fluorescence spectroscopy. The structure that was designed is a poly(acrylamide)-$h$-poly(5-hydroxyethyl methacrylate) system, where the two blocks are synthesized by ARGET ATRP and connected through a photocleavable junction containing an o-nitrobenzyl ester. A panel of comparable dye-labeled and non-dye labeled polymers was produced. The poly(acrylamide) blocks are labeled with a green
fluorophore, 4-nitro-7-(piperazin-1-yl)-2,1,3-benzoxadiazole, while the poly(5-hydroxyethyl methacrylate) blocks were labeled with methacrylamide-functionalized Nile Blue. The polymers were characterized by $^1$H NMR to demonstrate that a spectrum of molecular weights were obtained for each block, and that the polymers are photocleavable. Due to the solubility behavior of the two blocks, both fully solubilized and partially insoluble systems can be investigated with these materials. Further, this synthetic paradigm can be extended to any two monomers that can be polymerized by ATRP chemistries, opening up the possibility of exploring many different photocleavable block copolymer systems.
References:


CHAPTER 3

THE O-NITROBENZYL-1,2,3-TRIAZOLE LINKER FOR CLICK/CLIP MATERIAL APPLICATIONS

In this section, the synthesis and characterization of a small molecule analog of the o-nitrobenzyl-1,2,3-triazole linker is described that was used to verify the linker’s photocleavage products. A small molecule analog of the established o-nitrobenzyl ester linker was also synthesized, and the two analogs were tested under several conditions to establish their thermal and chemical stability profiles. Once the behavior of the ONBTz linker was established, a facile, high-yield method for producing o-nitrobenzyl azides was developed. This synthesis was intended to enable the preparation of a mono-ATRP initiator o-nitrobenzyl azide (MAIZ) that was then used with CuAAC/ARGET ATRP polymerization methods to attempt to prepare clicked-together and photocleavable block copolymers. However, chain extension of an alkyne-functionalized PEO with HEMA via MAIZ was not achieved. A hypothesis to explain this result is discussed near the end of the chapter.

3.1. Materials and Methods

Unless otherwise noted, all materials and methods are the same as those noted in chapter two. 2-nitrobenzyl bromide, copper (II) sulfate pentahydrate, tert-butyl alcohol, 2-nitrobenzaldehyde, and carbon tetrabromide were obtained from Alfa Aesar. Ethanol was obtained from Acros Organics. Sodium ascorbate, chloromethyl methyl ether (MOMCl), triphenylphosphine (TPP), and α-bromoisobutyryl bromide (BIB) were obtained from Aldrich Chemical Co., Inc. Ammonium hydroxide, sodium chloride, anhydrous magnesium sulfate, hydrochloric acid (aq., con.), and potassium hydroxide were obtained
from Fisher Scientific. Hexanes were obtained from Mallinckrodt. Deuterated chloroform, deuterated methanol, deuterated acetic acid, and deuterated water were obtained from Cambridge Isotopes. 5-hydroxyethyl methacrylate was obtained from TCI America. Ethanol was purified by distillation.

$^1$H and $^{13}$C NMR spectra were obtained on a Bruker 400 MHz spectrometer. Thermogravimetric analysis was performed on a Thermal Analysis TGA Q500. Gas chromatography-mass spectrometry was performed on a HP 5890 GC-MS instrument. ESI-MS was performed on a Bruker MicrOTOF mass spectrometer, and EI-MS was performed on a JEOL JMS700 MStation Sector mass spectrometer. GPC analysis was performed on a Knauer instrument eluted with 0.05 M LiCl in DMF using RI detection and calibrated with linear PMMA standards.

3.2. Synthesis and characterization of the o-nitrobenzyl-1,2,3-triazole linker

In order to verify the hypothesized behavior of the o-nitrobenzyl-1,2,3-triazole (ONBTz) linker, a small molecule analog was synthesized for both this linker and for the established o-nitrobenzyl ester (ONB) linker (figure 3.1)

![Figure 3.1: Small molecule analogs for ONBTz (left) and ONB (right) linkers.](image)

These analogs were characterized by $^1$H and $^{13}$C NMR, ATR-FTIR, mass spectrometry, and UV-Vis, and then compared in terms of thermal, acid, and base stability
in a series of NMR experiments. The stability experiments will be detailed in following sections.

Scheme 3.1: Synthetic scheme for ONBTz small molecule analog.

3.2.1. Synthesis of o-nitrobenzyl azide

A 25 mL RBF was charged with 0.5177 g (2.396 mmol) 2-nitrobenzyl bromide and 0.1701 g (2.617 mmol) sodium azide dissolved in 7 mL dry EtOH. The flask was fitted with a water-cooled condenser and heated to 40 °C for 24 hrs. The EtOH was removed by rotovap, then the remaining solid was suspended in 40 mL diethyl ether. The ether solution was filtered, and the ether removed in vacuo to yield the product as a clear, light yellow oil. 75% isolated yield. $^1$H NMR (300 MHz, CDCl3): $\delta$ (ppm) = 8.119 (d, 1H, $H_{Ar}$), 7.671 (m, 2H, $H_{Ar}$), 7.514 (m, 1H, $H_{Ar}$), 4.857 (s, 2H, Ar-CH$_2$-N$_3$). FTIR (ATR, cm$^{-1}$): 2937 (w), 2097 (s), 1565 (s).

3.2.2. Synthesis of ONBTz small molecule analog

A 20 mL scintillation vial was charged with 319.9 g (1.792 mmol) 2-nitrobenzyl azide, 62.1 mg (0.249 mmol) CuSO$_4$$\cdot$5H$_2$O, and 68.4 mg (0.345 mmol) sodium ascorbate dissolved in 10 mL of a 2:1 v:v t-butyl alcohol:water mixture. The flask was stirred at 35 °C for 48 hrs. The reaction was transferred to a separatory funnel and diluted with diethyl ether. The organic layer was washed twice with 5% NH$_4$OH (aq) and once with brine. The organic layer was dried over MgSO$_4$ and the volatiles removed in vacuo to yield ONBTz as a pearly, crystalline solid. 89% isolated yield M.P.: 101-102 °C. $^1$H NMR (300 MHz,
MeOH-$d_4$): $\delta$ (ppm) = 8.138 (d, 1H, $H_{Ar}$), 7.798 (s, 1H, $H_{Ar}$), 7.678 (t, 1H, $H_{Ar}$), 7.602 (t, 1H, $H_{Ar}$), 7.066 (d, 1H, $H_{Ar}$), 5.952 (s, 2H, Ar-CH$_2$-Ar), 2.720 (t, 2H, Ar-CH$_2$-CH$_2$-), 1.660 (m, 2H, -CH$_2$-CH$_2$-CH$_2$-), 1.387 (m, 2H, -CH$_2$-CH$_2$-CH$_3$), 0.950 (t, 3H, -CH$_2$-CH$_3$). $^{13}$C NMR (75 MHz, MeOH-$d_4$): $\delta$ (ppm) = 148.262 ($C_{Ar}$=NO$_2$), 147.82 ($C_{Ar}$-CH$_2$-), 133.83 ($C_{Ar}$), 130.72 (triazole $C_{Ar}$-CH$_2$-), 129.87 ($C_{Ar}$), 129.34 ($C_{Ar}$), 124.88 ($C_{Ar}$), 122.70 (triazole $C_{Ar}$), 50.41 (Ar-CH$_2$-triazole), 31.27 (triazole-CH$_2$-CH$_2$-), 24.58 (triazole-CH$_2$-CH$_2$-), 21.82 (-CH$_2$-CH$_2$-CH$_3$), 12.71 (-CH$_2$-CH$_3$). FTIR (ATR, cm$^{-1}$): 1515 (s). ESI-MS: formula: $C_{13}H_{16}N_{4}O_{2}$, calculated $M^+$=261.1346, observed $M^+$=261.1337 m/z.

3.2.3. Synthesis of ONB small molecule analog

![Scheme 3.2: Synthetic scheme for ONB small molecule analog.](image)

3.2.3.1. Synthesis of 2-nitrobenzyl alcohol:

A 25 mL RBF was charged with 501.1 mg (3.316 mmol) 2-nitrobenzaldehyde dissolved in 10 mL methanol. The flask was placed in an ice/water bath, and 300.9 mg (7.954 mmol) NaBH$_4$ were added slowly. The flask was stirred for 90 minutes, then quenched with 1 M HCl (aq). The solution was transferred to a separatory funnel, diluted with diethyl ether and washed twice with water and once with brine. The organic layer was dried over MgSO$_4$ and the volatiles removed in vacuo to yield ONB as a cream-colored solid. 64 % isolated yield. M.P.: 74-75 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.090 (d, 1H, $H_{Ar}$), 7.701 (m, 2H, $H_{Ar}$), 7.486 (d, 1H, $H_{Ar}$), 4.977 (s, 2H, Ar-CH$_2$-O-), 2.642 (s, 1H, -CH$_2$-O-H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 147.46 ($C_{Ar}$), 136.98 ($C_{Ar}$), 134.16 ($C_{Ar}$), 129.91 ($C_{Ar}$).
128.49 (C<sub>Ar</sub>), 125.10 (C<sub>Ar</sub>), 62.55 (Ar-CH<sub>2</sub>-OH). FTIR (ATR, cm<sup>-1</sup>): 3310 (b), 1515 (s). EIMS: formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>, calculated M<sup>+</sup>=176.0318 m/z, observed M<sup>+</sup>=176.0319 m/z.

3.2.3.2. Synthesis of ONB small molecule analog:
A 20 mL scintillation vial was charged with 266.7 mg (1.742 mmol) 2-nitrobenzyl alcohol and 10 mL dry, freshly distilled THF. 0.41 mL (0.297 g, 2.94 mmol) dry, freshly distilled TEA and 0.25 mL (0.302 g, 2.152 mmol) benzoyl chloride were added by syringe and the solution stirred at room temp overnight. The solution was transferred to a separatory funnel and diluted with diethyl ether and washed twice with water and once with brine. The organic layer was dried over MgSO<sub>4</sub> and the volatiles removed in vacuo, resulting in ONB as a pale yellow solid. 89% isolated yield. M.P.: 84-88 °C. <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>): δ (ppm) = 8.131 (d, 1H, H-C<sub>Ar</sub>-C<sub>Ar</sub>-NO<sub>2</sub>), 8.060 (d, 2H, H-C<sub>Ar</sub>-C=O), 7.997 (1H, H<sub>Ar</sub>), 7.752 (2H, H<sub>Ar</sub>), 7.615 (2H, H<sub>Ar</sub>), 7.501 (3H, H<sub>Ar</sub>), 5.714 (2H, Ar-CH<sub>2</sub>-O-). <sup>13</sup>C NMR (75 MHz, MeOH-d<sub>4</sub>): δ (ppm) = 136.17 (C=O), 135.18 (C<sub>Ar</sub>-NO<sub>2</sub>), 134.86 (C<sub>Ar</sub>), 134.29 (C<sub>Ar</sub>-C=O), 131.75 (C<sub>Ar</sub>), 130.96 (C<sub>Ar</sub>), 130.89 (C<sub>Ar</sub>), 130.76 (C<sub>Ar</sub>-CH<sub>2</sub>-), 130.54 (C<sub>Ar</sub>), 130.47 (C<sub>Ar</sub>), 129.9 (C<sub>Ar</sub>), 129.71 (C<sub>Ar</sub>), 126.30 (C<sub>Ar</sub>), 64.81 (C<sub>Ar</sub>-CH<sub>2</sub>-C=O). FTIR (ATR, cm<sup>-1</sup>): 1730 (s), 1580 (s), 1515 (s). ESI-MS: formula: C<sub>14</sub>H<sub>11</sub>NO<sub>4</sub>, calculated M<sup>+</sup>: 280.05803 m/z, observed M<sup>+</sup>: 280.06037 m/z.

3.2.4. Photocleavage products of ONBTz

![Scheme 3.3: Photocleavage products of ONBTz](image-url)
A sample of ONBTz small molecule analog in methanol solution (63 mg/mL methanol) was exposed to 365 nm light at an intensity of 1.32 mW/cm² for 4 days, then the solution was separated into its components on a silica gel column eluted with 5:1 v:v hexanes:EtOAc. The materials were characterized by ATR-FTIR and by GC-MS of a small sample of the photocleavage solution after exposure.

**Figure 3.2:** ATR-FTIR traces of pristine ONBTz (top), and photocleavage products 4-butyl-1,2,3-triazole (middle) and o-nitrosobenzaldehyde (bottom).
The FTIR trace of pristine ONBTz shows a distinct band at 1520 cm\(^{-1}\) originating from the aryl nitro group. The trace for \(o\)-nitrosobenzaldehyde displays a strong band at 1734 cm\(^{-1}\), attributed to the carbonyl, as well as a shift from an aryl nitro signature to an aryl nitroso at 1540 cm\(^{-1}\). The 4-butyl-1,2,3-triazole shows no bands between 1500 and 1600 cm\(^{-1}\) that would indicate the presence of aryl nitro or nitroso groups, while displaying bands at 792 and 1009 cm\(^{-1}\) that are associated with free 1,2,3-triazoles.

The GC-MS data provides strong evidence that the hypothesized \(o\)-nitrosobenzaldehyde and 4-butyl-1,2,3-triazole products do indeed result from photocleavage of the ONBTz linker. Two GC signals were observed. A M\(^+\) at 136 m/z is the molecular ion of the \(o\)-nitrosobenzaldehyde, while the fragment at 106 (m/z) corresponds to the molecular ion’s loss of CHO, which is characteristic of benzaldehydes. The second GC peak does not display a M\(^+\) for 4-butyl-1,2,3-triazole, but the fragmentation pattern still identifies this compound. Free 1,2,3-triazoles prefer to exist in the 2H isomer, where the labile hydrogen is carried on the nitrogen atom in the 2 position. Under high energy conditions (such as ionization in a mass spectrometer), this isomer decomposes into nitrilimine and a corresponding nitrile fragment (see scheme 3.4 below).\(^1\) The masses of nitrilimine and the predicted nitrile fragment from the decomposition of 4-butyl-1,2,3-triazole correspond well to the masses observed in the MS data.

<table>
<thead>
<tr>
<th>GC Peak</th>
<th>M/z</th>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>136</td>
<td>2-nitrosobenzaldehyde M(^+)</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>M(^+) minus CHO</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>Nitrile fragment of decomposed 4-butyl-1,2,3-triazole</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>Nitrilimine</td>
</tr>
</tbody>
</table>
Scheme 3.4: High-energy decomposition of 4-butyl-1,2,3-triazole.

3.2.5. Stability Assays of ONBTz

Understanding the stability profile of a cleavable linker structure to conditions such as heat, acid, and base is critical to identifying applications to which the linker is suited. Therefore, a series of $^1$H NMR experiments were performed during which the ONBTz and ONB small molecule analogs were exposed to a variety of conditions. NMR spectra were taken directly after sample preparation, and after 24 hours of incubation. These were then compared with each other and the spectrum of the pristine compound to assess general stability.

3.2.5.1. Preparation of the samples:

**Thermal:** 4.1 mg (0.016 mmol) ONBTz was dissolved in 1.00 mL methanol-$d_4$. 11.7 mg (0.045 mmol) ONB was dissolved in methanol-$d_4$. Both samples were then heated to 50 °C for 24 hours.

**Acid:** 3.6 mg (0.014 mmol) ONBTz was dissolved in 0.95 mL methanol-$d_4$ to which 0.05 mL acetic acid-$d_4$ was added. 6.2 mg (0.024 mmol) ONB were dissolved in 0.95 mL methanol-$d_4$ to which 0.05 mL acetic acid-$d_4$ was added.

**Base:** 3.2 mg (0.012 mmol) ONBTz was dissolved in 0.80 mL methanol-$d_4$ to which was added 0.20 mL 1 M KOH in D$_2$O. 6.2 mg (0.024 mmol) ONB were dissolved in 0.80 mL methanol-$d_4$ to which was added 0.20 mL 1 M KOH in D$_2$O.
The results of these experiments are summarized in table 3.2, as well as comparisons to non-nitrat ed benzyl triazoles and two common triazole protecting groups, pivalate and trimethylsilyl (TMS). 

**Table 3.2:** Stability profiles of ONBTz compared to several other common linkers and protecting groups. (*=benzylidene proton exchange observed by NMR, but no cleavage observed by TLC, †=stable over short periods, but hydrolysis is unavoidable over long time scales)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pivalate</th>
<th>TMS</th>
<th>Benzyl</th>
<th>ONB Ester</th>
<th>ONBTz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat</td>
<td>Stable</td>
<td>Labile</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Acid</td>
<td>Labile</td>
<td>Labile</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Base</td>
<td>Labile</td>
<td>Labile</td>
<td>Stable*</td>
<td>Labile</td>
<td>Stable*</td>
</tr>
<tr>
<td>Water</td>
<td>Stable</td>
<td>Labile</td>
<td>Stable</td>
<td>Stable†</td>
<td>Stable</td>
</tr>
<tr>
<td>Visible light</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>UV light</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Labile</td>
<td>Labile</td>
</tr>
</tbody>
</table>

These stability experiments indicate that the ONBTz linker is relatively stable to a variety of conditions, but labile when exposed to 300-365 nm light. This stability profile follows well from observations made of non-nitrat ed benzyl triazoles, which share the ONBTz’s overall stability. As compared to the pivalate or TMS protecting groups, the ONBTz group has several distinct advantages in terms of thermal and chemical tolerance, indicating the ONBTz group could be applicable as a triazole protecting group during syntheses that require the use of reaction conditions that would deprotect a pivalate or trimethylsilyl ether. The ONBTz linker has superior base tolerance to the ONB ester. As seen in figure 3.3 below, the $^1$H NMR traces of the ONBTz base samples show benzylidene proton exchange, but there is no evidence of cleavage when TLC is performed on the NMR sample. However, the ONB small molecule analog cleaved quantitatively into o-nitrobenzyl alcohol and benzoic acid immediately upon exposure to the base, as can be seen from the aromatic resonances in the NMR spectrum. Further, the benzylidene protons in the ONB sample can be observed to shift their resonance from $\delta$ 5.75 ppm to $\delta$ 4.90 ppm,
as a result of the transformation from a benzyl ester to a benzyl alcohol. This benzyl alcohol resonance is in good agreement with previously prepared compounds.

**Figure 3.3:** (top) ONBTz 1H NMR showing pristine (upper trace) and base-treated (lower trace) material; (bottom) ONB 1H NMR showing pristine (upper trace) and base-treated (lower trace) material.
Both small molecule analogs were also analyzed by thermogravimetric analysis (TGA) under nitrogen to determine their decomposition profiles. The ONB ester displayed 2% mass loss at 110 °C, with full volatilization by 250 °C. The ONBTz small molecule analog, by contrast, did not show 2% mass loss until nearly 230 °C, and at the end of the TGA ramp (500 °C), 60% of the mass still remained as char. This indicates that the ONBTz linker would be a better candidate for use in photocleavable materials that will be exposed to high temperatures.

3.3. Synthesis of 5-hydroxy-2-nitrobenzyl azide

This section covers the preparation of 5-hydroxy-2-nitrobenzyl azide, the primary feedstock for 3-(azidomethyl)-4-nitrophenyl-2-bromo-2-methylpropanoate (MAIZ). As the transformation of commercially available o-nitrobenzyl alcohols to o-nitrobenzyl azides has been challenging, time was devoted to developing a facile, high-yield method to achieve this transformation involving the Appel reaction.

3.3.1. A Facile, high-yield method for preparing o-nitrobenzyl azides from o-nitrobenzyl alcohols

In the search for an efficient way of converting commercially available 5-hydroxy-2-nitrobenzyl alcohol substrates into the required o-nitrobenzyl azides, attempts were made to use the Mitsunobu reaction, activated phosphoester chemistries (diphenylphosphoryl azide and DBU, 2,4-bidisclorophosphate, DMAP and sodium azide), tosylolation and mesylation. None of these methods afforded more than a 35% isolated yield of the desired product MAIZ. Tosylations were difficult to purify and required azide substitution conditions that destroyed the phenyl ester bearing the ATRP initiating site. The mesylates were too reactive to purify before substitution, but attempts at simultaneous mesylation and
azide substitution resulted in side reactions that consumed mesyl chloride and sodium azide. The Mitsunobu reaction and activated phosphoesters had two issues; the first was that neglecting to protect the phenol resulted in phosphoester formation at that position; the second was that while the phosphoester could form at the benzyl position, it was not sufficiently active to be displaced by the azide nucleophile even when highly activated reagents such as 2,4-bisdichlorophosphate were used.

After realizing that one-pot methods were not going to produce the yields of o-nitrobenzyl azides required, two-step methods were considered. A simple way of producing azides is by SN$_2$ displacement of an alkyl halide.$^3$ One of the oldest known reactions for transforming alcohols into alkyl halides is the Appel reaction.$^4$ By using this transformation as a stepping-stone to the desired azide, not only were process yields increased (35% product to better than 50%), the intermediate benzyl bromide is itself a highly useful compound that can be functionalized in numerous ways by nucleophilic substitution of the halide.

With optimization, it was possible to design a synthesis for MAIZ, and the alkyne-azide monomer that will be discussed in chapter 4 of this thesis, that could be completed in as little as four days with a single column chromatography purification. This method also relies mainly on abundant, relatively inexpensive reagents, and is readily scalable. This method has been used to produce compounds on the multi-gram scale, with the main limitation being the column chromatography purification after the Appel reaction. Any further attempts to improve this process would be best invested in finding alternative methods of purification like recrystallization, rather than using chromatography.
3.3.2. Synthesis and Characterization of MAIZ

\[
\text{MOMCl (1.5 equiv.) TEA (2 equiv.) THF, r.t., 24 hrs 90\% yield}
\]

\[
\begin{align*}
\text{NaBH}_4 & (3 \text{ equiv.) MeOH, 0 °C, 2 hrs 87\% yield} \\
\text{TPP (1.5 equiv.) CBr}_4 (1.5 \text{ equiv.) THF, r.t., 1 hr 87\% yield} \\
\text{NaN}_3 & (2 \text{ equiv.) THF, reflux, 7 hrs 88\% yield} \\
\text{BIB (1.5 equiv.) TEA (2 equiv.) THF, r.t., 24 hrs 78\% yield} \\
\end{align*}
\]

\text{MAIZ, 43\% process yield}

\textbf{Scheme 3.5: Full synthesis of MAIZ.}

3.3.2.1. Synthesis of 2-nitro-5-(methoxy methoxy)benzaldehyde:

5.2004 g (3.11 mmol) 5-hydroxy-2-nitrobenzaldehyde were dissolved in 125 mL dry, freshly distilled THF. 8.5 mL (6.1 mmol) dry, freshly distilled TEA were added by syringe, then 4.5 mL (5.9 mmol) chloromethyl methyl ether were added in 0.5 mL aliquots every 30 seconds. The solution was stirred at room temperature overnight. The solution was diluted with ethyl acetate and water, and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, then dried over MgSO\textsubscript{4} and the volatiles removed in vacuo. 2-Nitro-5-(methoxy methoxy)benzaldehyde was obtained as a beige, crystalline solid. 90\% isolated yield. M.P.: 68-69 °C \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 10.45 (s, 1H, H-C=O), 8.136 (d, 1H, H\textsubscript{Ar}), 7.474 (s, 1H, H\textsubscript{Ar}), 7.302 (d, 1H, H\textsubscript{Ar}), 5.278 (s, 2H, O-CH\textsubscript{2}-O), 3.479 (s, 3H, O-CH\textsubscript{3}). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) = 188.38 (-C=O), 161.64 (C\textsubscript{Ar}-NO\textsubscript{2}), 142.80 (C\textsubscript{Ar}-O-), 134.19 (C\textsubscript{Ar}-C=O), 127.22 (C\textsubscript{Ar}), 120.01 (C\textsubscript{Ar}), 116.05 (C\textsubscript{Ar}), 94.42 (-O-CH\textsubscript{2}-O-), 56.75 (-O-CH\textsubscript{3}). FTIR (ATR, cm\textsuperscript{-1}): 1691
s, 1584 s, 1505 s, 1279 s, 1245 s, 1158 s, 1062 s. Mass spec (ESI-MS): calculated M⁺: 234.1613 m/z, observed M⁺: 234.1644 m/z.

3.3.2.2. Synthesis of 2-nitro-5-(methoxy methoxy)benzyl alcohol:

2.4118 g (11.3 mmol) 2-nitro-5-(methoxy methoxy)benzaldehyde were dissolved in 50 mL MeOH, and the solution placed in an ice/water bath. 1.2353 g (33.1 mmol) NaBH₄ granules were added slowly, then the cold solution was stirred for 1 hour. The solution was diluted with water and extracted with three aliquots of ethyl acetate. The organic layers were dried over MgSO₄ and the volatiles removed in vacuo. Compound 2-nitro-5-(methoxy methoxy)benzyl alcohol was obtained as a beige, crystalline solid. 87 % isolated yield. M.P.: 51-52 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.149 (d, 1H, H₆), 7.355 (s, 1H, H₅), 7.038 (d, 1H, H₄), 5.265 (s, 2H, -O-CH₂-O-), 4.974 (s, 2H, Ar-CH₂-OH), 3.479 (s, 3H, -O-CH₃), 2.752 (s, broad, 1H, OH). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 161.52 (C₆=NO₂), 140.54 (C₆=O-), 139.98 (C₄=CH₂-OH), 127.53 (C₅), 115.65 (C₆), 114.67 (C₆), 93.83 (-O-CH₂-O-), 62.37 (-O-CH₃), 56.22 (Ar-CH₂-OH). FTIR (ATR, cm⁻¹): 3333 b, 1578 s, 1509 s, 1236 s, 1154 s, 1071 s. Mass spec (ESI): formula: C₉H₁₁NO₅ theoretical M⁺: 236.0529 m/z observed M⁺: 236.0453 m/z.

3.3.2.3. Synthesis of 2-nitro-5-(methoxy methoxy)benzyl bromide:

2.000 g (9.38 mmol) 2-nitro-5-(methoxy methoxy)benzyl alcohol and 3.859 g (14.1 mmol) TPP were dissolved in 50 mL dry, freshly distilled THF. 4.657 g (14.1 mmol) CBr₄ were dissolved in 50 mL dry, freshly distilled THF. The CBr₄/THF was transferred to the other flask by cannula, and the solution stirred at room temperature for 1 hour. TLC indicated quantitative conversion at this time. The reaction solution was filtered and reduced by rotary evaporator. The crude product was purified on a silica gel column eluted with 1:1
v:v hex:EtOAc. 2-Nitro-5-(methoxy methoxy)benzyl bromide was obtained as a beige, crystalline solid. 87 % isolated yield. M.P.: 50-51 °C ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.070 (d, 1H, H₆), 7.126 (s, 1H, H₅), 7.029 (d, 1H, H₆), 5.228 (s, 2H, -O-CH₂-O-), 4.816 (s, 2H, -CH₂-Br), 3.449 (s, 3H, -O-CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 161.03 (C₅=NO₂), 141.37 (C₆-O-), 135.50 (C₆-CH₂-OH), 128.15 (C₇), 119.44 (C₆), 116.061 (C₇), 94.32 (-O-CH₂-O-), 56.53 (-O-CH₃), 29.66 (-CH₂-Br). FTIR (ATR, cm⁻¹): 1582 s, 1518 s, 1248 s, 1149 s. Mass spec (EI): formula: C₉H₁₀NO₄Br theoretical M⁺: 274.9779 m/z observed M⁺: 274.9784 m/z.

3. 3. 2. 4. Synthesis of 2-nitro-5-(methoxy methoxy)benzyl azide:

A 10 mL RBF was charged with 266.1 mg (0.963 mmol) 2-nitro-5-(methoxy methoxy)benzyl bromide, 133.1 mg (2.05 mmol) sodium azide, and 5.0 mL dry EtOH. The flask was fitted with a condenser, wrapped in Al foil, and heated to reflux for 6 hours. The flask was then cooled to room temperature and filtered, then dried over MgSO₄ and reduced in vacuo. 2-nitro(methoxy methoxy)benzyl azide was obtained as an orange-yellow viscous oil. 88 % isolated yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.130 (d, 1H, H₆), 7.115 (s, 1H, H₅), 7.011 (d, 1H, H₆), 5.240 (s, 2H, O-CH₂-O), 4.826 (s, 2H, Ar-CH₂-N₃), 3.428 (s, 3H, O-CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 161.11 (C₅=NO₂), 141.62 (C₆-O), 153.24 (C₆-CH₂-N₃), 129.03 (C₇), 119.56 (C₈), 116.02 (C₇), 94.46 (O-CH₂-O), 56.62 (O-CH₃), 54.12 (CH₂-N₃). FTIR (ATR, cm⁻¹): 2107 s, 1581 s, 1516 s, 1118 s. Mass spec (ESI-MS): theoretical M⁺: 261.0594 m/z, observed M⁺: 261.0608 m/z.

3. 3. 2. 5. Synthesis of 5-hydroxy-2-nitrobenzyl azide:

A 25 mL RBF was charged with 552.4 mg (2.32 mmol) 2-nitro-5-(methoxy methoxy)benzyl azide dissolved in 6 mL acetone. 3.0 mL 1 M aqueous HCl were added,
and the flask was fitted with a condenser and heated to 50 °C for 5 hours. The flask was cooled to room temperature, and the solution transferred to a separatory funnel and diluted with ethyl acetate. The organic layer was washed twice with water and once with brine, then dried over MgSO₄ and the volatiles were removed in vacuo. 5-Hydroxy-2-nitrobenzyl azide was obtained as a yellow solid. 92 % isolated yield. M. P.: 88-90 °C. ¹H NMR (300 MHz, methanol-ᵈ⁾: δ (ppm) = 8.098 (d, 1H, Hₐ), 7.031 (s, 1H, Hₐ), 6.867 (d, 1H, Hₐ), 4.814 (s, 2H, Ar-CH₂-N₃), 4.680 (broad, 1H, OH). ¹³C NMR (75 MHz, methanol-ᵈ⁾: δ 164.75 (Cₐ-NO₂), 141.42 (Cₐ-O), 136.33 (Cₐ-CH₂-N₃), 129.89 (Cₐ), 118.08 (Cₐ), 116.11 (Cₐ), 53.70 (CH₂-N₃). FTIR (ATR, cm⁻¹): 3325 b, 2107 s, 1589 s, 1503 s. Mass spec (ESI-MS): theoretical M⁺: 217.0332 m/z, observed M⁺: 217.0338 m/z.

Previous experiments indicated that the phenyl ester formed by the addition of the ATRP initiating site was unstable to strong nucleophilic substitution conditions, and therefore had to be added to MAIZ in the final step of the synthesis. Attempts to generate 5-hydroxy-2-nitrobenzyl azide without protecting the phenol suffered from significant solubility issues that made the transformations and purifications extremely challenging. Thus, the methoxy methyl ether, or MOM, protecting group was used at the phenolic position. The MOM group greatly improved substrate solubility in organics, allowing for efficient transformation and purification. All byproducts of the MOM functionalization are water soluble, as are the byproducts of the borohydride reduction. Both the MOM-protected o-nitrobenzaldehyde and the MOM-protected o-nitrobenzyl alcohol are shelf-stable for months, provided they are kept in the dark.

The Appel reaction is simple to perform, but care must be taken to keep all reagents and solvents free of water, and the reaction proceeds best when the TPP and CBr₄ are in as
close to a 1:1 ratio as possible. Optimization experiments determined that the reaction proceeds best when the benzyl alcohol and TPP are stirred in THF solution in one flask, with a solution of the CBr₄ added by cannula. The TPP should not be added by cannula as it has a strong tendency to clog cannulae. The Appel reaction is monitored by TLC, and as soon as quantitative conversion is observed the reaction should be worked up as noted in the procedure. Allowing the Appel reaction to stir after complete conversion results in the formation of byproducts such as CH₂Br₂ and the occurrence of side reactions that reduce the yield of the target benzyl bromide. Byproduct triphenylphosphine oxide (TPPO) crashes out as a precipitate that is filtered off, and a column removes excess TPP, CBr₄ and byproduct CHBr₃. The benzyl bromide, once pure, can be stored in a refrigerator for weeks to months without degradation.

To deprotect the phenol before adding the ATRP initiating site, initial attempts were made using NaHSO₄ adsorbed onto silica gel, a reagent that had been developed specifically for the deprotection of p-nitrophenols. Typical results for this reagent are full deprotection within 1 hour at room temperature. However, these substrates with the para nitro group only reached 50% deprotection after 24 hours, even when heated to 50 °C. Knowing that organic azides are generally acid tolerant, classic MOM deprotection conditions of 1 M HCl (aq) were assayed. These conditions were successful, producing fully deprotected 5-hydroxy-2-nitrobenzyl azide within 5 hours at 50 °C. Because the aqueous phase is already highly acidified, causing the phenol to be protonated, the target compound can be extracted into organic solvents for purification. The final addition of the ATRP initiating site usually proceeds with no need for a column chromatography purification step provided the 5-hydroxy-2-nitrobenzyl azide has been thoroughly dried
beforehand. The resulting MAIZ needs to be stored in a dark refrigerator, but has similar storage stability as conventional ATRP initiators.

3. 4. Preparation of photocleavable block copolymers using one-pot click/ARGET and MAIZ

Due to its greater thermal and chemical stability when compared to the conventional ONB ester, the ONBTz photocleavable linker is a better-performing junction in materials that must withstand long storage or harsher conditions while still retaining the complex polymer architecture and photocleavable ability. The azide-functionalized ATRP initiator MAIZ was designed as a model junction structure to study the behavior of the ONBTz linker in one-pot click/polymerization methods of synthesizing complex polymer architectures.

To demonstrate the capabilities of this linker, a series of polymerizations were attempted to produce PEO-\(\text{hv}\)-PHEMA via CuAAC/ARGET ATRP with MAIZ and PEO-alkyne.

![Scheme 3.6](image)

**Scheme 3.6:** General synthesis of one-pot click/ARGET ATRP polymers.

3. 4. 1. Synthesis of MAIZ

![Scheme 3.7](image)

**Scheme 3.7:** Synthesis of MAIZ.
A 50 mL RBF was charged with 407.6 mg (2.10 mmol) 5-hydroxy-2-nitrobenzyl azide and 20 mL dry, freshly distilled THF. To this was added 0.41 mL (2.94 mmol) dry, freshly distilled TEA, followed by 0.36 mL (2.91 mmol) BIB. The flask was stirred at room temperature overnight, then the reaction mixture was transferred to a separatory funnel, diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc, then the combined organic layers were washed with brine. The volatiles were removed by rotovap, yielding MAIZ as light brown crystals. 72% isolated yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 8.216 (d, 1H, \(H_{A_1}\)), 7.500 (s, 1H, \(H_{A_2}\)), 7.304 (d, 1H, \(H_{A_3}\)), 4.922 (s, 2H, \(\text{Ar-CH}_2\)-N\(_3\)), 2.096 (s, 6H, -C(CH\(_3\))\(_2\)). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) (ppm) = 169.60 (C=O), 154.20 (\(C_{A_2}\)-NO\(_2\)), 144.93 (\(C_{A_2}\)-O-), 134.62 (\(C_{A_1}\)), 126.92 (\(C_{A_3}\)-CH\(_2\)-), 121.99 (\(C_{A_3}\)), 121.6 (\(C_{A_2}\)), 54.86 (-CH\(_2\)-N\(_3\)), 51.99 (-C(CH\(_3\))\(_2\)), 30.68 (-C-Br). FTIR (ATR, cm\(^{-1}\)): 2107 (s), 1710 (s), 1585 (m), 1525 (s), 1216 (s). A mass spectrum could not be obtained for MAIZ.

3.4.2. Synthesis of PEO-alkyne

\[
\text{[Scheme 3.8: Synthesis of PEO-alkyne.]} \\
\text{A 50 mL RBF was charged with 1.013 g (0.2 mmol) PEO-OH monomethyl ether (5 kDa/mol) that was dissolved in 20 mL dry, freshly distilled THF. 95.6 mg (2.0 mmol) NaH were suspended in 5 mL dry, freshly distilled THF, and the resulting slurry was transferred to the PEO/THF flask by cannula. After bubbling ceased, 0.44 mL (4.0 mmol) propargyl bromide was added as an 80 %wt solution in toluene. The flask was stirred at room temperature for 24 hours, then the reaction solution was dripped into 300 mL diethyl}
\]
ether. The precipitate polymer was collected by vacuum filtration and dried overnight in a room temperature vacuum oven. Isolated yield: 95%. Functionalization: Quantitative by $^1$H NMR. 1H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 4.20 (propargyl methylene, 2H), 3.64 (backbone methylene units, 456H), 3.38 (methyl ether endgroup, 3H), 2.43 (alkyne endgroup, 1H). GPC (0.05 M LiCl in DMF, RI detection, linear PMMA standards): $M_N$: 9730 Da, $M_W$: 10,100 Da, $D$: 1.04.

3.4.3. ARGET ATRP Chain Extension with MAIZ

Three different molecular weights for the PHEMA block were targeted. For trials A, B, and C the PHEMA target was 5 kDa, 10 kDa and 20 kDa, respectively.

![Scheme 3.9: One-pot CuAAC/ARGET ATRP synthesis of PEO-$hv$-PHEMA.](image)

General procedure for chain extension:

100 mg (20 $\mu$mol) PEO-alkyne was dissolved in 0.5 mL DMSO, then 1 equiv. MAIZ was added from a stock solution in DMSO, followed by 0.1 mol%. 5:1 HMTETA:CuBr$_2$ from a stock solution in DMSO. The appropriate amount of HEMA was added, and the solution bubbled with dry N$_2$ for 1 minute. 6 mol% ascorbic acid was added from a stock solution in DMSO to initiate polymerization. The vial was stirred at 35 $^\circ$C for 2 hours, after which the polymerization solution was dripped into 20 mL diethyl ether to precipitate the
polymer. The precipitate was collected by vacuum filtration and dried in a room temperature vacuum oven overnight. Isolated yield: 50-80%. \(^1\)H NMR (methanol-\(d_4\)): \(\delta\) (ppm) = 4.86 (b, overlaps with water, PHEMA side chain methylene units), 3.64 (b, PEO methylene units), 2.66 (PEMA backbone methylene and methyl). GPC (0.05 LiCl in DMF, linear PMMA standards): Trial A \(M_N\): 9990 Da, \(M_W\): 10660 Da, \(\bar{D}\):1.06; Trial B \(M_N\):10370 Da, \(M_W\): 13070 Da, \(\bar{D}\): 1.26; Trial C: \(M_N\): 35460 Da, \(M_W\): 42770 Da, \(\bar{D}\): 1.20.

![Overlay of PEO-alkyne and PEO-hv-PEMA A, B, C](image)

**Figure 3.4:** Overlay of PEO-alkyne and all three PEO-hv-PEMA block copolymers.

**Table 3.3:** The block lengths for each trial of PEO-hv-PEMA.

<table>
<thead>
<tr>
<th>BCP</th>
<th>PEO (M_N) (Da)</th>
<th>PHEMA (M_{N,GPC}) (Da)</th>
<th>PHEMA (M_{N,NMR}) (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5,000</td>
<td>220</td>
<td>445</td>
</tr>
<tr>
<td>B</td>
<td>5,000</td>
<td>640</td>
<td>2990</td>
</tr>
<tr>
<td>C</td>
<td>5,000</td>
<td>25730</td>
<td>11570</td>
</tr>
</tbody>
</table>

In all cases, unfunctionalized PEO-alkyne can be observed in the GPC traces. This has been noted before in the literature by the original reporters of the one-pot CuAAC/ATRP technique.\(^6\) All polymerization solutions were clear and colorless from the
addition of the ascorbic acid until the polymers were precipitated, indicating that the copper ions were predominantly in their +1 rather than +2 oxidation state, which has a distinct blue tint. This indicates that the proper catalytic copper species was present throughout the reaction. Obtained PHEMA block molecular weights were lower than expected, based upon reference to a previous article on the ARGET ATRP of 5-hydroxyethyl methacrylate. There is also a significant difference between the molecular weights estimated by $^1$H NMR and GPC. The shape of the GPC traces suggests that only a small fraction of the PEO was chain extended, but the source of this phenomenon was unclear as there was compelling spectral evidence for the composition of both PEO-alkyne and MAIZ.

3.5. Photocleavage of PEO-$h_v$-PHEMA Copolymers

![Diagram of photocleavage reaction]

**Scheme 3.10:** Expected photocleavage products of PEO-$h_v$-PHEMA.

A 3 mg sample of each block copolymer was dissolved in 1.00 mL methanol-$d_4$. The samples were analyzed by $^1$H NMR, then placed under a 1.36 mW/cm$^2$, 365 nm UV source for 17 hours. The methanol-$d_4$ was removed under a stream of dry N$_2$, then the remaining solid was prepared for DMF GPC analysis. The overlapping GPC traces for each block copolymer can be seen in figure 3.5.
**Figure 3.5:** Pre- and post-UV exposure DMF GPC traces for the PEO-$h_v$-PHEMA materials A-C.

The pre- and post-UV exposure DMF GPC traces show no difference for any of the block copolymers. Based upon the evidence gathered, two hypotheses were formed; either
the UV source was not sufficiently intense to generate substantial photocleavage in the ONBTz-based systems, or the MAIZ had decomposed in some way. To test these hypotheses, another series of block copolymers were synthesized (D-F) according to the exact same procedures used to prepare copolymers A-C and exposed under a much more intense 365 nm source.

3.6. Exposure of PEO-hv-PHEMA under a 200 mW/cm² source

Block copolymers D-F were prepared according to the same procedures as series A-C, targeting 5, 10 and 20 kDa PHEMA blocks. The results of these reactions are shown in table 3.4. A similar trend in molecular weight was noted, with very short (~1 kDa) PHEMA blocks being indicated by ¹H NMR. For D and E, the ¹H NMR estimates were much higher than the GPC value, but copolymer F displayed the inverse behavior. These observations could not rule out either the UV intensity or the MAIZ quality hypothesis, so photocleavage experiments were performed.

**Table 3.4:** The molecular weight estimates by ¹H NMR and DMF GPC for PEO-hv-
PHEMA trials D-F.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target HEMA Mₙ (Da)</th>
<th>HEMA Mₙ, NMR (Da)</th>
<th>HEMA Mₙ, GPC (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>5,000</td>
<td>960</td>
<td>210</td>
</tr>
<tr>
<td>E</td>
<td>10,000</td>
<td>670</td>
<td>80</td>
</tr>
<tr>
<td>F</td>
<td>20,000</td>
<td>3,120</td>
<td>24,570</td>
</tr>
</tbody>
</table>

3.6.2. General procedure for high-intensity UV exposure

A solution of 3-5 mg block copolymer was prepared in 0.66 mL MeOH-<i>d₄</i>. Each solution was loaded into a NMR tube, sealed, then the solutions were exposed under a 200 mW/cm² 365 nm source for 30 minutes. The tubes were inverted three times to mix every five minutes to ensure even exposure. The solutions were then reduced under a stream of dry N₂, and the residue analyzed by DMF GPC. The pre- and post-UV exposure traces are shown in figure 3.6 below.
Figure 3.6: The pre- and post-UV exposure GPC traces for trials D-F.

The GPC traces showed, once again, that no significant photocleavage occurred. This rules out the low intensity of the source as the issue, and indicates that there is a
problem either with MAIZ or the CuAAC/ARGET ATRP system. The fact that photocleavable block copolymers were prepared by this one-pot click/polymerization method in chapter two demonstrates that the one-pot method can work for both ATRP and ARGET ATRP systems. Earlier in this chapter, it was shown that o-nitrobenzyl azides react similarly to other azides. All the prepared polymers were analyzed within 24 hours after preparation, and all were shielded from extraneous light during polymerization and storage, making premature cleavage unlikely. Therefore, either the ATRP initiating site is decomposing, or MAIZ is otherwise cleaving before polymerization occurs.

Good $^1\text{H}$ and $^{13}\text{C}$ NMR, ATR-FTIR and mass spectra were obtained of 5-hydroxy-2-nitrobenzyl azide, the direct precursor of MAIZ, even though a week passed between the NMR/ATR-FTIR analysis and the performance of mass spectrometry. This indicates that the o-nitrobenzyl azide itself is fairly stable. A similar amount of time passed between the analysis of MAIZ by NMR/ATR-FTIR and its analysis by mass spectrometry. No M$^+$ peak was observed, and none of the resulting fragments could be attributed to any likely decomposition fragments. This is despite storage both in a foil-wrapped vial and in a 0 °C freezer. Based upon the observation of relatively narrow dispersity PHEMA materials, at least a small fraction of ATRP initiating sites must remain intact. These sites, however, are not attached to a CuAAC-active structure.

A likely weak point in MAIZ is the phenyl ester. Given that it is para on the aryl ring to a strongly electron-withdrawing nitro group, the carbonyl carbon is particularly electrophilic and the C-O bond particularly weak. When this synthesis was designed, it was anticipated that the $p$-nitrophenyl ester would be vulnerable to extremes of pH or exposure to strong nucleophiles, it was not anticipated to be an issue because a very similar
structure, 3-hydroxyethyl-4-nitrophenyl-2-bromo-2-methylpropanoate (MAI, seen in figure 3.7 below) was used previously in the Coughlin group to prepare PMMA-$hv$-poly(lactide). While it was noted that the ATRP had to be performed first, to generate a PMMA chain that would sterically protect the phenyl ester on the linker during the poly(lactide) ring-opening polymerization, the material was otherwise fairly stable and displayed good photocleavage behavior. It is worth noting, however, that all the reaction systems in this paper were anhydrous, nor did they include ascorbic acid as a reducing agent. Therefore, it is unlikely that MAIZ is an appropriate linker structure for one-pot CuAAC/ARGET ATRP systems. It should, however, be suitable for conventional ATRP.

![MAIZ benzyl alcohol structure analog: MAI.](image)

**Figure 3.7:** MAIZ benzyl alcohol structure analog: MAI.

3.7. Conclusion

Small molecule analog tests of the established $o$-nitrobenzyl ester (ONB) and novel $o$-nitrobenzyl-1,2,3-triazole (ONBTz) linkers indicated that the ONBTz linker has a distinct advantage over the ONB ester in terms of thermal stability (decomposition at 240 °C rather than 140 °C), as well as improved stability to non-neutral pH. Exposure of the ONBTz analog to 365 nm light established that it produces the predicted $o$-nitrosobenzaldehyde and free 1,2,3-triazole products upon photocleavage. Therefore, it is a drop-in alternative to ONB linker structures when this greater stability is needed.

To address the previous difficulty of preparing $o$-nitrobenzyl azides from the corresponding commercially available $o$-nitrobenzyl alcohols, a technique relying on
preparation of an o-nitrobenzyl bromide intermediate structure by Appel reaction was
developed and optimized to the point that these azides could be produced in multi-gram
batches with an over 50% process yield. This synthetic method also requires only a single
column chromatography purification step, while the other reactions can be purified by
recrystallization. In this chapter, a methoxy methyl ether protecting group was used on the
phenol, allowing the preparation of 5-hydroxy-2-nitrobenzyl azide, the precursor to MAIZ,
the focal component of CuAAC/ARGET ATRP preparation of block copolymers linked
through the ONBTz junction.

Chain extension experiments of PEO-alkyne with MAIZ and HEMA were
unsuccessful. It was determined that the most likely reason for this was the instability of
MAIZ under ARGET ATRP conditions. An alternative ATRP initiating site structure will
have to be developed for the ONBTz junction to be a practical linker for click/clip paradigm
materials.
References

1. Maier, G.; Eckwert, J.; Bothur, A.; Reisenauer, H. P.; Schmidt, C., Photochemical fragmentation of unsubstituted tetrazole, 1,2,3-triazole and 1,2,4-triazole: first matrix-spectroscopic identification of nitrilimine HCNNH. Liebigs Annalen 1996, 7, 1041-1053.


CHAPTER 4

PHOTODEGRADABLE POLYTRIAZOLES

The previous two sections in this dissertation dealt with the application of photocleavable linkers at critical junction points in complex polymer architectures, where the cleavage of a single bond has the capability to radically change the system’s behavior. This project takes the application of photocleavage in a different direction, as the foundation for a directly photoetchable thermoplastic that can be patterned with photolithographic methods without requiring the use of a photoresist.

Such a material would have to be readily synthesized, polymerized, and processed. It would need to possess good chemical and thermal stability, as well as sufficient mechanical strength and toughness to serve as a coating or bulk material. Additionally, it would need to possess a sufficient number of photocleavable units in the backbone to allow UV exposure to break the polymer into small molecule sized fragments with greatly increased solubility compared to the parent material.

In this chapter, the synthesis and characterization of a prototype photodegradable polytriazole will be described. It can be prepared by CuAAC polymerization, and the monomer synthesis has been optimized to the point that multi-gram batches can be prepared from a commercially available starting material with an overall 53 % process yield. This polymer was characterized by various spectroscopic methods and GPC, and its thermal characteristics were investigated by DSC and TGA. Its photodegradation behavior was analyzed by NMR, and proof-of-concept photopatterning experiments were performed.
4.1. Preparation of 5-(Prop-2-yn-1-yloxy)-2-nitrobenzyl azide (pONBz)

**Scheme 4.1:** Synthesis of pONBz from 5-hydroxy-2-nitrobenzaldehyde

4.1.1. Preparation of 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde:

1.0417 g (6.23 mmol) 5-hydroxy-2-nitrobenzaldehyde and 1.4456 g (10.5 mmol) anhydrous K$_2$CO$_3$ were dissolved in 25 mL anhydrous DMF. The solution was stirred at 60 °C for 30 minutes, then 1.5 mL (13.4 mmol) propargyl bromide (80 wt% in toluene) were added slowly by syringe. The solution was stirred at 60 °C for 1 hour. The solution was diluted with ethyl acetate and water. The organic layer was washed with water and brine, then dried over MgSO$_4$ and the volatiles removed in vacuo. 2-Nitro-5-(prop-2-yn-1-yloxy)benzaldehyde was obtained as a light brown crystalline solid. 86% isolated yield.

M.P.: 62-63°C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.28 (s, 1H, H-C=O), 8.198 (d, 1H, H$_A$), 7.455 (d, 1H, H$_A$), 7.350 (s, 1H, H$_A$), 5.075 (s, 2H, -O-CH$_2$-C=), 3.729 (s, 1H, C≡C-H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 189.88 (-C=O), 161.34 (C$_{Ar}$-NO$_2$), 142.69 (C$_{Ar}$-O-), 134.21 (C$_{Ar}$-C=O), 127.43 (C$_{Ar}$), 119.24 (C$_{Ar}$), 114.72 (C$_{Ar}$), 79.68 (-C≡C-H), 77.70 (-CH$_2$-C≡C-). FTIR (ATR, cm$^{-1}$): 3280 m, 2120 w, 1688 s, 1583 s, 1520 s, 1232 s. Mass spec (EI): formula: C$_{10}$H$_7$NO$_4$, theoretical mass: 205.1669 m/z, observed mass: 205.0381 m/z.
4. 1. 2. Preparation of 2-nitro-5-(prop-2-yn-1-yloxy)-benzyl alcohol:

4.2620 g (20.8 mmol) 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde were dissolved in 100 mL MeOH, and the flask was placed in an ice/water bath. 2.9838 g (78.9 mmol) NaBH₄ granules were added slowly. The solution was stirred at 0 °C for 1 hour. The solution was diluted with water and diethyl ether. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, then dried over MgSO₄ and the volatiles were removed in vacuo. 2-Nitro-2-(prop-2-yn-1-yloxy)benzyl alcohol was obtained as a beige, crystalline solid. 84 % isolated yield. M.P.: 133-134 °C. ^1H NMR (300 MHz, CDCl₃): δ 8.190 (d, 1H, H₆), 7.333 (s, 1H, H₅), 6.990 (d, 1H, H₄), 5.013 (d, 2H, -O-CH₂-C=), 4.811 (s, 2H, Ar-CH₂-OH), 2.572 (t, 1H, -C=C-H), 2.520 (s, 1H, -O-H). ^13C NMR (75 MHz, CDCl₃): 162.30 (C₆=NO₂), 141.190 (C₆-O-), 140.25 (C₆-CH₂-OH), 128.37 (C₆), 115.65 (C₆), 113.95 (C₆), 77.47 (-C≡C-H), 77.00 (-CH₂-C≡C-), 63.34 (-O-CH₂-C=), 56.55 (Ar-CH₂-OH). FTIR (ATR, cm⁻¹): 3274 b, 3266 s, 2125 w, 1587 s, 1507 s, 1240 s. Mass spec (EI): formula: C₁₀H₉NO₄, theoretical mass: 207.1828 m/z, observed mass: 207.0538 m/z.

4. 1. 3. Preparation of 2-nitro-5-(prop-2-yn-1-yloxy)-benzyl bromide:

5.1713 g (25.0 mmol) 2-nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol and 10.7804 g (39.3 mmol) TPP were dissolved in 100 mL dry, freshly distilled THF. 13.8419 g (41.8 mmol) CBr₄ were dissolved in 70 mL dry, freshly distilled THF. The CBr₄/THF was transferred to the other flask by cannula. The solution was stirred at room temperature for 20 minutes. TLC indicated quantitative conversion. The solution was diluted with 70 mL diethyl ether and filtered. The solution was reduced by rotary evaporator, and the crude product was purified on a silica gel column eluted with 5:1 v:v hexanes:ethyl acetate. 2-Nitro-5-(prop-
2-yn-1-yloxy)nitrobenzyl bromide was obtained as a beige, crystalline solid. 76 % isolated yield. M.P.: 69-70 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.144 (d, 1H, H\(_{Ar}\)), 7.114 (s, 1H, H\(_{Ar}\)), 7.008 (d, 1H, H\(_{Ar}\)), 4.863 (s, 2H, -O-CH\(_2\)-C\(\equiv\)), 4.810 (s, 2H, Ar-CH\(_2\)-Br), 2.633 (s, 1H, -C\(\equiv\)C-H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 161.00 (C\(_{Ar}\)-NO\(_2\)), 141.09 (C\(_{Ar}\)-O-), 135.55 (C\(_{Ar}\)-CH\(_2\)-Br), 128.28 (C\(_{Ar}\)), 118.59 (C\(_{Ar}\)), 114.95 (C\(_{Ar}\)), 76.98 (-C\(\equiv\)C-H), 76.86 (-CH\(_2\)-C\(\equiv\)C-), 56.26 (-O-CH\(_2\)-C\(\equiv\)), 29.78 (Ar-CH\(_2\)-Br). FTIR (ATR, cm\(^{-1}\)): 3310 b, 3285 s, 2125 w, 1582 s, 1513 s, 1258 s. Mass spec (EI): formula: C\(_{10}\)H\(_8\)NO\(_3\)Br, theoretical mass: 270.0794 m/z, observed mass: 268.97 m/z and 270.97 m/z.

4. 1. 4. Preparation of 2-nitro-5-(prop-2-yn-1-yloxy)-benzyl azide:

0.3331 g (1.2 mmol) 2-nitro-5-(prop-2-yn-1-yloxy)benzyl bromide and 0.1245 g (1.9 mmol) NaN\(_3\) were dissolved in 6 mL dry EtOH. The flask was fitted with a water-coil condenser and stirred at reflux for 6 hrs. The reaction solution was cooled in an ice/water bath, filtered, and the resulting solution was reduced in vacuo to produce 2-nitro-5-(prop-2-yn-1-yloxy)benzyl azide as a yellow, crystalline solid. 83 % isolated yield. M.P.: 67-69 °C \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.150 (d, 1H, H\(_{Ar}\)), 7.105 (s, 1H, H\(_{Ar}\)), 7.022 (d, 1H, H\(_{Ar}\)), 4.839 (s, 2H, O-CH\(_2\)-C\(\equiv\)), 4.788 (s, 2H, Ar-CH\(_2\)-N\(_3\)), 2.585 (s, 1H, C\(\equiv\)C-H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 161.33 (C\(_{Ar}\)-NO\(_2\)), 141.21 (C\(_{Ar}\)-O), 135.53 (C\(_{Ar}\)-CH\(_2\)-N\(_3\)), 128.28 (C\(_{Ar}\)), 118.62 (C\(_{Ar}\)), 115.01 (C\(_{Ar}\)), 76.92 (C\(\equiv\)C-H), 76.75 (-C\(\equiv\)C), 56.74 (-CH\(_2\)-N\(_3\)). FTIR (ATR, cm\(^{-1}\)): 3198 m, 2187 w, 2107 s, 1583 s, 1514 s. Mass spec (ESI-MS): theoretical M\(^\ddagger\): 255.0489 m/z, observed M\(^\ddagger\): 255.0496 m/z.

The synthesis of pONBz begins from commercially available 5-hydroxy-2-nitrobenzaldehyde. The corresponding diol, 5-hydroxy-2-nitrobenzyl alcohol, is also commercially available, but it is generally five times more expensive than the
benzaldehyde. It is possible to selectively functionalize the phenol rather than the benzyl alcohol of this substrate, but the diol itself is only freely soluble in methanol and water, neither of which are appropriate solvents for the selected reactions. The diol is moderately soluble in ethyl acetate, THF, acetone and higher alcohols, but its solubility in these solvents is generally too low to make multi-gram reactions feasible. The benzaldehyde, by contrast, is freely soluble in alcohols, acetone, THF and diethyl ether, making it a good substrate for larger-scale reactions. Neither molecule is soluble in chlorinated solvents until the phenol has been masked by the propargyl group or the MOM protecting group discussed in the previous chapter.

Adding the propargyl group before reducing the benzaldehyde serves two functions; first, it masks the phenol and greatly improves the solubility of the substrate and second, it increases the specificity of the modification so that only the phenol is functionalized in the first step. In reactions performed on the diol, some product functionalized at the benzyl position was always obtained and had to be removed by column chromatography. When beginning from the benzaldehyde, this is not the case and the solid product can be obtained simply by removing the extraction solvent. The propargyl-functionalized benzaldehyde may be isolated at this step and can be stored for months at room temperature if kept in a dark, tightly sealed vial. However, if the synthesis is streamlined by dissolving the propargyl-functionalized benzaldehyde in methanol and performing the borohydride reduction right away, it both saves time (as these two steps can be performed in one day) and increases the yield. The procedure for this streamlined synthesis is reproduced below.
4.1.5. Streamlined synthesis of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol:

A 250 mL RBF was charged with 4.0361 g (24.2 mmol) 5-hydroxy-2-nitrobenzaldehyde, 4.7960 g (34.7 mmol) anhydrous K₂CO₃, and 125 mL anhydrous DMF, and the resulting solution was stirred at 60 °C for 30 minutes. 6.0 mL (6.4 g, 54 mmol) propargyl bromide were added by syringe as an 80 wt% solution in toluene. The flask was stirred at 60 °C for 60 minutes, when the reaction progress was checked by TLC (silica plate developed in 2:1 hex:EtOAc and visualized by short wave UV), which indicated quantitative conversion. The solution was transferred to a separatory funnel and diluted with EtOAc. The organic layer was washed twice with water and once with brine, then dried over MgSO₄ and the volatiles removed by rotary evaporator. The resulting mass of crystals was dissolved in 100 mL methanol, and the flask was placed in an ice/water bath. 2.9838 g (79 mmol) NaBH₄ granules were added slowly to control foaming and the exotherm generated by the reaction. The flask was stirred for 60 minutes at 0 °C after the reducing agent addition, then carefully quenched with a small amount of 1 M HCl (aq.). The reaction solution was transferred to a separatory funnel and diluted with water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, then dried over MgSO₄ and the volatiles removed in vacuo. The result was crystalline 2-nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol in 84% yield.

By using this streamlined technique, the process yield of pONBz synthesis increases to 53%. FTIR experiments indicate that the product organic azide is not shelf-stable in the long term, with the azide band near 2100 cm⁻¹ disappearing over time. The sample left out at room temperature lost its azide within two weeks, while storage at 0 °C or -60 °C increased the shelf life of pONBz to 2-3 months. The intermediate benzyl alcohol
and benzyl bromide are very stable, as long as they are kept away from light in a tightly sealed container stored in a 0 °C freezer. It is therefore recommended that these compounds be kept as feedstocks, with the desired azide being prepared as needed.

As discussed in chapter three, the azide transformation is best achieved through the bromide intermediate, which is made by an Appel reaction. This step is the only part of the synthetic process that currently requires a column chromatography step for purification. All of the intermediate compounds are solids, making purification by recrystallization a promising avenue for further optimization of the synthesis.

4.2. Click polymerization of pONBz

\[
\begin{align*}
\text{NO}_2 & \quad \text{Cu(I)} \\
\text{N}_3 & \quad \text{Ligand} \\
\text{O} & \quad \text{Reducing agent} \\
\text{Various solvents} & \quad \text{N}_2
\end{align*}
\]

Scheme 4.2: General synthetic scheme for preparation of polytriazoles.

Polymerization of azides and alkynes via copper-catalyzed “click” chemistry is relatively new in the field of polymer chemistry.\textsuperscript{41, 49} This reaction is more commonly employed to construct complex polymer architectures from macromolecular components,\textsuperscript{31, 35, 50} though a novel application to one-pot tandem click and ATRP has recently been reported and was discussed in the previous chapter.\textsuperscript{32a, 51} The necessary components of a click polymerization system are a solvent, and a copper source. The solvent could be a pure chemical or a mixture, or even the molten monomer to produce a bulk polymerization system. The copper source is generally a salt. With pONBz in hand, a variety of potential polymerization conditions were evaluated, as summarized in table 4.1.
Table 4.1: Click polymerization parameters assayed for optimization.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Reducing Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1 t-BuOH:H₂O</td>
<td>CuSO₄·5H₂O</td>
<td>no ligand</td>
<td>Sodium ascorbate</td>
</tr>
<tr>
<td>DMF</td>
<td>CuBr(TPP)₃</td>
<td>HMTETA</td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>DMSO</td>
<td>CuBr₂</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The first polymerization system studied was one in common use for click reactions on the small molecule scale: 2:1 v:v tert-butanol:water with CuSO₄·5H₂O as copper source and sodium ascorbate as the reducing agent. Experiments were performed to determine optimal copper loading, with the results summarized in table 4.2.

Table 4.2: Effect of Cu loading on pONBz polymerization using CuSO₄ as catalyst in 2:1 v:v water:t-BuOH as solvent.

<table>
<thead>
<tr>
<th>Cu loading (mol %)</th>
<th>M₅₆, GPC (Da)</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>6700</td>
<td>1.98</td>
</tr>
<tr>
<td>5</td>
<td>5880</td>
<td>1.50</td>
</tr>
<tr>
<td>1</td>
<td>10200</td>
<td>1.26</td>
</tr>
<tr>
<td>0.1</td>
<td>5300</td>
<td>2.32</td>
</tr>
</tbody>
</table>

The resulting PTz was insoluble in the 2:1 water:t-BuOH, but the copper loading results are still useful. The highest molecular weight was obtained with 1 mol % catalyst loading relative to monomer content. As pONBz is a bifunctional monomer, it is expected to behave according to step-growth polymerization models, which would predict a dispersity of 2 for the polymerization. The fact that several trials produced polymers with narrower dispersities may indicate that the growing chains simply precipitated out of solution when they became too large, halting polymerization.

To improve the solubility of the polymer and obtain higher molecular weights, the solvent was switched to anhydrous DMF. Initial trials with the CuSO₄:sodium ascorbate catalyst system and later trials using CuBr(TPP)₃ as catalyst failed to produce any polymerized material. This was attributed to the ability of the DMF nitrogen to
preferentially coordinate the copper catalyst, preventing reaction. Even though the amide nitrogen has less electron density than an amine, it is present in much higher concentration than the nitrogenous ligand, overwhelming the coordination equilibrium. The solvent was then switched to DMSO. In this solvent, using 1 mol% catalyst and 10 mol% sodium ascorbate at room temperature, polymers were produced. Samples were drawn from polymerization attempt M and analyzed by DMF GPC to assess polymerization kinetics, as see in figure 4.1 below.

![PTz M<sub>N</sub> and D vs. Time](image)

**Figure 4.1:** Polytriazole M<sub>N</sub> and D as a function of time during polymerization.

The click polymerization proceeds quickly, reaching a peak molecular weight within one hour of initiation. The slow molecular weight drop over the following hours was attributed to insufficient exclusion of light leading to premature photocleavage. As polytriazoles have a more rigid backbone compared to the PMMA GPC standards, it is likely that the polytriazole chains are eluting from the GPC column more quickly than a PMMA of comparable molecular weight. This means that the molecular weight estimates obtained by GPC are likely lower than the actual chain mass.
The last attempt at optimization changed the copper catalyst from CuBr(TPP)₃ to 1:5:30 CuBr₂: HMTETA: Ascorbic acid. It was hypothesized that the limited solubility of sodium ascorbate in DMSO was preventing effective reduction of oxidized copper, therefore inhibiting polymerization. Ascorbic acid has good solubility in DMSO, and the whole catalyst system had already been used for the ARGET ATRP in previous chapters. All other polymerization conditions were kept the same. The produced polytriazole was found to have a $M_N$ of 5580 Da by DMF GPC, and it was collected in 68% yield by mass.

![DMF GPC of PTzE](image)

**Figure 4.2:** DMF GPC of PTz trial E (CuBr₂ and ascorbic acid).

Based upon our exploration of possible click polymerization conditions, higher molecular weight materials are best produced in DMSO solution, using a copper catalyst in tandem with a reducing agent. Both catalysts that begin in the Cu⁺¹ and Cu⁺² oxidation states were successful at producing polymer, but the CuBr₂/ascorbic acid system yields the best material in terms of mass yield and requires much lower copper loading than the other methods evaluated. Polymerization reaches a peak molecular weight approximately one hour after polymerization starts. The resulting materials can be collected by precipitation
from dichloromethane or water, the latter being useful for removal of catalyst, and oxidized/excess reducing agent. Currently, the best avenue for increasing molecular weight lies in better purification of the pONBz monomer, as even small amounts of improperly functionalized monomer can drastically reduce the maximum molecular weight.

4.3 Properties of photodegradable polytriazoles

Once the polymerization conditions were sufficiently optimized to provide material with higher molecular weight, the material properties of these PTzs could be determined. These polymers were only soluble in DMF and DMSO, limiting the solution processing possibilities significantly. All other solvents tested showed no qualitative evidence of dissolving or even swelling the PTz. This is not unexpected, due to the high fraction of aromatic content in the repeat unit.

Thermal analysis by TGA and DSC were performed, and representative traces can be seen in figure 4.2 and 4.3. The TGA indicates PTz does not display 2% mass loss until 245 °C, as compared to 230 °C for the small molecule analog analyzed in chapter three. The DSC data for this material show a $T_g$ of 130-135 °C, a value that compares favorably to polycarbonates, and displays no evidence of crystallinity in the temperature range explored. Considering that the gap between the $T_g$ of PTz and its onset of thermal decomposition is only about 100 °C, thermal processing methods are not recommended for this material.
**Figure 4.3:** TGA under nitrogen of PTz synthesized in trial K.

**Figure 4.4:** DSC of PTz synthesized in trial K, showing a cooling curve and overlaid 2\textsuperscript{nd} and 3\textsuperscript{rd} heating cycles.

While the high $T_g$ and thermal stability of the high-aromatic-content PTz materials are desirable, increasing the applicability of these materials as photoetchable thermoplastics requires better processing capabilities. A suggested avenue of further exploration is to incorporate more aliphatic content in the polymer in an attempt to lower the $T_g$ and improve the material’s solubility in solvents other than DMF and DMSO. This
could be done through either a redesign of the AB-style monomer or the inclusion of comonomers.

4.4. Photodegradation profile of polytriazoles analyzed by $^1$H NMR

A $^1$H NMR sample of polytriazole was prepared in methanol-$d_4$ and exposed under a 1.36 mW/cm$^2$ 365 nm source. At several points in time, the sample was analyzed by $^1$H NMR and the aromatic region was used to assess the fraction of repeat units that had undergone photocleavage. The overlaid NMR spectra for this experiment can be seen in figure 4.5 below.

![Overlaid NMR spectra](image)

**Figure 4.5:** Overlaid $^1$H NMR spectra, focused on the aromatic and benzyl proton region from 4.5-9.5 ppm. From bottom to top: pristine, 4 hours exposure, 8 hours exposure, 30 hours exposure to 365 nm at 1.36 mW/cm$^2$.

The increased signal in between the pristine material resonances derives from the new aromatic species that are generated from photocleavage, as seen in scheme 4.3 below. The known pristine resonances were integrated, as well as the growing cleaved material signals, and the ratio of the two expressed as the mole fraction of polytriazole consisting
of cleaved material. The mole fraction of cleaved material steadily increased until it reached over 75% of the material. This means that after 30 hours exposure, 75% of the polytriazole repeat units were cleaved. The increase in cleaved fraction with irradiation time appears to be roughly linear, with a cleavage rate of ~2 mol % of the sample per hour at this light intensity. A more intense UV source should cause a higher rate of photocleavage.

Scheme 4.3: Photocleavage products of polytriazole.

Figure 4.6: Mole fraction of polytriazole that was cleaved at certain amounts of exposure time.
4.5. Macro- and micro-scale patterning

Two polytriazole films were drop-cast from 100 mg/mL DMF solution onto glass slides, followed by 24 hrs in a 40 °C vacuum oven to remove the DMF. The macroscale template was made by cutting the UMass PSE Department logo from an index card, and the microscale template was a small number of copper TEM sample grids. The templates were placed on each film, and the films were then exposed to 365 nm light at an intensity of 1.34 mW/cm² for 8 hours to induce photocleavage. Using the cleavage rate obtained in the previous section, at the end of the irradiation time approximately 16 % of the ONBTz junctions should be cleaved. The results of these experiments can be seen in figure 4.7.

![Figure 4.7: Counterclockwise from upper left: Photograph of film exposed under macroscale template, photograph of film exposed under microscale TEM grid template, optical microscopy image of small boxed area displaying the reproduction of fine template structure.](image)

In the photographs, areas that are darkened were the areas exposed to the UV source. The dark color derives from the formation of an azobenzene compound from continued irradiation of the o-nitrosobenzaldehyde photocleavage product (scheme 4.4).
As can be seen from the PSE logo, reproduction of millimeter-scale features is good even with a simple exposure setup. The images of the film exposed under copper TEM grids supports the capability of PTz to reproduce micron-scale features, as the fine structure of the copper grid is sub-50 microns in size.

**Scheme 4.4:** Photodimerization of \( o \)-nitrosobenzaldehyde

4.6. Summary of Chapter Four

Based on the ONBTz photocleavable linker chemistry described in chapter three of this dissertation, an AB-style monomer was designed that generates a fully photodegradable polytriazole upon CuAAC polymerization. The monomer synthesis was optimized to the point that multi-gram scale batches could be produced in over 50% process yield from commercially available starting materials. The effects of different copper catalyst systems and solvents were explored, determining that a copper(I) or copper(II) salt with added reducing agent in DMSO solution produced the highest molecular weight materials in the highest mass yield. The timescale of photocleavage was explored, and basic photopatterning experiments were performed to demonstrate the potential of polytriazoles as a directly photoetchable material.
References


CHAPTER 5

PROSPECTIVE AVENUES OF NEW RESEARCH AND POSSIBLE APPLICATIONS

5. 1. Dissertation Summary

Photocleavable junctions have become a powerful tool for the generation of complex polymer structures that display specific behaviors upon exposure to UV light. Many questions remain about the physical processes behind these behaviors that may be explored by correlation fluorescence spectroscopy. In chapter two, a method was described by which a photocleavable, dual-dye labeled block copolymer was prepared, poly(acrylamide)-hv-poly(hydroxyethyl methacrylate), that is a suitable substrate for both fully soluble experiments and for experiments on amphiphilic structures. This block copolymer features the established o-nitrobenzyl ester linker.

In chapter three a novel photocleavable linker was introduced, the o-nitrobenzyl-1,2,3-triazole (ONBTz). This linker can be prepared by copper-catalyzed 3+2 Huisgen cycloaddition of azides and alkynes (CuAAC), and its photocleavage into the predicted o-nitrosobenzaldehyde and a free 1,2,3-triazole was demonstrated. Attemps were made to prepare photocleavable block copolymers by one-pot CuAAC/chain extension by activator regenerated by electron transfer atom transfer radical polymerization, but they were unsuccessful due to the chemical vulnerability of the prepared linker structure to the polymerization conditions.

This ONBTz linker was used in chapter four to prepare a bulk photodegradable polytriazole by CuAAC polymerization of an azide-alkyne difunctional monomer. An optimized synthesis for this monomer was described that began with a commercially available substrate and produced the desired monomer in four steps with a greater than
50% process yield. Optimized polymerization conditions were developed, and the photodegradation behavior was explored through NMR experiments. Proof-of-concept photopatterning experiments verified the capability of the polytriazole to reproduce features on the macro- to micron-scale.

5.2. Perspective on Chapter Two

In order to explore poorly understood physical phenomena in amphiphilic polymer systems such as micelles, bilayers, and phase separated thin films; a block copolymer was designed for use in correlation fluorescence spectroscopy (CFS) experiments. This material met the following requirements:

- Two polymer blocks of known molecular weight that can form both fully soluble and amphiphilic systems
- A separate dye label in each block
- A photocleavable junction between the two blocks

The material produced is a poly(acrylamide)-hv-poly(hydroxyethyl methacrylate) copolymer, which can be analyzed fully solubilized in aqueous systems, but forms amphiphilic systems in aqueous methanol. The fully dissolved material will provide a tool for calibrating the CFS measurements. The observed diffusion constants can be compared to the theoretical values derived from the molecular weights determined spectroscopically or chromatographically. The rate of photocleavage can also be established in preparation for experiments in amphiphilic systems. The acrylamide block is insoluble in methanol, and will therefore form micelles at the proper polymer concentration. Photocleavage experiments performed on these systems will help determine how many chains must be
cleaved to cause collapse of the micelle, and indicate whether cleaved chains diffuse into solution or remain entangled in the micelle corona or core.

Such experiments will allow refinement of physical models describing this phenomenon. This is critical to applications like payload delivery, especially that focused on using micelles to protect and release drugs within the body.¹ Nitroso-functionalized compounds like the o-nitrosobenzaldehyde photocleavage product have been known to be cytotoxic and mutagenic.² While it is straightforward to measure the cytotoxicity of these compounds in vitro, tests for mutagenicity often focus on short-lived cells like bacteria, while use of nitroso compounds in humans may not show signs of mutagenic behavior until many years later. Therefore, understanding what fraction of the chains in the micelle must be cleaved to allow efficient payload release will allow researchers to minimize the amount of photocleavable polymer in the micelles and reduce human exposure to these potentially hazardous structures.

These experiments will also track both blocks independently. This will enable researchers to determine how quickly cleaved corona chains diffuse away from the collapsing micelle, which may happen on a longer time scale than simple diffusion of a similar linear polymer due to chain entanglements with chains that have not yet been cleaved. This delayed diffusion may be strongly affected by the corona material’s solubility in the matrix solvent, indicating that different time scales for micelle collapse must be used in an in vitro phosphate buffer solution experiment and an in vivo test of payload release in the complex solution of a living cell’s cytoplasm. Further, tracking the insoluble block’s diffusion constant will allow researchers to determine how the particle size of the micelles changes with degradation. It has been shown that the size of a polymer
nanoparticle has large effects on its uptake into cells, as well as on particle circulation time in the body and the method by which the particle is excreted from the body. By using CFS experiments to document the time scale and size effects of degradation, researchers will be able to more accurately determine drug dosing and release kinetics, as well as predict what physiological systems are likely to be affected by the administration of the drug. All of these will help minimize side effects and increase drug efficiency.

Beyond the direct implications of the CFS experiments that will be performed, the synthetic method described here is not specific to the materials used and can serve as a broad platform for the construction of complex polymer architectures that are functionalized with various amounts of functionalities added either during polymer synthesis as with the NBD fluorophore, or used for post-modification of the activated ester. The ATRP initiating site employed is competent to polymerize many monomers of styrene, (meth)acrylate and (meth)acrylamide structure, opening up a wide variety of polymer materials that are available through this general method. The activated ester chemistry can work with many different amines, and the necessary pentafluorophenyl methacrylate monomer and photocleavable junction/ATRP initiating structure can be synthesized through straightforward methods. As all the required synthetic steps are relatively simple to perform and do not require sophisticated chemical infrastructure, this method can be used even by researchers at smaller or less advanced institutions to prepare complex materials with photocleavable junctions, placing some new, powerful tools in the hands of more investigators.

A possible simplification of this technique is to use the activated ester chemistry in each block to affix dyes, rather than relying on dyes functionalized with a polymerizable
group. Activated ester chemistry should work with any amine-functionalized moiety, and the pentafluorophenyl group can be attached to methacrylic or acrylic polymerizable handles in a facile manner. As the activated ester-functionalized monomer is used in such a small amount compared to the bulk monomer, there is a low likelihood of its presence affecting overall polymerization kinetics. The low dilution is also of benefit concerning the dye-functionalized monomers, which can be expensive. Only a small amount is needed to be used for labeling, meaning that costly dyes or those that are time-consuming to produce become viable reagents.

The first block can be produced by ATRP chemistry, with or without a reducing agent as may be required, then the alkyl halide can be displaced with azide to provide a handle for clicking the junction molecule to the block. The alkyne-functionalized ATRP initiator used in this dissertation, pMAI, can be produced in substantial amounts and good purity through a facile synthetic method. The one-pot CuAAC/ATRP or ARGET ATRP method produces a well-defined block copolymer from two small molecule components (junction/initiator and monomer) and one relatively simple macromolecular component.

A further degree of sophistication in structure can readily be obtained by repeating the azide conversion and chain extension step with more monomers. Triblock copolymer systems can take on more complex phase-segregated architectures than diblocks, and having the ability to remove one or more blocks after photocleavage via washing may yield nanoscale morphologies that have not been previously reported. The use of a multi-functional small molecule core or a polymer with reactive side chains can undergo the chain extension process to yield photocleavable star and graft polymers. These systems have different physical models than linear chains, and these models may benefit from the use of
fluorescently labeled materials and CFS, to study the effects of grafted chain density on coil length or the rheology of these systems as arms or side chains are removed.

Lastly, there is also no need to be limited to dyes for functionalization. The activated ester chemistry allows facile modification of complex structures, leading to many intriguing possibilities for modification of polymers. By using a combination of the CuAAC/ATRP method and simultaneous activated ester substitution, a combinatorial approach may yield a panel of highly complex materials arising from simple components strategically employed in one-pot transformations. The ability to rapidly produce polymers with varied block identities and lengths, varied amounts of moieties added in by activated ester, and precisely placed photocleavable junctions places a great many tools in the hands of polymer scientists; allowing the refinement of designs for the production of polymers with sophisticated behavior.

5.3. Perspective on chapter three

Despite the fact that no photocleavable block copolymers were produced with MAIZ via ARGET/ATRP, MAIZ may be useful in anhydrous ATRP systems for one-pot production of block copolymers with an ONBTz junction. A method was also described for the transformation of o-nitrobenzyl alcohols to o-nitrobenzyl azides, a transformation that has historically been difficult to perform in a single step and previously required hazardous or costly reagents. While the reported method requires two steps, the overall yield of isolated azide is higher than previously published one-step techniques. Furthermore, the intermediate bromide is itself a useful functionality, which can be readily replaced with a wide variety of nucleophiles. There are in fact numerous o-nitrobenzyl
style photocleavable linkers, and this bromide may offer a simplified synthetic pathway to many of them.

The panel of stability test applied to the ONBTz and ONB ester small molecule analogs established that the triazole linker superior water and nucleophile tolerance to the ester, as well as a thermal decomposition temperature 100 °C higher. The higher thermal tolerance indicates that ONBTz based materials have a greater ability to be thermally processed, opening up melt processing in addition to the already established solvent processing techniques. Melt processing can allow for the preparation of different structures like thick films, fibers and beads that have not yet been substrates used in conjunction with photocleavable junctions. The greater chemical stability will allow for ONBTz-based materials to be post-modified by a greater variety of chemistries, as well as for greater flexibility in multiple-junction materials. Many different chemical stimuli can be used to cleave junctions, including acids, bases, redox reagents and various kinds of organometallic chemistries, and the increased stability of the ONBTz linker will allow for their inclusion, facilitating the preparation of polymers that can respond to multiple stimuli.

In order to fully utilize the improved thermal and chemical stability of the ONBTz linker, an improved azide-functionalized initiator structure should feature a $p$-nitrophenyl ether rather than the corresponding ester. A proposed structure and synthesis is presented in scheme 5.1. This structure can be prepared from 5-hyrdoxy-2-nitrobenzyl azide (as synthesized in chapter three of this dissertation) and has two useful features. First, it avoids the labile $p$-nitrophenyl ester. Second, the ATRP initiating site is anchored to the molecule through an amide, rather than an ester, which further adds thermal and chemical stability to the molecule.
Scheme 5.1: Proposed alternative azide-functionalized ATRP initiator.

With this hypothetically more stable junction structure, the ability of CuAAC/ARGET ATRP to produce complex polymer architectures could be more fully explored. The use of a reducing agent allows for performing polymerizations in systems that are not rigorously purified, and can easily be done from stock solutions to rapidly produce entire panels of materials with varied component monomers and additives such as the aforementioned dyes.

5.4. Perspective on chapter four

The optimized monomer synthesis and click polymerization methods described in this chapter have now been used to produce gram quantities of photodegradable polytriazoles for photolithographic experimentation. However, the described monomer structure still suffers from limited processability: its solubility is limited to DMF and DMSO, both of which are challenging to completely remove from cast films. Furthermore, the gap between its $T_g$ and onset of thermal decomposition is too narrow for it to be thermally processed. The incorporation of more aliphatic content into the material may alleviate these drawbacks. This could be done by altering the core molecule used for the alkyne-azide monomer synthesis, installing an aliphatic tether between the phenyl ring and the alkyne, or through the use of comonomers. Exploring these avenues should be the immediate next step, producing a photocleavable material that is more readily processed and useful.
Acetovanillone may be used as the core molecule for photocleavable structures, as it offers several potential advantages. Firstly, acetovanillone is an industrial commodity and is therefore inexpensive and available in large quantities. Second, the methoxy group \textit{para} to the nitro group red-shifts the onset of absorption meaning that the linker has a greater molar absorptivity at easily accessible 300-365 nm wavelengths thus increasing the rate of photocleavage. Third, the presence of methyl substitution at the benzyl position decreases the rate of the formation of the azo byproduct of the \textit{o}-nitrosobenzaldehyde photocleavage product. This byproduct is a competitive absorber, and its presence decreases the efficiency of photocleavage. However, this structure requires more synthetic investment, including a particularly delicate aromatic nitration.

\textbf{Figure 5.1}: Acetovanillone (left) and its corresponding potential ONBTz linker structure (right).

Once a readily processed polytriazole is obtained, exploration of its capabilities as a material that can be directly topographically patterned with light can be explored. One important feature of this polymer is that wherever photoetching takes place, the new surface will be decorated with several well-defined functional groups produced by the cleavage reaction. These include free 1,2,3-triazoles, aldehydes, or even carboxylic acids and azobenzene groups if byproduct formation is allowed. The aldehydes and acids can be used as handles for further functionalization of the surface, while the triazoles can
contribute pH response or proton conduction and the azobenzene groups have been known to undergo reversible photoswitching between cis and trans conformations. Different areas can be patterned this way simply by using photolithographic masks to control where the desired functionalities are generated.

Another possible tool for the application of these resins is the development of a passivating treatment that could be applied to the patterned surface when etching is complete that would protect the resin from further photoreaction. The most direct way to achieve this would be to reduce the aryl nitro group. This would hypothetically render the material light insensitive while leaving the backbone intact, if the correct reducing agent is selected. A possible reagent is iron in acidic media that would reduce the nitro to an amine. There have been no reports of o-aminobenzyl structures displaying photocleavable activity.

Surfaces with chemical or topological patterning on the nanoscale are known to affect phenomena as disparate as cell migration and wetting behavior,\(^6\) with potential applications to antibiofouling coatings,\(^7\) self-cleaning surfaces,\(^8\) nanoimprint lithography,\(^9\) and inherently antimicrobial surfaces.\(^10\) A directly photoetchable thermoplastic, especially one that could be passivated after patterning and post functionalized, would allow for more efficient preparation of these finely structured surfaces in terms of time and material. The monomer and polymer syntheses reported in this dissertation may serve as a platform from which such materials can be developed.
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APPENDIX A

CHARACTERIZATION OF COMPOUNDS IN CHAPTER TWO

A. 1. Spectral characterization of 2-nitro-4-(prop-2-yn-1-yloxy)benzyl-2-bromo-2-methylpropanoate (pMA1)

The characterization of the following intermediates in the synthesis of this compound can be found in Appendix C for the compounds of chapter three:

- 2-Nitro-5-(prop-2-yn-1-yloxy)benzaldehyde
- 2-Nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol

$^1$H NMR Spectrum of pMA1 in CDCl$_3$
$^{13}$C NMR Spectrum of pMAI in CDCl$_3$
The following expansion of the \(^{13}\text{C}\) NMR displays the two alkynyl carbon resonances in between the solvent triplet of CDCl\(_3\).

ATR-FTIR spectrum of pMAI (pure compound)
A. 2. Characterization spectra of polyacrylamide (PAAm) blocks

$^{1}$H NMR spectra in DMSO-$d_{6}$ used for molecular weight determination, and FTIR spectra

PAAm A – target 5kDa, unlabeled, obtained 4,890 Da

ATR-FTIR Spectrum of PAAm A
PAAm B – target 10 kDa, unlabeled, obtained 17,300 Da

ATR-FTIR of PAAm B
$^1$H NMR of PAAm C (target 20 kDa, unlabeled, obtained 25,400 Da)

ATR-FTIR of PAAm C
$^1$H NMR of PAAm D (target 5 kDa, labeled, obtained 7,400 Da)

ATR-FTIR of PAAm D
$^1$H NMR of PAAm E (target 10 kDa, labeled, obtained 14,500 Da)

ATR FTIR of PAAm E
$^1$H NMR of PAAm F (target 20 kDa, labeled, obtained 26,400 Da)

ATR-FTIR of PAAm F
Overlaid ATR-FTIR spectra of PAAm blocks

$^1$H NMR in DMSO-d$_6$ and FTIR spectra of PAAm azides

$^1$H NMR of PAAm A azide
ATR-FTIR of PAAm A azide

1H NMR of PAAm B azide
ATR-FTIR of PAAm B azide

\[ \text{PAAm B azide} \]

\[ \text{Wave number (cm}^{-1}\text{)} \]

1H NMR of PAAm C azide

\[ \text{ppm (δ)} \]

110
ATR FTIR of PAAm C azide

\[ \text{PAAm C azide} \]

\[
\begin{array}{c}
\text{Wave number (cm}^{-1}\text{)}
\end{array}
\]

\[
\begin{array}{c}
\text{% Transmittance}
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\[ \text{1H NMR of PAAm D azide} \]

\[
\begin{array}{c}
\text{ppm (d)}
\end{array}
\]

\[ \text{7.60, 7.23, 6.877} \]

\[ \text{2.898, 2.788, 2.117, 1.527} \]
ATR-FTIR of PAAm D azide

\[ \text{PAAm D azide} \]

$^1$H NMR of PAAm E azide

\[ \text{ppm (d)} \]
ATR-FTIR of PAAm E azide

\[ \text{PAAm E azide} \]

\[ \text{Wave number (cm}^{-1}) \]

\[ 3600 \quad 3100 \quad 2600 \quad 2100 \quad 1600 \quad 1100 \quad 600 \]

\[ \% \text{ Transmittance} \]

\[ 100 \quad 90 \quad 80 \quad 70 \quad 60 \quad 50 \quad 40 \quad 30 \quad 20 \quad 10 \quad 0 \]

\[ \text{ppm (d)} \]

\[ 7.94 \quad 7.98 \quad 8.94 \quad 2.19 \quad 1.94 \]

\[ \text{ppm (d)} \]

\[ 200 \quad 5.0 \quad 2.12 \quad 2.20 \]

\[ \text{ppm (d)} \]

\[ 113 \]
ATR-FTIR of PAAm F azide
\(^1\)H NMR of PAAm-hv-PHEMA copolymers in DMSO-d\(_6\)/MeOH-d\(_4\) after UV exposure, PAAm precipitation by MeOH and filtration

PAAm-hv-PHEMA B
PAAm-\textit{hv}-PHEMA C
PEO-\textit{hv}-PHEMA E
PEO-\textit{hv}-PHEMA F
$^1$H NMR and of PHEMA blocks in DMSO/MeOH-$d_6$

PHEMA B
PHEMA D
PHEMA E
APPENDIX B

CHARACTERIZATION DATA FOR CHAPTER THREE

B. 1. Characterization spectra for the synthesis of ONBTz small molecular analog

$^1$H NMR spectrum of o-nitrobenzyl azide in CDCl$_3$
ATR-FTIR spectrum of $o$-nitrobenzyl azide

$^1$H NMR of ONBtz SMA in Methanol-$d_4$
$^{13}$C NMR of ONBTz SMA in Methanol-$d_4$
ATR-FTIR Spectrum of ONBTz SMA

[Graph showing the ATR-FTIR spectrum of ONBTz SMA with labeled axes for wave number and transmittance.]
B. 2. Characterization spectra for the synthesis of o-nitrobenzyl ester small molecule analog (ONBSMA)

$^1$H NMR of $o$-nitrobenzyl alcohol in CDCl$_3$
$^{13}$C NMR of o-nitrobenzyl alcohol in CDCl$_3$
ATR-FTIR of o-nitrobenzyl alcohol

![ATR-FTIR of o-nitrobenzyl alcohol](image)
$^1$H NMR of ONBSMA in Methanol-$d_4$
$^{13}$C NMR of ONBSMA in Methanol-$d_4$
B. 3. Products of ONBTz SMA photoleavage

ATR-FTIR of o-nitrosobenzaldehyde

ATR-FTIR of 4-butyl-1,2,3-triazole
B. 4. Stability Assays of ONBTz SMA

$^1$H NMR spectra assessing acid stability (5% acetic acid-$d_4$ in MeOH-$d_4$)

**Top:** Sample just after preparation.

**Bottom:** Sample after 24 h incubation at room temperature in the dark.
$^1$H NMR spectra assessing thermal stability (50 °C, 24 h)

**Top:** Sample just after preparation.

**Bottom:** Sample after 24 h incubation at 50 °C in the dark.
$^1$H NMR spectra assessing base stability (0.01 M KOH in D$_2$O/MeOH-$d_4$)

**Top:** Sample with no base added.
**Middle:** Sample just after base addition.
**Bottom:** Sample after 24 h incubation at room temperature in the dark.
$^{13}$C NMR spectra assaying base stability

**Top:** Sample before addition of base.
**Bottom:** Sample after 24 h incubation with base at room temperature in the dark.
TGA of ONBTz SMA under $N_2$
B. 5. Stability Assays of ONBSMA

$^1$H NMR spectra assaying acid stability (5% acetic acid-$d_4$ in MeOH-$d_4$)

**Top:** Sample just after preparation.
**Bottom:** Sample after 24 h incubation at room temperature in the dark.
$^1$H NMR spectra assaying thermal stability (50 °C, 24 h)

**Top:** Sample just after preparation.

**Bottom:** Sample after 24 h incubation at 50 °C in the dark.
$^1$H NMR spectra assaying base stability (0.01 KOH in D$_2$O/MeOH-$d_4$)

**Top:** Sample before base addition.

**Middle:** Sample just after base addition.

**Bottom:** Sample after 24 h incubation at room temperature in the dark.
TGA of ONBSMA

ONBSMA TGA in N₂

Sample mass (mg) vs. Temperature (deg C)
B. 6. Characterization spectra for the synthesis of 3-(azidomethyl)-4-nitrophenyl-2-bromo-2-methylpropanoate (MAIZ)

$^1$H NMR of 2-nitro-5-(methoxy methoxy)benzaldehyde in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(methoxy methoxy)benzaldehyde in CDCl$_3$

ATR-FTIR of 2-nitro-5-(methoxy methoxy)benzaldehyde
$^1$H NMR of 2-nitro-5-(methoxy methoxy)benzyl alcohol in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(methoxy methoxy)benzyl alcohol in CDCl$_3$

ATR-FTIR of 2-nitro-5-(methoxy methoxy)benzyl alcohol
$^1$H NMR of 2-nitro-5-(methoxy methoxy)benzyl bromide in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(methoxy methoxy)benzyl bromide

IR of 2-nitro-5-(methoxy methoxy)benzyl bromide
$^1$H NMR of 2-nitro-5-(methoxy methoxy)benzyl azide in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(methoxy methoxy)benzyl azide in CDCl$_3$

ATR-FTIR of 2-nitro-5-(methoxy methoxy)benzyl azide
$^1$H NMR of 5-hydroxy-2-nitrobenzyl azide
$^{13}$C NMR of 5-hydroxy-2-nitrobenzyl azide in Methanol-$d_4$

![](image)

ATR-FTIR of 5-hydroxy-2-nitrobenzyl azide

![](image)
$^1$H NMR of 3-(azidomethyl)-4-nitrophenyl-2-bromo-2-methylpropanoate in CDCl$_3$
$^{13}\text{C}$ NMR of 3-(azidomethyl)-4-nitrophenyl-2-bromo-2-methylpropanoate in CDCl$_3$

ATR-FTIR of 3-(azidomethyl)-4-nitrophenyl-2-bromo-2-methylpropanoate
B. 7. Characterization spectra of PEO-alkyne

$^1$H NMR of PEO-alkyne in CDCl$_3$
ATR-FTIR of PEO-alkyne

DMF GPC of PEO-alkyne

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$^1$H NMR of PEO-$hv$-PHEMA A in Methanol-$d_4$

Calculated $M_N$: 390 Da
DMF GPC of PEO-\textit{hv}-PHEMA A

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$^1$H NMR of PEO-$hv$-PHEMA B in Methanol-$d_4$

Calculated PHEMA $M_N$: 710 Da
DMF GPC of PEO-\textit{hv}-PHHEMA B

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$^1$H NMR of PEO-$hv$-PHEMA C in Methanol-$d_4$

Calculated PHEMA $M_N$: 1840 Da
DMF GPC of PEO-\textit{hv}-PHEMA C

![PEO-hv-PHEMA C](image)

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B. 9. Characterization of PEO-hv-PHEMA A, B, and C after UV exposure at 1.36 mW/cm²

DMF GPC of PEO-hv-PHEMA A post UV exposure

![PEO-hv-PHEMA A post UV](image)

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DMF GPC of PEO-hv-PHEMA B post UV exposure

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DMF GPC of PEO-hv-PHEMA C post UV exposure

![Graph](image)

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<tr>
<td></td>
<td>$M_W$</td>
<td>12620 Da</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\tilde{\eta}$</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>Peak at 1100 s</td>
<td>$M_N$</td>
<td>1040 Da</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>870 Da</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\tilde{\eta}$</td>
<td>1.19</td>
<td></td>
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</table>
B. 10. Characterization spectra of PEO-hv-PHEMA D,E, and F

$^1$H NMR of PEO-hv-PHEMA D

Calculated PHEMA $M_N$: 9230 Da
DMF GPC of PEO-\textit{hv}-PHEMA D:

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak at 900 s</td>
<td>(M_N)</td>
<td>9090 Da</td>
</tr>
<tr>
<td></td>
<td>(M_W)</td>
<td>10890 Da</td>
</tr>
<tr>
<td></td>
<td>(\mathcal{D})</td>
<td>1.20</td>
</tr>
<tr>
<td>Peak at 1050 s</td>
<td>(M_N)</td>
<td>1840 Da</td>
</tr>
<tr>
<td></td>
<td>(M_W)</td>
<td>1890 Da</td>
</tr>
<tr>
<td></td>
<td>(\mathcal{D})</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Calculated PHEMA (M_N)</td>
<td>below 0</td>
</tr>
</tbody>
</table>
$^1$H NMR of PEO-$h$v-PHEMA E

Calculated PHEMA $M_N$: 670 Da
DMF GPC of PEO-\textit{hv}-PHEMA E

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak at 900 s</td>
<td>$M_N$</td>
<td>9670 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>12700 Da</td>
</tr>
<tr>
<td></td>
<td>$D$</td>
<td>1.31</td>
</tr>
<tr>
<td>Peak at 1050 s</td>
<td>$M_N$</td>
<td>1860 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>1920 Da</td>
</tr>
<tr>
<td></td>
<td>$D$</td>
<td>1.03</td>
</tr>
<tr>
<td><em>Calculated PHEMA</em></td>
<td>$M_N$</td>
<td>below 0</td>
</tr>
</tbody>
</table>
$^1$H NMR of PEO-$hv$-PHEMA F

Calculated $M_N$: 3120 Da
DMF GPC of PEO-hv-PHEMA F

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Peak at 800 s</td>
<td>$M_N \quad 35930 \text{ Da}$</td>
</tr>
<tr>
<td></td>
<td>$M_W \quad 47600 \text{ Da}$</td>
</tr>
<tr>
<td></td>
<td>$\bar{D} \quad 1.32$</td>
</tr>
<tr>
<td>Peak at 900 s</td>
<td>$M_N \quad 8490 \text{ Da}$</td>
</tr>
<tr>
<td></td>
<td>$M_W \quad 9870 \text{ Da}$</td>
</tr>
<tr>
<td></td>
<td>$\bar{D} \quad 1.16$</td>
</tr>
<tr>
<td></td>
<td>Calculated PHEMA $M_N \quad 24570 \text{ Da}$</td>
</tr>
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</table>
B. 11. DMF GPC Spectra of PEO-hv-PHEMA post-UV exposure at 200 mW/cm²

DMF GPC of PEO-hv-PHEMA D post UV

![Graph showing PEO-hv-PHEMA D post UV](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak at 900 s</td>
<td>$M_N$</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
</tr>
<tr>
<td>Peak at 1050 s</td>
<td>$M_N$</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
</tr>
</tbody>
</table>
DMF GPC of PEO-\textit{hv}-PHEMA E

![Graph of PEO-hv-PHEMA E post UV](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak at 900 s</td>
<td>$M_N$</td>
<td>9810 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>12880 Da</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
<td>1.31</td>
</tr>
<tr>
<td>Peak at 1050 s</td>
<td>$M_N$</td>
<td>1980 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>2050 Da</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
<td>1.03</td>
</tr>
</tbody>
</table>
DMF GPC of PEO-hv-PHEMA F

![PEO-hv-PHEMA F post UV](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak at 800 s</td>
<td>$M_N$</td>
<td>34300 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>45200 Da</td>
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<tr>
<td></td>
<td>$\bar{D}$</td>
<td>1.31</td>
</tr>
<tr>
<td>Peak at 900 s</td>
<td>$M_N$</td>
<td>8880 Da</td>
</tr>
<tr>
<td></td>
<td>$M_W$</td>
<td>9750 Da</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
<td>1.10</td>
</tr>
<tr>
<td>Peak at 1050 s</td>
<td>$M_N$</td>
<td>1780 Da</td>
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<tr>
<td></td>
<td>$M_W$</td>
<td>1830 Da</td>
</tr>
<tr>
<td></td>
<td>$\bar{D}$</td>
<td>1.03</td>
</tr>
</tbody>
</table>
APPENDIX C

CHARACTERIZATION DATA FOR CHAPTER FOUR

C. 1. Characterization spectra for the synthesis of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl azide

$^1$H NMR of 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde in DMSO-$d_6$
\(^{13}\)C NMR of 2-nitro-5-(prop-2-y-1-yloxy)benzaldehyde in DMSO-\(d_6\)

ATR-FTIR of 2-nitro-5-(prop-2-yn-1-yloxy)benzaldehyde
$^1$H NMR of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(prop-2-yn-1-yl oxy)benzyl alcohol in CDCl$_3$
Detail of CDCl₃ solvent peak showing alkyne resonances between the triplet splitting

ATR-FTIR of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl alcohol
$^1$H NMR of 2-nitro-5-(prop-2-yn-1-yl)oxy)benzyl bromide in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl bromide in CDCl$_3$
Detail of the solvent peak from the $^{13}$C NMR, showing the alkyne carbon resonances

ATR-FTIR of 2-nitro-5-(prop-2-yn-1-ylxy)benzyl bromide
$^1$H NMR of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl azide in CDCl$_3$
$^{13}$C NMR of 2-nitro-5-(prop-2-yn-1-yloxy)benzyl azide in CDCl$_3$
Detail of the CDCl₃ solvent resonance showing alkyne carbon resonances between the triplet resonances.

ATR-FTIR of 2-nitro-5-(prop-2-yn-1-ylxy)benzyl azide
C. 2. Characterization spectra of polytriazoles

$^1$H NMR of polytriazole in DMSO-$d_6$

![NMR Spectrum](image)

ATR-FTIR of polytriazole

![ATR-FTIR Spectrum](image)
DMF GPC of Polytriazole E (CuBr$_2$:HMTETA:ascorbic acid catalyst)

<table>
<thead>
<tr>
<th>Peak at 900 s</th>
<th>Value</th>
<th></th>
<th>Value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_N$</td>
<td>4920 Da</td>
<td>$M_W$</td>
<td>5700 Da</td>
<td>$\bar{D}$</td>
</tr>
<tr>
<td>$M_W$</td>
<td>5700 Da</td>
<td>$M_N$</td>
<td>1380 Da</td>
<td>$\bar{D}$</td>
</tr>
</tbody>
</table>

TGA of Polytriazole L (degree of polymerization: 20-30) under nitrogen
TGA of Polytriazole L (degree of polymerization: 20-30) under air

DSC of Polytriazole K (degree of polymerization: 25-35)
C. 3. $^1$H NMR Analysis of Polytriazole Photodegradation

The pristine material spectrum is the same as that listed in section C. 2.

Spectrum detail taken after 4 hours exposure
Spectrum detail taken after 8 hours exposure
Spectrum detail taken after 30 hours exposure
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77. Tornoe, C. W.; Christensen, C.; Meldal, M., Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides. Journal of Organic Chemistry 2002, 76, 3057-3064.


