ABSTRACT

DESOUSA, JOSEPH DORO. Unmasking of Polycarbodiimides: The Synthesis and Characterization of Polyguanides. (Under the direction of Bruce M. Novak.)

The impact of polymer sciences, namely polymer chemistry and polymer physics, cannot be oversold. The advancement of the science can be directly linked to the explosive modernization of technology and global society over the last 150 years. Applications of the science are omnipresent and found in virtually every aspect of everyday life today ranging from critical life saving medical technology such as indwelling medical devices, i.e., heart stints and valves, to the trivial and mundane, i.e., removal coatings on lottery tickets or non-toxic, crosslinkable adhesives for children’s toys. All of these uses sprung from the exploration and exploitation of property-structure relationships of synthetic macromolecular systems. This document will discuss and focus on three endeavors carried out for the advancement of this important science within the framework of the polymer chemistry. Novak at el. have recently been focused on the development of an interesting class of functional polymers known as polycarbodiimides. These helical polymers, often referred to as polyguanidines given to the highly basic nature and structural similarity to the backbone, are linear macromolecules constructed by the polymerization of carbodiimide monomer using early- or late- transition metal catalysts, typically Ti(IV) organic complexes. This structure similarity to guanidine was the inspiration first thrust of work undertaken, the unmasking of polycarbodiimide via hydrogenolysis of poly(N,N’-dibenzyl)carbodiimide revealing the poly(guanidine) backbone as a carbon nitride precursor. The unsubstituted polycarbodiimide, also known as polyguanide a departure from the guanidine nomenclature reduce confusion with polymers functionalized with guanidine, exhibited a high degree of
solubility in various organic solvents and water, in addition to a resistance to elevated
temperature and strong oxidizers as carbon nitride is expected to exhibit. In the course of
these investigations it was found the precursor polymer, poly(N,N'-dibenzyl)carbodiimide,
departed for our conventionally understanding of regioregularity of polycarbodiimides as
observed from the diagnostic imine, C=N, IR stretch. Poly(N,N'-dibenzyl)carbodiimide, a
symmetric polymer demonstrated to be regioirregular by IR which is unlikely prompting the
development of a more definitive approach to regioisomer assessment. The isotopic labeling
of the backbone nitrogen of polycarbodiimide with $^{15}$N allowed unambiguous assignment of
the regioisomers via $^{15}$N-NMR spectroscopy. It was discovered polycarbodiimides are highly
regio-regular systems when the pendant groups are sufficiently different, alkyl/aryl, and
completely regioirregular when similar, alkyl/alkyl.

Additionally, other work was undertaken with the covalent tethering of anti-biofilm
inhibitors to polymer surfaces. These inhibitors, developed by Melander et al., were
functionalized with a methacrylatic pendant group for UV-initiated, radical polymerization
with a polyurethane methacrylate crosslinker. The polymer films resisted biofilm formation
of Acinetobacter baumannii up to 90 % when compared to a blank, with minimal leaching of
active inhibitor as observed by limited loss of bio-activity follow organic (80 %) and aqueous
(79%) soaks. Control experiments were also done using the precursor non-methacrylated
inhibitor formulated into the polymer film. Anti-biofilm activity was observed following
aqueous wash, however complete loss of activity occur following organic leaching studies.
Unmasking of Polycarbodiimides: The Synthesis and Characterization of Polyguanides

by

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APPROVED BY:

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David A. Shultz                 Christian C. Melander
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Alan E. Tonelli                      Bruce M. Novak
Chair of Advisory Committee
DEDICATION

This body of work is dedicated to the four persons, my grandparents, whom had the borne and raised the two most influential individuals in my life, Manuel Gaspar de Sousa (my father) and Margarita Fernandes de Sousa (my mother). Apolinar de Sousa & Maria Emilia Gaspar (paternal grandparent) and Jose Gaspar Doro & Maria Martins Fernandes (maternal grandparents) raised my parents in neighboring small villages in a post-World War II Portugal. They endured severe poverty, restrictive civil rights and education (until the late 1960s), all under an oppressive, corrupt, fascist regime. I learned from their experiences what meaning of perseverance under impossible odds and the value of believing in one’s self. Those values shown through my parents, whom may not fully appreciate the beauty of a clean $^1$H-NMR spectra, but are the wisest teachers one could ask for. They instilled in me the lesson that an honest day’s work is its own reward regardless the profession, as long as it is honest and noble work.
BIOGRAPHY

Joseph Doro DeSousa was born and raised in Waterbury, Connecticut at Waterbury Hospital in January 1979. The author was educated in the City of Waterbury Public School System through junior high followed by acceptance to the W.F. Kaynor Vocational Technical High School to study the electrical trade. During his time there he was recognized as Salutatorian of his graduating class and was invited to speak at his high school graduation. At the technical school he learned important skills in construction and fabrication. Following a few years in the trade, he enrolled part time in at the local community college to study chemical engineering technology. Once completing the two year program transferred to a bachelors program in chemical engineering at the University of New Haven, in New Haven, CT. The B.S. was acquired part time while working at Bomar Specialties Company in Torrington, CT. The author was hired as a Technology Associate and was quickly promoted to Research Chemist followed by Product Development Manager, and finally Plant Manager. During this time, the author acquired a working knowledge of both academic and industrial chemical practices and application. Finally enrolling at NC State Chemistry Dept. Ph.D. program in the Fall 2006.
ACKNOWLEDGMENTS

There are so many people I would like and need to thank during my time here. First, let’s start with the most important people, my family. My parents have been always supportive in my life choices. There are also my brothers, Tony and Mike, who are my closest friends. I could always count on them. I can’t forget to thank Helder Antunes, Dr. Rika, Dave Zopf, and Gadget for their friendship.

I was inspired to make this decision to continue my education by a good friend and mentor Dr. Dick Finch. His honest and frank assessment of my abilities as a scientist allowed me to dream that I can reach this point. I cannot tell him enough how much those days and seemingly trivial conversations affected me for the better. Also, cannot forget to mention Dick Hagstrom, the person who took a chance on me and hired me as a technology associate at Bomar. Truth be told, they were more interested in my technical and construction background than my scientific, but once I was there, curiosity took over.

Once I enrolled here at NC State, I began working for Dr. Novak. He allow me to explore chemistries I had not previously imagined or thought about all while provided the supportive and simulating environment to grow as an independent scientist. He would always just give me enough rope to hang myself but stop me before it happened… figuratively speaking of course. I cannot put into words how grateful I am for this once in a lifetime chance to work for and learn from him.

Adding to this environment were some of the best people I’ve had the privilege to work alongside with. Dr. Keitaro Seto and Dr. Yoko Aoyama, post-docs at the beginning,
warmly welcomed me in to the lab and helped me get used to this new environment. All my fellow group members during my time were amazing: Januka Budhathoki-Uprety was a wonderful labmate and a good friend, J.B. Clark challenged my opinion and perception of chemistry and life, Ying Zhang helped me learn so many new techniques and fun to work with. Last by not least, I had the honor of working with one of the most talented chemist I think I’ve ever met, Justin G. Kennemur who challenged me, mostly indirectly and probably completely unaware of it, to be the best I can be at everything I do.

Outside the research... wait a minute there was a world outside the research??? Yes, yes there was… I made some wonderful friends here such as Xiaomeng Wu, Elke Feese, Lingling Peng, Sergey Tsukanov, Gorman group, Molly Brannock, and so many other friends I have met here but I cannot name for lack of space, I hope to say in touch with for many years to come.
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<th>Poly(N,N'-dibenzyl)carbodiimide</th>
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<td>Poly(N,N'-di(methoxymethyl)carbodiimide)</td>
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<td>Poly-3</td>
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Poly-19  Poly($^{15}$N-hexyl-$N'$-propyl)carbodiimide
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Poly-21  Poly($N,N'$-di-(4-n-butylphenyl))carbodiimide
Poly-22  (R)-Poly(N-hexyl-$N'$-benzyl)carbodiimide
Poly-23  Poly(N-(4-n-butylphenyl)-$N'$-benzyl)carbodiimide
Poly-24  Poly(N-(1-methylnaphthyl)-$N'$-decyl)carbodiimide
Poly-25  Poly(N-(1-naphthyl)-$N'$-octadecyl)carbodiimide
DePoly-1  Deprotected Poly($N,N'$-dibenzyl)carbodiimide
DePoly-6  Deprotected Poly($N$-methyl-$N'$-(2-nitrobenzyl))carbodiimide
DePoly-7  Deprotected Poly($N$-(2-nitrobenzyl)-$N'$-propyl)carbodiimide
DePoly-8  Deprotected Poly($N$-hexyl-$N'$-(2-nitrobenzyl))carbodiimide

List of Catalysts

Cat-1  Trichloro-titanium(IV)-(2,2,2-trifluoroethoxide)
Cat-2  (R)-BINOL-titanium(IV)-diisopropoxide

General Abbreviations Used

HRMS  high resolution mass spectrometry
ESI   Electrospray ionization
THF   Tetrahydrofuran
CP/MAS  cross polarized/magic angle spinning
NMR   nuclear magnetic resonance
DMSO  dimethylsulfoxide
DMSO$_{d6}$ deuterated dimethylsulfoxide
<table>
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<tr>
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Chapter 1: An Introduction to Polyguanides

1.1 Superhard Materials

Throughout human history physical and chemical scientists and engineers have taken on the challenge of developing synthetic superhard materials that can rival nature’s hardest material, diamond. These materials are of both scientific and practical interest due to the dependence of society’s advancement and our material wealth on new materials. The hardness of a material can be defined as a resistance of that material to permanent or elastic deformation, i.e., incompressibility, and is measured by the Vicker’s Hardness Test. As a reference, diamond is the hardest known material with a hardness of greater than 70 GPa and retains much of the incompressibility even at high temperatures (1300°C, 10 GPa). Hardness can be categorized broadly into three main categories: (1) common materials of construction such as organics and steels, (2) harder materials which include aluminum oxides, silicon carbide, and most hard materials of construction, and (3) superhard materials which as of 1980 included diamond and cubic boron nitride. Toward the end of the 1980s, Liu and Cohen predicted crystal structure of a β-C₃N₄, a β-carbon nitride, would have a resistance to compressibility equal to that of diamond. Since that time there have been over 3800 scientific articles discussing synthesis and characterization C₃N₄.

1.2 Guanidine

In considering the synthesis of carbon nitride we looked to a ubiquitous reagent, guanidine. As a starting point we will explore the synthetic history of guanidine and its application to carbon nitride and polymeric linear guanidine derivatives. In the next few
sections a brief account of guanidine, biguanide, and larger guanidine derivatives are discussed as background and impetus for the studies undertaken in this manuscript.

![Guanidine and Derivatives](image)

**Figure 1.1:** Guanidine, Biguanides, and larger derivatives.

1.2.1 **Identity**

Guanidine is one of the earliest organic compounds isolated from nature. First found in meat extracts by Michel Chevreul in 1835 in the form of (α-methylguanido)acetic acid, also known as creatine. Later guanidine was extracted as a pure substance from the oxidation of guanine by Adolph Strecker in 1861. It is from this route that guanidine acquired its name. Schulze and Steiger in 1887 were the first to isolate the amino acid arginine. L-Arginine is an essential amino acid containing a guanidine residue. Among others, arginine is necessary for biological functions such as the production of nitric oxide utilized in muscle control. Structurally, guanidine has a triangular planar spatial arrangement. The structure is composed of a sp² hybridized carbon bonded to three nitrogen groups, two amino groups and one imino group.
Figure 1.2: Guanidine resonance structures: (a) neutral guanidine and two minor resonance forms, (b) guanidinium cation four resonance forms, (c) guanidinium anion two resonance forms.
This electronic arrangement provides two minor resonance structures as a free base. The hydrogens can rapidly exchange with one another in solution as seen with a single $^1$H-NMR signal at 7.1 ppm, relative to TMS, in DMSO$_{d6}$. Arguably one of the more interesting properties of guanidine is its acid/base behavior. Guanidine’s acid/base properties are directly attributed to this ability to delocalize the positive charge across three bonds and negative charge across two. Four resonance structures can be drawn for the guanidinium cation and two for the guanidinium anion. As a result, the pKa values of the guanidinium cation and neutral guanidine are respectively more apt to appear as a base or acid when compared to a representative nitrogen containing compounds as seen in Table 1.1. The pKa of the guanidine cation is one of the highest values for any protonated nitrogen compound. Guanidine is basic enough to remain protonated in most biological environments.$^6,7$

Table 1.1: The pKa of selected organic bases in DMSO and aqueous$^a$ solutions.$^8$-$12$

<table>
<thead>
<tr>
<th>Chemical Species</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanidinium</td>
<td>13.6</td>
</tr>
<tr>
<td>Ammonium</td>
<td>10.5</td>
</tr>
<tr>
<td>Anilinium</td>
<td>3.6</td>
</tr>
<tr>
<td>Ethylammonium</td>
<td>10.6$^a$</td>
</tr>
<tr>
<td>Triethylammonium</td>
<td>9.0</td>
</tr>
<tr>
<td>Neutral Guanidine</td>
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</tr>
<tr>
<td>Ammonia</td>
<td>41.0</td>
</tr>
<tr>
<td>Aniline</td>
<td>30.6</td>
</tr>
<tr>
<td>$p$-nitroaniline</td>
<td>20.9</td>
</tr>
<tr>
<td>Urea</td>
<td>26.9</td>
</tr>
<tr>
<td>Water</td>
<td>15.74$^a$</td>
</tr>
<tr>
<td>Carbonate ion</td>
<td>10.3$^a$</td>
</tr>
<tr>
<td>Bicarbonate ion</td>
<td>6.4$^a$</td>
</tr>
</tbody>
</table>
1.2.2 Guanidine in Organic Chemistry

To provide a comprehensive introduction to the chemistry and applications of guanidine would be outside the scope of this work, but some key applications would be appropriate to discuss. Such applications would be the use of guanidine as base catalysis,\(^\text{13}\) in host-guest complexes,\(^\text{14}\) and as carbon nitride precursors.\(^\text{15}\)

Returning to the acid/base chemistry, guanidine’s high, neutral pKa would aptly fit as a base catalyst in organic synthesis. Sterically hindered pentaalkyl-guanidines, also known as Barton Bases, were reported by Barton et al.,\(^\text{16}\) and have been effectively employed as base catalysts in Ullmann reactions,\(^\text{17}\) Baylis-Hillman Reactions,\(^\text{18}\) and Michael reactions.\(^\text{19}\) The development of chiral guanidine compounds also have used to catalyze enantioselective synthesis of chiral allenoates.\(^\text{20}\) Larger derivatives of guanidine such as 1,8-bis(tetramethylguanidino)naphthalene have been referred to as kinetically active ‘proton sponges’ with pKa values near of 25.1 in acetonitrile.\(^\text{21}\)

![Figure 1.3](image_url)

**Figure 1.3:** Examples of guanidine base catalysts, (a) enantioselective guanidine catalyst, (b) Barton Base, (c) 1,8-Bis(tetramethylguanidino)naphthalene, a diguanidine proton sponge.
In host-guest chemistry, guanidine has found a natural home in anionic binding applications.\textsuperscript{14, 22, 23} One of the first uses of guanidine as an anion receptor was described by Lehn et al.\textsuperscript{24} Later, Schmidtchen et al., continued the theme of using guanidinium containing compounds by incorporating a bicyclic motif which provides significantly increased sensitivity and binding strength over previous compounds.\textsuperscript{25} The breakthrough scaffolding in this area was a 1,3,4,6,7,8-hexahydro-2\textsuperscript{H}-pyrimido[1,2-\textit{a}]pyrimidine with n-butanol groups adjacent to the binding site as shown in Figure 1.4(a).* With the synthetic versatility of guanidine, complex and robust compounds can be constructed with multiple functions, which are all contingent on the guanidinium binding. deSaliva et al., synthesized the compound shown in Figure 1.4(b) with a guanidinium moiety bound to an anthracene in the 9-position and an 18-crown-6 ether on the 10-position. This combination of sensor and fluorophore was used to observe interactions with zwitterions such as γ-aminobutyric acid.\textsuperscript{26}

Figure 1.4: Examples of guanidine base catalysts, (a) 1,3,4,6,7,8-Hexahydro-2\textsuperscript{H}-pyrimido[1,2-\textit{a}]pyrimidine based anion receptor, and (b) combination crown ether/guanidine anion receptor.

In the field of superhard materials guanidine has also enjoyed some successful applications. Horvath-Bordon et al.\textsuperscript{15} recently reported the synthesis of a carbon nitride imide
crystal by way of high pressure, high temperature reaction of cyanoguanidine using a CO₂ laser and a diamond anvil cell.

\[
\text{H}_2\text{N}^+\text{C}_3\text{N}^+\text{NH}_2 \xrightarrow{P > 27 \text{ GPa}, T > 1700\text{C}} \text{C}_2\text{N}_2\text{NH}^{-} \quad -\frac{1}{2}\text{N}_2, -1.5\text{H}_2 \quad \rightarrow \quad \text{C}_2\text{N}_2\text{NH}
\]

**Scheme 1.1:** High pressure and temperature synthesis of a carbon nitride derivative.\(^{15}\)

The resulting product was evaluated by use of transmission electron microscopy techniques and Raman spectroscopy that together revealed signal crystals with the composition, C₂N₂(NH). The presence of N-H bonds that do not contribute to the covalent structure adversely effects the compressibility of proposed carbon nitride hardness.

### 1.3 Expanding Guanidine to Biguanide – Guanidine Dimers

Building on guanidine, dimers of guanidine or biguanides, have also been extensively studied in over the last century with approximately 7000 citations on Scifinder (June 2011). Biguanide shares many of the same properties as guanidine such as a high pKa near the same value as guanidine. The applications of biguanide are as wide as that of guanidine if not more so. Three interesting areas of study for biguanide have been metal complexes, pharmaceuticals, and antimicrobial polymers.

Biguanide can readily form highly colored metal complexes with many hard and soft acid metal cations such as Pd(III), Cr(III), Ag(III), B(III), Au(III), and Hg(II).\(^{27, 28}\) These metal complex also are not limited to one oxidation state, for instance silver can bind in all three oxidation states Ag(I), Ag (II), and Ag (III). In the pharmaceutical, field biguanide
derivatives have been extensively used. Some examples of biguanide drugs include Metformin, a drug for treating type 2 diabetes, and Proguanil, an antimalarial drug, both of which are widely used and are listed by the World Health Organization as Essential Medicines.

Of particular interest to us are polymers of biguanide that show antimicrobial and antiviral properties. Poly(alkyl) biguanides have found commercial use as a disinfectant and wound dressing. Recently, they have been studied as preventive treatments against HIV-1 for women. Preparation of poly(alkyl) biguanides are generally done by condensation polymerization of a diamine and cyanoguanidine.

Scheme 1.2: Condensation polymerization of alkyl diamine and cyanoguanidine to a poly(alkyl) biguanide.

1.4 Beyond Biguanide - Melamine

Triguanide and higher linear derivatives guanidine are not readily found in literature. A structural search on chemical abstract database returns only 11 references (July 2011) and do not include detailed synthetic procedures or convincing characterization. However, there are some interesting reports of endo-imine guanidine oligomers synthesized from amino substituted oligonitriles that show interesting cyclovoltametric properties and helicity.
Figure 1.5: Examples of generic oligonitriles: (a) substituted oligonitrile (b) amino-substituted oligonitrile.

As departure from linear guanidines, another common organic, high nitrogen containing material related to guanidine is the aromatic trimer of cyanoamide known as melamine. Melamines have been used in polymer chemistry for decades and have enjoyed widespread applications as commercial resins crosslinking agents in the form of melamine-formaldehyde resins. Melamine can be formed from the reaction of biguanide and cyanamide, however generally melamine is prepared from 3 equivalents of urea treated at high temperatures. In addition to the utility of melamine as a crosslinking agent for polymers, it has been recently used as a starting point for the synthesis of g-C$_3$N$_4$ (graphitic carbon nitride) by way by high temperature reactions of melem.37, 38

1.5 Polyguanides – N-Enchained Guanidine Polymers

Although little has been reported on the direct synthesis of linear guanidines larger than biguanide, some do report their theoretical properties. In these works Maksic et al. focused on the calculations of a linear and branched polyguanide structures in respect to their expected high pKa and absolute proton affinity. Acid/base properties of polyguanides are a natural extension of the properties seen by guanidine and biguanide, other properties such as thermal resistance and solubility has not been theoretically explored.
1.6 Summary and Outlook

Beyond the dimer of guanidine, very little new chemistry has been reported. In this work we aim to exploit polycarbodiimide chemistry to develop an indirect strategy for the synthesis of a linear guanidine polymer, a polyguanide. Attempts at characterizing a polyguanide are also outlined. Moving past the polyguanide synthesis, a structural characterization of polycarbodiimide regioregularity was also studied in an attempt to explain the unusual infrared signals of the precursor, debenzylated polycarbodiimide.
1.7 References


Chapter 2: Synthesis of Polyguanides via Polycarbodiimides

2.1 Synopsis

As previously discussed in Chapter 1, the synthesis of linear, unsubstituted polyguanides, or polyguanidines, are challenging due to their propensity to cyclize during polymerization to form melamine.¹ To the best of our knowledge no synthetic routes to such polymers have been reported. One of our goals for this work is to prepare relatively high molecular weight polyguanides that could serve as precursor polymers for the formation of carbon nitride under mild conditions. Carbon nitride is postulated to be a superhard material useful in a number of applications.² In attempting to develop a strategy for the synthesis of polyguanides, an indirect approach was proposed to avoid the inherit handicaps of a direct approach. Inspiration was drawn upon from one branch of research conducted in recent years in the Novak Group, involving the synthesis, characterization, and study of polycarbodiimides. It became readily evident that polycarbodiimides, possessing the necessary N-encheded nitrogen-rich motif, would serve as a platform for carbon nitride precursors. In addition to the precursor development, routes to partial functionalized polyguanides were explored, which will be referred to as mono-substituted polycarbodiimides in this manuscript. Based on literature precedent, these mono-substituted polycarbodiimides were hypothesized to have antimicrobial properties.³,⁴

Before moving forward into a discussion of the findings, a general account of polycarbodiimide chemistry is warranted. An extensive review of the latest advances in carbodiimide and polycarbodiimide synthesis has been recently published, and therefore, a comprehensive review will not be included here.⁵
2.2 Polycarbodiimides

Polycarbodiimides are a members of an exclusive and unique family of synthetic polymers that possess a conformational helical sense both in solution and the solid state. These materials are useful for prospective applications as chiro-optical switches, liquid crystals, and asymmetric catalysts to name a few.\textsuperscript{5-8} Other members of this family include polymethacrylates, polymethacrylamides, polyisocyanides, polyisocyanates, polysilanes, polychlorals, and polyphenylacetylates.\textsuperscript{9} In this section, emphasis will be placed on the chemistry and synthesis of polycarbodiimides and their precursors, while a more in-depth discussion of the chirality, helicity, regioregularity, and structural asymmetry of polycarbodiimides will be found in the following chapter.

2.2.1 Synthesis of Carbodiimide Monomers

Carbodiimides comprise a class of organic compounds known as heterocumulenes with the structure of $R\text{-N}=C=\text{N}-R$ and are isoelectronic to isocyanates.\textsuperscript{10} These compounds can be properly referred to as diimides of carbon dioxide with substituents including alkyl, aryl, aroyl, heteroatoms and sometimes metals. In addition to this variety of functionalities, there are principally two types of carbodiimides, i.e., those whose pendants groups are equivalent (symmetric) or pendant groups are not equivalent (non-symmetric). The simplest member of this class is the unsubstituted carbodiimide, H–N=\text{C}=\text{N}–H, which exists predominately as the cyanamide tautomer, H$_2$N–C≡N, is not useful in this research, but is a major feedstock for commodity reagents and polymers. Although the common, commercially available carbodiimides, dicyclohexyl carbodiimide and diisopropyl carbodiimide, used in
peptide coupling reactions are not appropriate candidates for polymerization due to steric problems that occur during the monomer insertion step of the polymerization (*vide infra*). Hence, all monomers used in the study of polycarbodiimides were synthesized from readily available starting materials, e.g., amines and isocyanates or isothiocyanates.

There are a hand full of strategies for the preparation of carbodiimides found in the literature. These include the coupling of isocyanates or isothiocyanates using catalytic amounts of cyclic phosphine oxides or from cyanamide and alkyl halides,\(^1\) and the conventional strategy of dehydration of ureas or the desulfurization of thioureas.

![Figure 2.1: Generic dehydration/desulfurization of a urea or thiourea.](image_url)

Symmetric ureas and thioureas are readily prepared via coupling reaction of the corresponding amines using phosgene and other phosgenating reagents, i.e., 1,1-carbonyldiimazole, di(4-nitrophenyl)carbonate, triphosgene, or by the reaction of an amine with an isocyanate/isothiocyanates. Non-symmetric monomers are generally prepared via the later route. These reactions are fairly straightforward, producing high yields under mild conditions and in short reaction times. The availability of the starting materials, and their relatively low cost, provide a diverse library that allows for the assembly of virtually a
limitless variety of unique polycarbodiimides. In spite of this, it is not possible to polymerize all possible carbodiimides due to catalyst poisoning and sterics limit the pendant groups to broadly aryl and alkyl.

Figure 2.2: The mechanism for O-urea dehydration using triphenyl phosphine, bromine, and triethyl amine.

The dehydration of ureas is done by the use of 1.2 molar equivalents of triphenylphosphine dibromide salt in the presence of an acid scavenger, normally triethylamine at loading of 2.5 molar equivalents. This salt can be purchased or generated in-situ from 1.2 molar equivalents of triphenylphoshine and 1.4 molar equivalents of bromide at 0 °C for thirty minutes. These conditions can be extended to the desulfurization of thioureas, albeit at lower yields than their oxygen analogs, which is the case in part of this manuscript. Thioureas can also be converted to carbodiimides by the use of a soft acid metal salt reagents such as mercury(II) oxide, lead(II) oxide, and cadmium(II) oxide. Typically, the
determining factors for choosing a metal salt or an organic salt in thiourea desulfurization are limited mainly to the sensitivity of the particular carbodiimide to hydrolysis. This reaction liberates one mole of water which can readily convert carbodiimide to O-urea. The water byproduct is trapped by using drying agents, such as sodium sulfate stirred into the reaction solution.

Traditionally, the final purification of carbodiimides following hydrocarbon extraction, normally pentane or hexanes, as done by vacuum distillation. However, in recent years column chromatography has been increasingly employed with the emergence of high boiling point, high molecular weight carbodiimide monomers. Vacuum distillation became an inefficient method for the purification of these higher carbodiimides as a result of long residence times at elevated temperatures. Prolonged heating causes partial to complete conversion of non-symmetric monomers by metastasis to products composed of two symmetric carbodiimides. While the avoidance of column chromatography has been due mainly to the vulnerability of carbodiimides to hydrolysis, which readily takes place when exposed to mildly acidic silica media. Under these conditions virtual all the monomer can be hydrolyzed back to urea. To overcome this limitation the stationary phase can be preconditioned with triethylamine or with specialty pH 7 preconditioned silica gel. This strategy is sufficiently successful that it has recently become the standard purification protocol for carbodiimides.
2.2.2 Polycarbodiimides From Carbodiimide Monomers

The polymerization of carbodiimides were first reported by Robinson in 1964 via anionic polymerization using n-butyllithium on a series of dialkyl- diaryl- and diallyl-carbodiimides at temperatures of – 40 to 25 °C. Robinson also reported the first indications of steric hinderance issues in polymerization of polycarbodiimides, as well as their low ceiling temperatures. The next reported polymerization of carbodiimides were with the use of titanium(IV) catalysts by Goodwin and Novak in 1994. A series of symmetric and non-symmetric carbodiimides were evaluated with three titanium(IV) complexes. Since these early discoveries, other transition metal complexes have been explored such as Cu, Zr, and Ni, but Ti(IV) remains the workhorse of modern polycarbodiimide polymerization. It was also discovered in this early work that not only do these catalyst produce higher molecular weight polymers than the anionic systems, but polymerization kinetics also follows a linear relationship between the $M_n$ and the monomer to catalyst ratio. This confirms one of the requirements for a ‘living’ polymerization system.

Figure 2.3: Generic polymerization of carbodiimides by the use of a titanium(IV) complex.

Prior to the application of titanium(IV) complexes by Goodwin to the polymerization of rigid rod, monodisperse polycarbodiimides, they were developed by Patten for the living polymerization of isocyanates. Conventional anionic polymerization of isocyanates have
been done at temperatures of −20°C to −100°C using cyanide initiators. Under these conditions, living polymerization has not been reported successful mainly due to side reactions which occur early in the polymerization broadening the molecular weight distribution. Organotitanium(IV) complexes proved to eliminate the formation of byproducts, such as cyclic trimers, at ambient temperatures advancing isocyanate polymerization to a living state. Although it is fair to view the active titanium(IV)-amidate complex, during polymerization, much like an anionic amide active end group, this is not entirely correct. The chemistry of an active titanium(IV)-amidate complex contains a N–Ti bond which is significantly more covalent in nature over the anionic amide propagating chain end.

Moving back to carbodiimides, these living polymerization conditions were observed to be retained. The polymerization of carbodiimides is generally a living process and is believed to follow in three steps as seen in Figure 2.4: (1) upon addition of the catalyst (initiation step) the first active titanium(IV)-amidinate complex is formed and is visible as a rust-red color, (2) followed by subsequent insertion of the carbodiimide monomer into the titanium(IV)-amidinate complex (propagation step). Returning to the overall scheme, 3) the polymer is terminated by precipitation of the crude polymer in methanol, cleaving the active chain end. There are two points of note here: firstly, in this outlined scheme there is no bias suggested, i.e., the pendent groups are equivalent, therefore insertion occurs across either of the N–Ti bonds. However, for non-symmetric monomers two regioisomers can potentially be produced. The preferred regioisomer and the regioregularity will be a topic of discussion in the following chapter. Secondly, when the subsequent monomer units are inserted into the titanium(IV)-amidinate complex steric becomes problematic.
2.3 Polycarbodiimides – A Motif for Polyguanides

As detailed above, polycarbodiimides are nitrogen rich polymers composed of amidine repeat units, and therefore a natural candidate for the indirect synthesis of polyguanide. To access this nitrogen-rich backbone, protection chemistry was employed with chemically removable pendent groups selected to mask the backbone.

Figure 2.5: General deprotection scheme of polycarbodiimides. Polycarbodiimides provide the necessary motif for polyguanide synthesis.
2.3.1 Protection Chemistry Restrictions

Protection chemistry is an evolving and dynamic application of organic chemistry in which a functional group is masked or derivatized to be later regenerated.\textsuperscript{18} The use of this concept is universal with applications in natural product synthesis, drug development, and polymer chemistry. In modern organic chemistry, the protection of functional groups is viewed typically as a ubiquitous transformation given to the large strides in the development of robust and nearly universal techniques. Examples such as converting an amine to a tert-butyl carbamate, an alcohol to benzyl ether, or carboxylic acid to an ester are routinely done. In regard to polycarbodiimdes, the nature and type of protecting pendent group would need to be evaluated and limitations assessed. As a general rule, pendent groups with $2^\circ$ or $3^\circ$ $\alpha$-atoms, i.e., isopropyl, t-butyl-, and trimethylsilyl are unable to polymerize due to steric hindrance. In addition, pendant groups containing carbonyls near the titanium(IV)-amidinate complex polymerize in a sluggish fashion. The poor polymerization would be amplified by steric at the $\alpha$-positions, tert-butyl carbamate, acetamide, and 2,2,2-trifluoroacetamide fall within this category.\textsuperscript{19} Moreover, the conditions for removing of masking groups need special attention. The thermal and chemical boundaries of polyguanides are yet unknown, but polycarbodiimides are constrained to mild temperatures owing to their low ceiling temperatures and, in general, limited solubility.
Figure 2.6: The nature of α-carbons or α-heteroatoms of pendant chains control the polymerization via sterics. Above are four examples of considered protected carbodiimides that were not chosen due to sterics.

Several protecting chemistries were considered in this work, but ultimately a dibenzylated polycarbodiimide was selected as the starting point owing to the relative ease of unmasking via hydrogenolysis.

2.3.2 Synthesis of Polyguanide via Debenzylation

A dibenzylated polycarbodiimide, poly(N,N'-dibenzylcarbodiimide), Poly-1, has been previously synthesized by Kim. The precursor polymer was only characterized by solid state 13C-NMR at that time due mainly to its very poor solubility in most organic solvents while, at best, only swellable in chloroform. The polymerization of Poly-1 was done under nitrogen atmosphere at a 150:1 N,N'-dibenzylcarbodiimide/trichloro-titanium(IV)-(2,2,2-trifluoroethoxide), Cat-I, molar ratio in dry chloroform. Solidification during polymerization was observed within thirty minutes of catalyst addition. The polymerization was allowed to
proceed further for two to four days or until the characteristic rust-red titanium(IV)-amidinate complex dissipated to a white solid.

Characterization of Poly-1 expended further revealing interesting spectroscopic information. As seen in Figure 2.7, \(^1\)H-NMR of Poly-1 has two features of interest: the diastereotopic benzyl proton signals and the large up field shift of the aromatic proton signals.

**Figure 2.7:** \(^1\)H-NMR of Poly-1 in CDCl\(_3\). Benzyl hydrogens are grouped together as a’/a” and b’/b”.

The anisotropy of proton signals in conformationally constricted molecules is not unusual, yet the increased shielding of the aromatic hydrogen, as indicated by the up field
shift, was unexpected and noteworthy. In addition to NMR spectra, the IR imine, C=N, stretch of Poly-1 was also anomalous with the appearance of two stretches at 1642 and 1626 cm$^{-1}$. This aspect will be explored further in the regioregularity section of this work.

The hydrogenolysis of benzyl masked heteroatoms, mainly oxygen as in benzyl ethers, is a ubiquitous reaction that is carried out under balloon pressure hydrogen gas. Along with hydrogen, catalytic amounts of palladium or platinum metal on carbon black in an alcoholic solvent at room temperature were used. As in the case here, unmasking of nitrogen functionalities by way of hydrogenolysis requires slightly more aggressive conditions and was done by doubling the hydrogen pressure (30 psi) and increasing the Pd concentration to as high as 15.0 wt. % polymer basis. The excess palladium metal was added to minimize the poisoning of the metal by free imine and amine unmasked during the reaction. The poor solubility of Poly-1 required the general alcoholic solution to contain 80 (v/v) % chloroform as a co-solvent. A purification protocol was developed by first filtering the heterogeneous metal catalyst and removing organic solvents via reduced pressure evaporation. The dried crude product was washed with acidic deionized water extract the deprotected polyguanide hydrochloride and vacuum dried. The dried, water soluble fraction is referred to as DePoly-1, while the crude remaining fraction is simply referred to as crude DePoly-1.
Figure 2.8: Pyrolysis of Poly-1, crude DePoly-1, and DePoly-1 under a nitrogen atmosphere at 10°C/min.

From the first successful debenzylation, pyrolysis of DePoly-1 was studied. The analysis was done under a nitrogen gas stream on Poly-1, crude DePoly-1, and DePoly-1 using a Universal V2.6D TA Instrument at 10°C/min. As mentioned earlier, polycarbodiimides have low ceiling temperatures and can be cleanly depolymerized back to the starting monomer. This depolymerization has been found to be robust and repeatable leading it to be explored as a method to elucidate the regiostructure of polycarbodiimides. For the pyrolysis of many polycarbodiimide, weight loss begins appearing at ~180°C; however the ceiling temperature, $T_c$, tends to be much lower. The observed weight loss is
actually the result of evaporation of the monomer following the depolymerization. Turning to DePoly-1 in Figure 2.8, there appears to be weight loss in the region from 25°C to 300°C followed by a plateau to the maximum instrument temperature of 600°C. The first 100°C of weight loss is believed to be from solvent evaporation; DePoly-1 is worked up from an aqueous solution and is expected to be hydroscopic. The crude DePoly-1 thermogram is interesting with a profile resembling more the precursor polymer with complete decomposition. The recovered crude material was significantly more soluble in a range of organic solvents after the modification indicating clear evidence of reaction, however as seen in Figure 2.8 there is no residue remaining of the crude at 600°C.

With few examples to compare to in literature, the closest chemical relatives were examined, namely guanidine, biguanide, and melamine. The thermal decomposition profiles for guanidine hydrochloride, 1,1-dimethylbiguanide hydrochloride (a commercially available biguanide), and melamine were collected revealing a complete weight loss by 600°C. Melamine has a melting point of 350°C and readily sublimes above 280°C, therefore observed weight loss is not decomposition. While biguanide is thought to lose one mole of ammonia during pyrolysis producing cyanoguanidine that can readily dimerize to form melamine which in turn sublimes. Evidence of this is has been previously reported in the formation of melamine crystals in the effluent gas line. Guanidine hydrochloride also has a similar thermal profile as melamine suggesting sublimation, with some persistent weight remaining to 600°C.
Figure 2.9: Thermograms of guanidine hydrochloride (blue), 1,1-dimethylbiguanide (red), and melamine (black) under a nitrogen atmosphere at 10°C/min.
Figure 2.10: Isothermal pyrolysis of DePoly-1 at 350°C for 15 hours with approximately 2 wt. % weight loss.

Figure 2.11: Pyrolysis of DePoly-1 at 10°C/min to maximum temperature of 1000°C.
To assess the robustness of DePoly-1 thermal properties, some control experiments were done. Two of interest involved the reduction of the heating rate during pyrolysis. Thermal decomposition of polycarbodiimides on the whole as well as DePoly-1 are typically done at 10°C/minute to 600°C. For this experiment the rate was first reduced to 5°C/minute with no appreciative change in the decomposition profile. Then isothermal decomposition was next studied as seen in Figure 2.10. In this experiment, DePoly-1 was heated to 100°C for 3 hours to drive off any remaining solvent accounting for approximately 5 wt. % of the sample mass. Following drying, the sample was rapidly heated to 350°C at 30°C/minute and held for 15 hours. During this period of time the weight loss was limited to 2 wt. % and with total weight retention of approximately 75 wt. %, closely matching Figure 2.9. A third experiment was conducted using a thermal gravimetric analyzer in the Martin Group which has the capability to reach 1000°C. From the thermogram in Figure 2.11, the characteristic weight loss at 150 to 250°C is observed. The weight is retained the region of 800°C, where a second decomposition is observed, with approximately 83 wt. % retained to 1000°C. The upward trend above 800°C is believed to be an artifact.
Table 2.1: Debenzylation optimization: (a) notebook experiment numbers, (b) the first successful debenzylation demonstrating thermal resistance, (c) complete loss of thermal properties, (d) no marked improvement in deprotection over 3-13, (e) maximum temperature, and (f) yield of DePoly-1 with 45 % deprotection determined by TGA.

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Poly-1 wt. (g)</th>
<th>H₂ (psig)</th>
<th>Time (hrs)</th>
<th>Pd %</th>
<th>Pt %</th>
<th>Solvent</th>
<th>Notes</th>
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<td>15</td>
<td>72</td>
<td>-</td>
<td>1.0</td>
<td>CHCl₃, EtOH</td>
<td>Successful Rxn b</td>
</tr>
<tr>
<td>3-50</td>
<td>1.040</td>
<td>15,90</td>
<td>24,24</td>
<td>-</td>
<td>0.5</td>
<td>CHCl₃, EtOH</td>
<td>Lost Properties c</td>
</tr>
<tr>
<td>3-57</td>
<td>0.481</td>
<td>30</td>
<td>48</td>
<td>0.5</td>
<td>-</td>
<td>CHCl₃, EtOH</td>
<td>NI d</td>
</tr>
<tr>
<td>4-24A</td>
<td>0.185</td>
<td>30</td>
<td>24</td>
<td>2.7</td>
<td>-</td>
<td>CHCl₃, EtOH</td>
<td>NI d</td>
</tr>
<tr>
<td>4-24B</td>
<td>0.220</td>
<td>30</td>
<td>24</td>
<td>4.8</td>
<td>-</td>
<td>CHCl₃, EtOH</td>
<td>NI d</td>
</tr>
<tr>
<td>4-28</td>
<td>0.101</td>
<td>30</td>
<td>24</td>
<td>2.5</td>
<td>-</td>
<td>Benz, BuOH</td>
<td>400 °C e</td>
</tr>
<tr>
<td>4-31</td>
<td>0.160</td>
<td>30</td>
<td>48</td>
<td>15</td>
<td>-</td>
<td>CHCl₃, EtOH HCl</td>
<td>Highly colored</td>
</tr>
<tr>
<td>4-50</td>
<td>0.723</td>
<td>30</td>
<td>60</td>
<td>15</td>
<td>-</td>
<td>CHCl₃, EtOH HCl</td>
<td>Complex free</td>
</tr>
<tr>
<td>4-75</td>
<td>0.930</td>
<td>15</td>
<td>90</td>
<td>15</td>
<td>-</td>
<td>CHCl₃, EtOH HCl</td>
<td>0.149g (45 %) f</td>
</tr>
</tbody>
</table>

From there we proceeded to optimize the synthesis by controlling system variables such as the catalyst loading, hydrogen pressure, and reaction time. Early attempts at optimizing DePoly-1 were puzzling. The IR indicated the loss of benzylic groups; however the material was intensely green in color and ¹H-NMR spectra could be collected owing to the inability to stabilize the magnetic field. This magnetic heterogeneity points to be presence of a NMR active species, which was confirmed with the assistance of Dr. Alex Simirnov using EPR. From these findings, it was hypothesized oxidized Pdⁿ⁺ ions, albeit trivial
quantities, native to the Pd/carbon black catalyst were complexing with the deprotected, bidentate biguanide sites of DePloy-1. Unsubstituted biguanide metal complexes have been long studied and will readily complex with many hard and soft metal cations including coinage metals to form stable and highly colored products.\textsuperscript{24}

![Proposed generic metal cation complex with DePoly-1 giving rise to the color and NMR characterization limitations.](image)

**Figure 2.12:** Proposed generic metal cation complex with DePoly-1 giving rise to the color and NMR characterization limitations.

The first effort at circumventing this complexion, which was a result of increasing metal catalyst loading, was to acidify the reaction medium with a few drops of concentrated HCl thereby bonding unshared electrons while minimizing catalyst poisoning prior to reaction. Acidification did not noticeably reduce the complexion, so preconditioning of the palladium catalyst by acidic organic solvent blank wash was attempted. The catalyst was recovered via diatomaceous earth filtration. The filtrate was a dark red to brown color indicating the removal of contaminants from the catalyst. The metal ion chelation phenomena following this treatment were virtually eliminated.
Figure 2.13: $^1$H-NMR of DePoly-1 in DMSO$_{d6}$. The anisotropy of the aromatic proton signals are lost as well as the diastereotopic nature of the benzyl proton signals as a result of debenzylation.

The $^1$H-NMR spectra for debenzylated polycarbodiimide, polyguanide, was now collected, free of paramagnetic interference, revealing evidence of debenzylation as observed by the appearance of exchangeable proton signals. Comparing these proton signals to guanidine at a chemical shift, $\delta = 7.31$ ppm in DMSO$_{d6}$, it could not be ruled out the reduction of the backbone C–N bond during hydrogenolysis is possible. The decomposition of the polymer yielding guanidine would have proton signals that overlay with the remaining aromatic groups. This backbone cleavage is believed possible during debenzylation as seen in experiment 3-13 in Table 2.1, for which hydrogenolysis was done at a hydrogen gas pressure of 90 psig or 6 atm. Under these conditions the thermal resistance properties were lost. Expanding to biguanide as comparison, in this case 1,1-dimethylbiguanide, the
exchangeable proton signals at $\delta = 7.2$ and 6.6 ppm which is a close must to the signal present in DePoly-1. Other cyanamide derivatives, such as melamine, are not present with a $\delta = 6.1$ ppm in DMSO$_{d6}$. Additional evidence of successful deprotection is found with the aromatic signals shifting back to a typical aromatic region of 8.2 to 7.0 ppm. The shift is due to the loss anisotropy effects of isolated aryl groups relative to the closely packed groups of the parent polymer.

![Image of Infrared Spectra](image)

**Figure 2.14:** Infrared spectra from a KBr pellet of (a) Poly-1 and (b) DePoly-1.

Along with the NMR spectral evidence, the IR spectra of DePoly-1 retains the imine stretch, albeit broadened, and the out of plane C–H bending of a single substituted aromatic
ring. The resolution of the signals is also substantially diminished owning to a less defined structure as a result of possible backbone tautomer structures.

Continuing with the characterization of DePoly-1, elemental analysis was a natural next step. Elemental analysis for samples of Poly-1 and DePoly-1 were performed by Altantic Microlabs, Atlanta, GA. In Table 2.2, the actual elemental analysis of Poly-1 is compared to the calculated value in row one, showing that they track closely to one another. The actual analysis for DePoly-1 only returns 31 wt. % of the sample as carbon, nitrogen and hydrogen. The analyzed 31 wt. % was normalized to 100 % revealing concentrations of C, N, and H also matching closely to Poly-1.

**Table 2.2: Elemental Analysis of Poly-1 and DePoly-1.**

<table>
<thead>
<tr>
<th></th>
<th>% Carbon</th>
<th>% Hydrogen</th>
<th>% Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cal. Poly-1</td>
<td>82</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Act. Poly-1</td>
<td>79</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Act. DePoly-1</td>
<td>24</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Normalized DePoly-1</td>
<td>78</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

Comparing the pyrolysis and elemental analysis results, a few conclusions can be made: (1) DePoly-1 during pyrolysis has weight loss of 25 – 30 wt. % in the temperature region associated to the weight loss of Poly-1 suggesting this weight loss is from portion of benzylated polycarbodiimide remaining, (2) confirming this hypothesis, the concentrations of the elementals recorded were in line with the ratios of Poly-1, (3) the synthesized polyguanide is thermally stable to temperatures of 1000°C under an inert atmosphere, and (4)
elemental analysis is conducted under a pure oxygen atmosphere at 900°C, therefore, **DePoly-1** is resistant to strong oxidizing gases.

### 2.3.3 Attempts at Determining the Degree of Debenzylation

To this point, the preliminary conclusion is deprotection is possible, nevertheless it is our goal to produce a completely deprotected polycarbodiimide.

Figure 2.15: A soluble version of a dibenzylated polymer, **Poly-2** and a fluorinated debenzylated polymer, **Poly-3**.

From the results of the first debenzylation, the poor solubility of **Poly-1** was identified as a possible reason for the lack of complete conversion. In an effort to remove this handicap, **Poly-2** was designed with linear alkyl chains on the para-position of the benzene ring in order to solublize **Poly-1**. The solubility significantly improved by this alteration, however alcoholic solvents were still challenging, so the original reaction solvent combination (80/20 CHCl$_3$/EtOH) was used for the debenzylation. Substituent effects are known to dramatically affect the rate of debenzylation via hydrogenoylisis, but for alkyl substituents in the para-position the effects are minor.$^{25}$ Ultimately the reaction was unsuccessful. Upon reflection,
the addition of an alkyl corona positioned around the rigid rod backbone is believed to be the cause. By restricting access of the heterogeneous metal catalyst to the inner benzyl-nitrogen bond arrested the deprotection. This was later confirmed by the first attempts at mono-debenzylation of polycarbodiimides.

Although living polymerization character is generally associated with carbodiimide polymerizations, molecular weight control and polydispersity of Poly-1 is important in showing the living character of this polymerization. Because of the insolubility of Poly-1, we hoped Poly-2 would serve as an appropriate model. Again, Poly-2 surprised us by not passing through a 0.4 μm syringe prefiler used prior to analysis with gel permeation chromatography. Solutions of Poly-2 in CHCl₃ and THF were transparent; unfortunately a significant fraction of this polymer is agglomerated in solution, yet invisible to the naked eye.

An alternate and common approach to gel permeation chromatography is end group analysis. The catalyst used for the generation of these polymers, Cat-1, transfers an 2,2,2-trifluoroethoxide ligand as an end group to each polymer chain. In principle, a fluorinated dibenzylated polymer could be studied via $^{19}$F-NMR. Poly-3 was originally polymerized at a monomer/Cat-1 ratio of 150:1 which would translate to two regions in the $^{19}$F spectra integrating 3 and 300. The aliphatic fluorine, however, could not readily disguised over the noise. Therefore, the catalyst loading was increased to a ratio of 25:1; the end group analysis showed an integration of 3 for the end group fluorine at $\delta = -72$ relative to hexafluorobenzene, and an integration of 88 for the aromatic fluorine in the region of $\delta = -101$ to – 120. These ratios suggest a $M_n = 11,352$ with a polymer of 44 repeat units. From the
Poly-3 model, it is reasonable to expect Poly-1 to be higher in $M_n$ than calculated from the catalyst loading. Catalyst efficiency may be the cause of this increased molecular weight.

At this point it is important to discuss the molecular weight of DePoly-1. Direct molecular weight analysis is not possible via gel permeation chromatography due the high nitrogen content that cause severe adhesion to polystyrene GPC columns. Also, end group analysis of a debenzylated Poly-3 was not effective as a result of reduced hydrogenolysis reaction rates associated with fluorinated benzyl groups. The most promising technique was static light scattering, which involves the measurement of light scattered from particles in solution. However, the concentrations required for stable data collection were higher than can be reasonably obtained from DePoly-1. Nevertheless, there are some conclusions concerning molecular weight that can be reasonability extracted. For instance, the maximum molecular weight of the polymer cannot be higher than Poly-1, $M_n = 40K$, while the minimum molecular weight is not less than that of biguanide. In addition, recalling the pyrolysis of biguanide, if there was significant low molecular weight species in DePoly-1 similar to biguanide, these compounds with further decompose and dimerize producing melamine that readily sublimes well below 600°C. Therefore, it can be preliminarily concluded that larger linear guanidine derivatives, which have not be previously reported, were successfully synthesized.

2.3.4 Alternative Deprotection Strategies

The blueprint for debenzylation of Poly-1 was successful, however, not ideal. The synthesis required large loading of palladium metal which precludes this scheme from being
reasonably scaled. The economic limitations are compounded by an 81 wt. % weight loss of **Poly-1** due to the removable benzyl group, i.e., poor atom economy. Although poor atom economy is problematic it is of secondary concern; use of large c. While being mindful of the limitations associated with polycarbodiimides, three additional polymers were proposed as second generation alternatives to **Poly-1**.

![Proposed 2nd generation polyguanide precursor polymers. Poly(dimethoxymethyl)carbodiimide **Poly-4**, Poly(di(4-methoxybenzyl))carbodiimide **Poly-5**, and Poly(di(2-nitrobenzyl))carbodiimide **Poly-13**.](image)

**Figure 2.16:** Proposed 2nd generation polyguanide precursor polymers. Poly(dimethoxymethyl)carbodiimide **Poly-4**, Poly(di(4-methoxybenzyl))carbodiimide **Poly-5**, and Poly(di(2-nitrobenzyl))carbodiimide **Poly-13**.

These candidates were selected as alternative precursors, two of which build on the **Poly-1** with modifications that allow for different to deprotection chemistry, along with a third dimethoxymethyl polycarbodiimide. Going in reverse order as seen in Figure 2.16, beginning with **Poly-13**, a di-(2-nitrobenzyl)polycarbodiimide was explored as a photo-decagible polycarbodiimide. Nitrobenzyl groups have been studied as photocaging groups of proteins in biological systems as well as in broader protection/deprotection applications.\textsuperscript{26, 27} The polymerization of di-(2-nitrobenzyl)carbodiimide to **Poly-13** was unsuccessful, due mainly to the poor solubility of the monomer. Moreover, with the addition of **Cat-1**, low
molecular weight oligomers quickly precipitated out of a dry DCM solution preventing polymerization to high polymers.

The next candidate examined was Poly-5, a di-4-methoxybenzylated polymer. p-Methoxybenzyl groups are known to be oxidatively cleaved from heteroatoms using ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under mild conditions or by using 2,2,2-trifluoroacetic acid and anisole. The conventional deprotection routes were ruled out due to the insolubility of Poly-5 in many organic solvents. However, Poly-5 was soluble in pure TFA so debenzylatation was examined over two days in the presence of anisole as a 4-methoxybenzyl group scavenger. The TFA solvent was removed and the crude sample was dried under high vacuum. The resulting crude material appeared unchanged by these deprotection reagents.

The remaining alternative candidate for a fully deprotected polycarbodiimide studied was Poly-4, a dimethoxymethyl polymer. This polymer appears to have advantages necessary to overcome the limitations of Poly-1. These advantages are threefold: no steric issues during polymerization, improved economy of atoms with 67 wt. % weight loss, and inexpensive starting materials and deprotection reagents. Due to the large quantities of methyl chloromethyl ether involved for successful synthesis, alternatives to direct methoxymethylation of urea were investigated.
Scheme 2.1: The facile synthesis of Poly-4 from dimethylol urea.

By starting the synthesis with the inexpensive methylation of dimethylol urea to form dimethoxymethyl urea in one step allowed for a direct, two step conversion to a dimethoxymethylated polycarbodiimide Poly-4. The resulting liquid polymer was highly soluble in most organic solvents and water. Pyrolysis of Poly-4 did not follow the typical polycarbodiimide profile with weight retention to higher temperature (>300°C) possibly as a result of thermal crosslinking of the methoxymethyl groups. The first attempt at acid catalyzed deprotection was unexpectedly unsuccessful.

The typical removal of the methoxymethyl ether masking group involves dilute acid, therefore, TFA was attempted first. The $^1$H spectra of Poly-4 shows three regions of signal (Figure 2.17). Upon the addition of one drop of TFA to the NMR solution and shaking for 1 minute, the $^1$H spectra changed, with the region centered at 4.5 ppm to 4.7 ppm broadening, while the region located 3.8 ppm sharpened and also shifted down field to 4.0 ppm. This is interesting and points to evidence of methanol present with $^1$H signals in DMSO$_{d6}$ at 4.0 ppm. Although after 24 hours, the acidified sample did not show marked progress toward deprotection.
A second attempt at unmasking the polyguanide backbone was attempted with 1 N HCl. Approximately 500 mg of Poly-4 was dissolved in 2 mL of methanol followed by 3 drops of 1N HCl. Following several hours at room temperature a solid formed. The solid was insoluble in alcohol, chloroform, and DMSO. Pyrolysis of the sample produced a distinct
formaldehyde odor, providing indication that partial deprotection occurred. However, the 
insolubility of the product is consistent with crosslinking of the precipitated the polymer. 
Upon reflection the crosslinking of Poly-4 is similar to the thermal curing to 
hexamethoxymethyl melamine, a commercial resin prepolymer. Future work with this 
polymer should involve deprotection in a dilute aqueous solution with acid to prevent 
crosslinking.

2.4 Partial Deprotection of Polycarbodiimides

The inspiration for this next section is drawn from the considerable volume of current 
research being conducted on the development of antimicrobial polymers for applications 
such as sanitary surfaces and wound dressing.\textsuperscript{3, 4, 28, 29} In particular, focus was brought to 
bear on polymeric biocides of biguanide, which are typical synthesized as linear block co-
polymers of alkyl diamines and cyanoguanidine. These biguanides contain both hydrophobic 
and hydrophilic regions. Along with antimicrobial properties, polymeric biocides of 
biguanide also showed some interesting antiviral activity against HIV-1.\textsuperscript{30} Krebs et al., 
studied polybiguandes such as poly(alkyl) biguanide with varying linker lengths to 
optimizing the binding to the HIV-1 virus. By taking advantage of the flexible 
polybiguanide family, it was discovered that a polyethylene polyhexamethylene biguanide 
co-polymer has microbiocidic activity against HIV-1 while at the same time having low 
cytotoxicity. It is not in the scope of this work to evaluate polycarbodiimides against HIV-1; 
however, we explored a partial deprotection strategy of polycarbodiimides to assess the
resulting polymeric materials against *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) with the assistance of Dr. Steve Rogers from the Melander Group.

![Structural Isomers: Polybiguanide and Mono-deprotected Polycarbodiimide](image)

**Figure 2.18:** Structural Isomers: Polybiguanide and Mono-deprotected polycarbodiimide.

As with the development of fully deprotected polycarbodiimides, the plan here, however, would involve the synthesis of non-symmetric carbodiimide monomers. There is no expectation of the same thermal properties observed for the fully deprotected polyguanide, therefore, deprotection conditions need to remain mild to prevent polymer decomposition. From the unsuccessful hydrogenolysis of *Poly-2*, we found bulky pendent group will significantly retard or prevent debenzylation, hence, these need to be avoided here. In this work, previously discussed groups such as para-methoxybenzyl and methoxymethyl are potential avenues for development, however, it was decided mild photolysis of 2-nitrobenzyl pendants was a much more attractive deprotection scheme to pursue because it just requires mild UV light exposure (365 nm, 20W).

The photolysis of 2-nitrobenzyl with a heteroatom attached to the benzyl carbon is reasonably straightforward.\(^3\)\(^1\) The first step of the photoysis is believed to involve hydrogen abstraction from the benzyl carbon followed by proton loss to the solvent, forming a acinitro
anion intermediate. This intermediate further reacts liberating the aromatic group as 2-nitrosobenzaldehyde. The resulting byproduct provides a diagnostic aldehyde proton handle readily observed via $^1$H-NMR at $\sim10.5$ ppm.

![Chemical Reaction Diagram](image)

**Figure 2.19:** Photolysis of 2-nitrobenzyl masking groups. The formation of 2-nitrosobenzaldehyde can be observed using $^1$H-NMR and the aldehyde hydrogen at $\sim10.5$ ppm.

Although a di-(2-nitrobenzyl)polycarbodiimide, **Poly-13**, was not successfully polymerized, likely due to the poor solubility of the monomer, three polymers were chosen for evaluation of photo-protection as seen in Figure 2.19. The preparation of these polymers was started by a urea synthesis through the reaction of 2-nitrobenzylamine hydrochloride with methyl isothiocyanate, propyl isocyanate, and hexyl isocyanate. The resulting ureas/thiourea were dehydrated/desulfurized to the corresponding monomers. These non-symmetric monomers were polymerized at approximately 150:1 monomer/Cat-1 ratios,
yielding Poly-6, Poly-7, and Poly-8. The short chain alkyl polymers, Poly-6 and Poly-7, were not soluble in CDCl3, THF, and DMSO, while Poly-8 was slightly soluble in CHCl3.

**Figure 2.20:** Precursor polymers containing photo-cleavable groups.

The photolysis of Poly-6, Poly-7, and Poly-8 was done under a 365 nm, 20 W lamp over 4 days at room temperature. Much like the debenzylation of Poly-1, over 50 wt. % of these polymers are lost during deprotection. The 2-nitrosobenzaldehyde acts as a photon sink reducing the quantum yield of the photo-deprotection. To overcome this efficiency loss, the polymers were dispersed in ethanol, a solvent most polycarbodiimides are not soluble in, and placed in dialysis bags with a molecular weight cut off of 2000 daltons. The dialysis bags were then placed in a 500 ml beaker partly filled with ethanol. Periodically, the ethanol was removed and recycled via reduced pressure evaporation.
The precursor polymers Poly-6 and Poly-7 were not soluble so NMR spectra could not be collected, but similar to debenzylation of Poly-1, the post-modified polymers were soluble in organic solvents. From Figure 2.21, some aromatic groups remain present following photolysis for both methylated and propylated polymers.

Figure 2.21: $^1$H-NMR of photo-deprotection (top) DePoly-6 and (bottom) DePoly-7.
Figure 2.22: $^1$H-NMR of Poly-8 (top) and post photolysis DePoly-8 (bottom). There is a reduction in aromatic groups following the UV light exposure.

In the case of Poly-8, $^1$H-NMR spectra collection was possible as seen in Figure 2.22. Evidence of successful photoylsis is presented more clearly in the aliphatic region of the $^1$H spectra with an increase in intensity of the hexyl proton signals over the precursor polymer when compared to the aromatic region. From the integrations, there was a deprotection efficiency of 75%.
With these polymers in hand, biocidic screening was undertaken with assistance of Dr. Steve Rogers from the Melander group. The polymers were split in two groups: neutral and acid salts. The acid salt were simply prepared by the addition of hydrogen chloride in methanol followed by vacuum drying. Of the three polymers tested, only DePoly-7 possessing the propyl side chains, demonstrated biocidic activity at the upper limit tested. These results are not significantly higher than poly(alkyl) biguanides but did show positive activity.

**Table 2.3:** Bioactivity of DePoly-6, DePoly-7, and DePoly-8 against a *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) bacteria. NA = no activity.

<table>
<thead>
<tr>
<th></th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Escherichia coli</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral</td>
<td>Acid Salt</td>
</tr>
<tr>
<td><strong>DePoly-6</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DePoly-7</strong></td>
<td>256 μg/mL</td>
<td>128 μg/mL</td>
</tr>
<tr>
<td><strong>DePoly-8</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

2.5 Conclusions

The work in this chapter outlined an approach at accessing the nitrogen rich polyguanide backbone by the unmasking of protected polycarbodiimides. The first attempt was the debenzylation of a dibenzylated polycarbodiimide, Poly-1, via hydrogenolysis. From pyrolysis and elemental analysis it was determined that up to 75 wt. % of Poly-1 was deprotected. Also, this resulting polymer was water soluble, thermally resistant to temperatures of 1000°C, and resistant to strong oxidizers. Other protection chemistries were explored with limited success.
The scope of this concept was broadened to include non-symmetric, mono-deprotected polycarbodiimides. Three mono-polymers were investigated for biocidic activity, which provide some antimicrobial activity against *Staphylococcus aureus*, however, there was no activity against *Escherichia coli*.

### 2.6 Experimental Section

#### 2.6.1 Materials

All materials were purchased from Sigma-Aldrich and used as is without further purification unless stated. Solvents and materials used for the synthesis of organotitanium catalysts and polymerizations of carbodiimides were distilled, degassed, and stored over molecular sieves prior to use. Common laboratory supplies were purchased from the NCSU Chemistry Stockroom and used as is.

#### 2.6.2 Instrumentation

$^{1}$H-, $^{13}$C-, $^{19}$F-NMR spectroscopy were performed on Mercury 300 or 400 spectrometers using deuterated solvents. Internal standards for $^{1}$H-NMR using CDCl$_3$ was tetramethyilsilane $\delta = 0.00$ ppm and DMSO$_{d6}$ used residual solvent peak $\delta = 2.50$ ppm. For $^{13}$C-NMR, CDCl$_3$ and DMSO$_{d6}$ both used the residual solvent peaks at $\delta = 77.23$ and 39.51 ppm, respectively. $^{19}$F-NMR used hexafluorobenzene set to $\delta = -163.0$ ppm.
2.6.3 Synthesis of Titanium(IV) Complexes

Synthesis of titanium(IV) catalyst was accomplished and confirmed by following a procedure previously reported in the literature.\textsuperscript{17} 

\[
\text{Trichloro-titanium(IV)-(2,2,2-trifluoroethoxide)}^{17} \text{ Cat-1: } 29\% \text{ Yield. } ^1\text{H NMR (300 MHz, toluene-d8 stored over molecular sieves)} \delta (ppm): 3.76 (br).
\]

2.6.4 General Procedure for the Preparation of Ureas and Thioureas

The synthesis of ureas and thiourea were conducted following two general procedures: Symmetric ureas were generated by the addition of amines into solution of 1,1’-carbonyldiimidazole (CDI) at a 1:2 molar ratio to the anime in 150 mL of DCM at room temperature. In the cases when anime salts were used, the amine salt was predissolved with triethylamine at a 3 molar equivalents based on the amine, and then added to the CDI solution. Typically the reaction was allowed to stir overnight or 12 hours at room temperature at which point the solvent was removed via reduced pressure evaporation and the crude product was crystallized from boiling ethanol. The purified urea was dried under high vacuum. If the imidzole byproduct persists, the urea was redissolved in CHCl\textsubscript{3} and washed with a brine solution, dried with sodium sulfate, and purified (\textit{vide supra}). Non-symmetric ureas and thioureas are generally prepared following the same procedure as
symmetric ureas at 1:1 ratio of amine to isocyanate/isothiocyanate from outlined purification above.

\[
\begin{align*}
\text{N,N'-Dibenzylurea U-1:} & \text{ Following outlined procedure for symmetric ureas: 150 mL of DCM, 10.35 g (63.9 mmol, 1.0 eq) of CDI, and 13.67 g (127.8 mmol, 2.0 eq) of benzylamine.} \\
\text{Yield: 10.69 g (43.8 mmol) white, sharp, needle-shaped crystals, 68.6 %. FTIR (KBr pellet, cm}^{-1}\text{): 3322 (s, N-H str), 3085 (w, C-H aryl), 3030 (w, C-H aryl), 2916 (m, C-H alkyl), 1627 (s, C=O), 1571 (m, C=C aryl).} \\
\text{1H-NMR (400 MHz, DMSO}_{d6}\text{): }\delta\text{ (ppm) 7.33 – 7.22 (Ar-H, 10H, m), 6.43 (N-H, } J = 6.0 \text{ Hz, 2H, t), 4.30 (benzyl-H, } J = 6.0 \text{ Hz, 4H, d).} \\
\text{13C-NMR (100 MHz, DMSO}_{d6}\text{): }\delta\text{ (ppm) 158.1, 140.9, 128.2, 126.9, 126.5, 42.9.}
\end{align*}
\]

\[
\begin{align*}
\text{N,N'-Di(4-n-butylbenzyl)urea U-2:} & \text{ Following outlined procedure for symmetric ureas: 150 mL of DCM, 1.24 g (7.67 mmol, 1.0 eq) of CDI, and 2.50 g (15.34 mmol, 2.0 eq) of 4-n-butylbenzylamine.} \\
\text{Yield: 1.68 g (4.78 mmol) small, white crystals, 62.3 %. FTIR (KBr pellet, cm}^{-1}\text{): 3359 (s, N-H str), 3304 (s, N-H str), 3047 (w, C-H aryl), 3022 (w, C-H aryl), 2958 (w, C-H alkyl), 2927 (w, C-H alkyl), 1626 (s, C=O), 1566 (s, C=C).} \\
\text{1H-NMR (400 MHz, DMSO}_{d6}\text{): }\delta
\end{align*}
\]
(ppm) 7.15 – 7.10 (Ar-H, 8H, m), 6.34 (N-H, J = 5.6 Hz, 2H, t), 4.17 (benzyl-H, 4H, d), 2.54 (-CH₂CH₂CH₂CH₃, J = 7.2 Hz, 4H, t), 1.52 (-CH₂CH₂CH₂CH₃, J = 7.2 Hz, 4H, q), 1.29 (-CH₂CH₂CH₂CH₃, J = 7.2 Hz, 4H, sextet), 0.88 (-CH₂CH₂CH₂CH₃, J = 7.2 Hz, 6H, t). ¹³C-NMR (100 MHz, DMSO₆): δ (ppm) 158.0, 140.5, 138.1, 128.1, 126.9, 42.7, 34.4, 33.2, 21.7, 13.7.

**N,N'-Di(4-fluorobenzyl)urea U-3**: Following outlined procedure for symmetric ureas: 150 mL of DCM, 3.88 g (23.99 mmol, 1.0 eq) CDI, and 6.00 g (47.98 mmol, 2.0 eq) 4-fluorobenzyl anime.

Yield: 5.09 g (18.42 mmol) white, sharp, needle-shaped crystals, 76.8 %.

FTIR (KBr pellet, cm⁻¹): 3323 (s, N-H), 3043 (w, C-H aryl), 2917 (w, C-H alkyl), 2954 (w, C-H alkyl), 2881 (w, C-H alkyl), 1614 (s, C=O), 1578 (s, C=C). ¹H-NMR (300 MHz, DMSO₆): δ (ppm) 7.27 (Ar-H, J = 5.7 Hz, 4H, td), 7.13 (Ar-H, J = 9.0 Hz, 4H, td), 6.47 (N-H, J = 6.0 Hz, 2H, t), 4.19 (benzyl-H, J = 6.3 Hz, 4H, d). ¹³C-NMR (100 MHz, DMSO₆): δ (ppm) 160.1 (J₁₉F-¹³C = 425 Hz), 159.8, 137.0, 128.9, 114.8, 42.2. ¹⁹F-NMR (376.3 MHz, DMSO₆): δ (ppm) -115.5.

**N,N'-Di(methoxymethyl)urea U-4**: To a 250 mL round bottom flask 125 mL of methanol was added along with an oval stir bar. To the solvent 10.00 g (83.3 mmol, 1.0 eq) of dimethylolurea and 12.48 g (89.9 mmol, 1.1 eq) of potassium carbonate were added. The
slurry was set to reflux for 1 hour. Following reflux, the solution was cooled to room
temperature and solids were filtered. Methanol was removed via reduced pressure
evaporation below 40 °C. The crude product was redissolved in chloroform followed by
filtration. The solution was concentrated and purified via column with silica gel and 50/50
solution of CHCl3/acetone.

Yield 4.52 g (30.5 mmol), white solid, 36.6 %. FTIR (KBr pellet, cm\(^{-1}\)): 3344 (s, N-
H), 2989 (m, Alkyl-H), 2935 (m, Alkyl-H), 1670(s, C=O). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 6.71 (N-H, 2H, s), 4.60 (N-CH\(_2\)-O, \(J = 8.0\) Hz, 4H, d), 3.31 (N-CH\(_2\)-O-CH\(_3\), 6H, s).
\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 158.9, 73.2, 55.2.

\[
\begin{align*}
  &\begin{array}{c}
    \text{N,N'-Di(4-methoxybenzyl)urea U-5: Following outlined procedure for symmetric}
    
    \text{ureas: 150 mL of DCM, 5.00 g (30.86 mmol, 1.0 eq) CDI, 8.46 g (61.75 mmol, 2.0 eq) 4-}
    
    \text{methoxybenzylamine.}
  
    \text{Yield: 6.14 g (20.47 mmol) white, sharp, needle-shaped crystals, 66.3 %. FTIR (KBr}
    
    \text{pellet, cm}^{-1}\text{): 3352 (m, N-H aryl), 3142 (w, C-H aryl), 3042 (w, C-H aryl), 3016 (w, C-H}
    
    \text{aryl), 2946 (w, C-H alkyl), 2925 (w, C-H alkyl), 2835 (w, C-H alkyl), 1623 (w, C=O), 1583}
    
    \text{(w, C=C). \(^1\)H-NMR (400 MHz, DMSO\(_{d6}\)): \(\delta\) (ppm) 7.16 (Ar-H, \(J = 8.0\) Hz, 4H, dd), 6.86}
    
    \text{(Ar-H, \(J = 8.4\) Hz, 4H, dd), 6.29 (N-H, \(J = 5.6\) Hz, 2H, t), 4.14 (benzyl-H, \(J = 5.6\) Hz, 4H, d),}
    
    3.72 (-OCH\(_3\), 4H, s). \(^{13}\)C-NMR (100 MHz, DMSO\(_{d6}\)): \(\delta\) (ppm) 158.1, 158.0, 132.8, 128.3, 113.6, 55.0, 42.4.}
\end{array}
\end{align*}
\]
\textit{N-methyl-N'-(2-nitrobenzyl)thiourea U-6:} Following outlined procedure for asymmetric ureas: 100 mL of DCM, 3.88 g (53.1 mmol, 2.0 eq) methyl isothiocyanate, 5.01 g (26.5 mmol, 1.0 eq) 2-nitrobenzylamine hydrochloride, and 14 mL (10.6 g, 4.0 mmol, 4.0 eq) of triethylamine.

Yield: 4.21 g (18.7 mmol) of a dark yellow/orange, granular solid, 70.4 %. FTIR (KBr pellet, cm\(^{-1}\)): 3222 (s, N-H), 3076 (w, C-H aryl), 3010 (w, C-H aryl), 2943 (w, C-H alkyl), 2903 (w, C-H alkyl), 2841 (w, C-H alkyl), 2808 (w, C-H alkyl), 1608 (m, C=C), 1554 (s, C=S), 1518 (s, NO\(_2\)), 1331 (s, NO\(_2\)). \textsuperscript{1}H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.04 – 8.02 (Ar-H, \(J = 8.0\) Hz, 1H, d), 7.99 (N-H, 1H, s), 7.75 – 7.71 (Ar-H, \(J = 8.0\) Hz, 1H, t), 7.62 (N-H, 1H, s), 7.53 – 7.50 (Ar-H, \(J = 7.6\) Hz, 2H, t), 4.92 (benzyl-H, 2H, s), 2.84 (-CH\(_3\), 3H, s). \textsuperscript{13}C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 183.0, 147.8, 135.0, 133.7, 129.1, 128.0, 124.5, 44.1, 30.9.

\textit{N-(2-nitrobenzyl)-N'-propylurea U-7:} Following outlined procedure for asymmetric ureas: 100 mL of DCM, 2.46 g (28.9 mmol, 1.1 eq) propyl isocyanate, 4.96 g (26.3 mmol, 1.0 eq) 2-nitrobenzylamine hydrochloride, and 14 mL (10.6 g, 4.0 mmol, 4.0 eq) of triethylamine.

Yield: 4.08 g (17.2 mmol) of a light yellow, crystalline solid, 65.5 %. FTIR (KBr pellet, cm\(^{-1}\)): 3334 (m, N-H), 3142 (w, C-H aryl), 3107 (w, C-H aryl), 2966 (m, C-H alkyl),
2937 (m, C-H alkyl), 1626 (s, C=O), 1589 (m, C=C), 1516 (m, NO$_2$), 1340 (m, NO$_2$). $^1$H-NMR (400 MHz, DMSO$_d6$): $\delta$ (ppm) 8.01 – 7.99 (Ar-H, $J = 8.0$ Hz, 1H, dd), 7.74 – 7.70 (Ar-H, $J = 7.2$ Hz, 1H, td), 7.53 (Ar-H, 2H, m), 6.39 (N-H, $J = 6.0$ Hz, 1H, t), 6.13 (N-H, $J = 5.6$ Hz, 1H, t), 4.46 (benzyl-H, $J = 6.0$ Hz, 2H, d), 2.94 ($CH_2CH_2CH_3$, $J = 6.8$ Hz, 2H, q), 1.36 ($CH_2CH_2CH_3$, $J = 7.2$ Hz, 2H, s), 0.82 ($CH_2CH_2CH_3$, $J = 7.2$ Hz, 3H, t). $^{13}$C-NMR (100 MHz, DMSO$_d6$): $\delta$ (ppm) 157.9, 147.9, 136.2, 133.7, 129.6, 127.9, 124.4, 41.1, 40.2, 23.1, 11.3.

$N$-hexyl-$N'$-(2-nitrobenzyl)urea U-8: Following outlined procedure for asymmetric ureas: 100 mL of DCM, 3.34 g (26.3 mmol, 1.0 eq) propyl isocyanate, 4.95 g (26.3 mmol, 1.0 eq) 2-nitrobenzylamine hydrochloride, and 14 mL (10.6 g, 4.0 mmol, 4.0 eq) of triethylamine.

Yield: 5.57 g (19.9 mmol) of a light yellow, crystalline solid, 76.0 %. FTIR (KBr pellet, cm$^{-1}$): 3331 (m, N-H), 3153 (w, C-H aryl), 3041 (w, C-H aryl), 2954 (m, C-H alkyl), 2922 (m, C-H alkyl), 2865 (m, C-H alkyl), 1628 (s, C=O), 1593 (s, C=C), 1562 (m, NO$_2$), 1336(m, NO$_2$). $^1$H-NMR (400 MHz, DMSO$_d6$): $\delta$ (ppm) 8.01 – 7.99 (Ar-H, $J = 6.4$ Hz, 1H, dd), 7.74 – 7.70 (Ar-H, $J = 7.6$ Hz, 1H, td), 7.54 – 7.48 (Ar-H, 2H, m), 6.38 (N-H, $J = 6.0$ Hz, 1H, t), 6.11 (N-H, $J = 5.6$ Hz, 1H, t), 4.45 (benzyl-H, $J = 6.4$ Hz, 2H, d), 2.97 ($CH_2CH_2(CH_2)_3CH_3$, $J = 5.6$ Hz, 2H, q), 1.36 ($CH_2CH_2(CH_2)_3CH_3$, $J = 6.0$ Hz, 2H, t), 1.23 ($CH_2CH_2(CH_2)_3CH_3$, 6H, m), 0.86 ($CH_2CH_2(CH_2)_3CH_3$, $J = 6.4$ Hz, 3H, t). $^{13}$C-NMR (400 MHz, DMSO$_d6$): $\delta$ (ppm) 157.9, 147.9, 136.2, 133.7, 129.6, 127.9, 124.4, 41.1, 40.2, 23.1, 11.3.
150 MHz, DMSO$_{d6}$: $\delta$ (ppm) 157.9, 149.0, 163.2, 133.6, 129.6, 127.9, 124.4, 40.2, 31.0, 29.9, 26.0, 22.1, 13.9.

$N,N'$-Di(2nitrobenzyl)urea U-9: Following outlined procedure for symmetric ureas:

150 mL of DCM, 1.59 g (9.84 mmol, 1.0 eq) CDI, 3.71 g (19.67 mmol, 2.0 eq) 2-nitrobenzylamine hydrochloride, and 16.3 mL (11.9 g, 118.0 mmol, 6.0 eq) of triethylamine.

Yield 1.48 g (4.49 mmol) 45.7%, yellow-orange, short needle-like crystals. FTIR (KBr pellet, cm$^{-1}$): 3325 (m, N-H), 3070 (m, C-H aryl), 3039 (m, C-H aryl), 2939 (m, C-H alkyl), 2850 (m, C-H alkyl), 2816 (m, C-H alkyl), 1628 (s, C=O), 1593 (s, C=C), 1520 (s, NO$_2$), 1338 (s, NO$_2$). $^1$H-NMR (400 MHz, DMSO$_{d6}$): $\delta$ (ppm) 8.01 (Ar-H, $J = 8.2$ Hz, 2H, dd), 7.72 (Ar-H, $J = 6.4$ Hz, 2H, td), 7.55 – 7.50 (Ar-H, 4H, m), 6.77 (N-H, $J = 6.0$ Hz, 2H, t), 4.48 (benzyl-H, $J = 6.0$ Hz, 2H, d). $^{13}$C-NMR (100 MHz, DMSO$_{d6}$): $\delta$ (ppm) 196.8, 135.8, 133.7, 129.6, 128.1, 124.5, 104.1.

2.6.5 General Procedure for the Dehydration of Ureas and Thioureas

The dehydration of all ureas were generally carried out in the same matter. A dry 250 or 500 mL round bottom flask was charged with 10 to 20 mL of DCM and triphosphine dibromide and cooled in an ice bath and placed under nitrogen. To the cool reaction solution triethylamine was added dropwise. During this addition vapors may form and must be allowed time to dissipate. Once the flask is clear of vapors, add the urea in two or three
portions over one hour and stir 2 to 12 hours. When reaction is complete, extract the monomer with pentane or hexanes and filter the solid byproducts. Purify by column chromatography using a 50/50 solution of hexanes and ethyl acetate and pH 7 preconditioned silica gel. In the case of thiourea: add thiourea, mercury(II) oxide, and sodium sulfate to a round bottom flask containing 150 ml DCM and stir from 2 to 6 hours. Once complete, filter metal reagent using diatomaceous earth and remove solvent via reduced pressure evaporation. Monomer is extracted from crude mixture using petroleum ethers. Further purification is typically not needed.

\[ \text{N}_2\text{N'}-\text{Dibenzylcarbodiimide M-1: } 10 \text{ mL of DCM, 6.33 grams (14.99 mmol) of triphenylphosphine dibromide, 4.32 mL (3.2 g, 31.23 mmol) triethylamine, and 3.0 g (12.5 mmol) } \text{N}_2\text{N'}-\text{dibenzylurea.} \]

Yield: 1.81 g (8.15 mmol) of yellow oil, 65.1 %. FTIR (thinfilm, cm\(^{-1}\)): 3062 (w, C-H aryl), 3030 (w, C-H aryl), 2933 (m, C-H alkyl), 2127 (s, N=C=N). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.34 – 7.20 (Ar-H, 6H, m), 7.18 (Ar-H, 4H, d), 4.30 (benzyl-H, 4H, s). \(^{13}\)C-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 141.5, 138.5, 128.8, 128.6, 127.7, 50.6. HRMS-ESI: \(M_{\text{theoretical}} = 223.1223, M_{\text{sample}} = 223.1232, \Delta M = -0.19 \text{ mass units (-0.87 ppm), C}_{15}\text{H}_{14}\text{N}_2.\)
**N,N’-Di(4-n-butylbenzyl)carbodiimide M-2:** 10 mL of DCM, 4.17 grams (9.87 mmol, 1.2 eq.) of triphenylphosphine dibromide, 2.85 mL (2.08 g, 20.57 mmol, 2.5 eq.) triethylamine, and 2.90 g (8.23 mmol, 1.0 eq.) N,N’-di(4-n-butylbenzyl)urea.

Yield: 0.72 g (2.15 mmol) of clear, water-white oil, 26.2 %. FTIR (thinfilm, cm\(^{-1}\)): 3047 (w, C-H aryl), 3022 (w, C-H aryl), 2956 (m, C-H alkyl), 2927 (m, C-H alkyl), 2858 (m, C-H alkyl), 2127 (s, N=C=N). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.11 (Ar-H, 8H, m), 4.25 (benzyl-H, 4H, s), 2.59 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.59 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, qt), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t), 1.36 (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), J = 7.6 Hz, 4H, t). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 142.3, 135.8, 128.8, 127.7, 50.4, 35.5, 33.8, 22.5, 14.1.

![N,N’-Di(4-n-butylbenzyl)carbodiimide M-2](image)

**N,N’-Di(4-fluorobenzyl)carbodiimide M-3:** 10 mL of DCM, 4.27 grams (16.3 mmol, 1.2 eq.) of triphenylphosphine, 0.84 mL (2.6 g, 16.3 mmol, 1.2 eq.) bromide, 6.1 mL (4.45 g, 43.43 mmol, 2.5 eq.) triethylamine, and 3.00 g (10.86 mmol, 1.0 eq.) N,N’-di(4-fluorobenzyl)urea.

Yield: 1.51 g (5.86 mmol) of yellow oil, 54.0 %. FTIR (thinfilm, cm\(^{-1}\)): 3043 (w, C-H aryl), 2937 (w, C-H alkyl), 2125 (s, N=C=N). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.16 – 7.10 (4H, tt), 7.01 – 6.96 (4H, tt), 4.25 (4H, s). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm)
$\text{N,N'-Di(methoxymethyl)carbodiimide M-4:}$ 10 mL of DCM, 6.26 grams (14.8 mmol, 1.2 eq.) of triphenylphosphine dibromide, 4.67 mL (3.42 g, 33.8 mmol, 2.5 eq.) triethylamine, and 2.0 g (13.5 mmol, 1.0 eq.) $N,N'$-di(methoxymethyl)urea.

Yield: 1.81 g (8.15 mmol) of pale liquid, 65.1 %. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 4.70 (N-CH$_2$-O, 4H, s), 3.45 (N-CH$_2$-O-CH$_3$, 6H, s).

$\text{N,N'-di(4-methoxybenzyl)carbodiimide M-5:}$ 10 mL of DCM, 8.43 g (19.97 mmol, 1.2 eq.) triphenylphosphine dibromide, 5.76 mL (4.2 g, 41.62 mmol, 2.5 eq.) triethylamine, and 5.00 g (16.60 mmol, 1.0 eq.) $N,N'$-di(4-methoxybenzyl)urea.

Yield: 2.00 g (7.08 mmol) of white solid, 42.5 %. FTIR (KBr pellet, cm$^{-1}$): 3012 (w, C-H aryl), 2937 (m, C-H alkyl), 2870 (m, C-H alkyl), 2835 (m, C-H alkyl), 2118 (s, N=C=N), $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.08 (Ar-H, $J = 8.4$ Hz, 4H, dt), 6.83 (Ar-H, $J = 6.8$ Hz, 4H, dt), 4.20 (benzyl-H, 4H, s), 3.81 (-OCH$_3$, 6H, s). $^{13}$C-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 159.1, 130.8, 129.1, 114.1, 55.5, 50.1.
**N-methyl-N’-(2-nitrobenzyl)carbodiimide M-6:** 200 mL of DCM, 2.10 g (9.32 mmol, 1.0 eq.) N-methyl-N’-(2-nitrobenzyl)thiourea, 3.43 g (15.83 mmol, 1.7 eq.) yellow mercury(II) oxide, and 1.00 g sodium sulfate.

Yield: 0.71 g (3.72 mmol) of clear, yellow oil, 40.0 %. FTIR (thin film, cm\(^{-1}\)): 3074 (w, C-H aryl), 2933 (m, C-H alkyl), 2879 (m, C-H alkyl), 2139 (s, N=C=N), 1524 (m, NO\(_2\)).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.08 (Ar-H, \(J = 8.0\) Hz, 1H, dd), 7.74 (Ar-H, \(J = 7.2\) Hz, 1H, d), 7.67 – 7.63 (Ar-H, \(J = 7.2\) Hz, 1H, td), 7.45 (Ar-H, \(J = 7.2\) Hz, 1H, tt), 4.84 (benzyl-H, 2H, s), 2.99 (methyl-H, 3H, s). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm) 134.0, 130.3, 128.5, 125.2, 48.1, 32.8.

**N-(2-nitrobenzyl)-N’-propylcarbodiimide M-7:** 10 mL of DCM, 6.41 g (15.17 mmol, 1.2 eq.) of triphenylphosphine dibromide, 4.37 mL (3.19 g, 31.64 mmol, 2.5 eq.) triethylamine, and 4.50 g (16.11 mmol, 1.0 eq.) N-(2-nitrobenzyl)-N’-propylurea.

Yield: 0.88 g (4.01 mmol) of clear, water-white oil, 31.8 %. FTIR (thin film, cm\(^{-1}\)): 3080 (w, C-H aryl), 2964 (m, C-H alkyl), 2935(m, C-H alkyl), 2875 (m, C-H alkyl), 2133 (s, N=C=N), 1525 (m, NO\(_2\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 8.08 (Ar-H, \(J = 8.4\) Hz, 1H, dd), 7.76 (Ar-H, \(J = 8.0\), 1H, d), 7.66 (Ar-H, \(J = 7.2\), 1H, td), 7.45 (Ar-H, \(J = 8.0\), 1H, td),
3.21 (-CH₂CH₂CH₃, J = 7.2, 2H, td), 1.58 (-CH₂CH₂CH₃, J = 7.2, 2H, td), 3.21 (-CH₂CH₂CH₃, J = 7.2, 2H, td). ¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 140.1, 134.6, 134.0, 130.2, 128.4, 125.1, 48.5, 48.2, 24.7, 11.6.

![Chemical Structure](image)

**N-hexyl-N’-(2-nitrobenzyl)carbodiimide M-8:** 10 mL of DCM, 8.16 g (19.33 mmol, 1.2 eq.) triphenylphosphine dibromide, 5.60 mL (4.07 g, 40.27 mmol, 2.5 eq.) triethylamine, and 4.50 g (16.11 mmol, 1.0 eq.) N-hexyl-N’-(2-nitrobenzyl)urea.

Yield: 0.98 g (3.75 mmol) of clear, yellow oil, 23.3%. FTIR (thin film, cm⁻¹): 3072 (w, C-H aryl), 2954 (m, C-H alkyl), 2931 (m, C-H alkyl), 2858 (m, C-H alkyl), 2133 (s, N=C=N), 1578 (m, NO₂). ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 8.08 (Ar-H, J = 8.4 Hz, 1H, dd), 7.76 (Ar-H, J = 8.4 Hz, 1H, d), 7.66 (Ar-H, J = 7.6 Hz, 1H, td), 7.46 (Ar-H, J = 8.0 Hz, 1H, tt), 4.84 (benzyl-H, 2H, s), 3.24 (-CH₂CH₂CH₂CH₂CH₂CH₃, J = 6.8 Hz, 2H, t), 1.55 (-CH₂CH₂CH₂CH₂CH₂CH₃, J = 6.8 Hz, 2H, pentet), 1.38 – 1.21 (-CH₂CH₂CH₂CH₂CH₂CH₃, 6H, m), 0.88 (-CH₂CH₂CH₂CH₂CH₂CH₃, J = 6.8 Hz, 3H, t). ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) 140.1, 134.6, 134.0, 130.3, 128.4, 125.1, 48.2, 46.7, 31.5, 31.3, 26.6, 22.7, 14.2.
\[\text{N,N’-di(2-nitrobenzyl)carbodiimide M-9:}\]

10 mL of DCM, 0.60 g (2.27 mmol, 1.5 eq.) triphenylphosphine, 0.12 mL (0.36 g, 2.27 mmol, 1.5 eq.) bromine, 0.83 mL (0.61 g, 6.05 mmol, 4.0 eq.) triethylamine, and 0.50 g (1.51 mmol, 1.0 eq.) \text{N,N’-di(2-nitrobenzyl)urea.}

Yield: 0.12 g (0.38 mmol) of yellow solid, 25 %. FTIR (KBr pellet, cm⁻¹): 3030 (w, C-H aryl), 2958 (w, C-H alkyl), 2922 (w, C-H alkyl), 2848 (w, C-H alkyl), 2160 (s, N=C=N).

\(^1\text{H-NMR (400 MHz, CDCl}_3\text{):}\) δ (ppm) 8.09 – 8.06 (Ar-H, \(J = 8.6\) Hz, 2H, dd), 7.72 – 7.63 (Ar-H, 4H, m), 7.46 (Ar-H, \(J = 8.4\) Hz, 2H, td), 4.88 (benzyl-H, 4H, s). \(^{13}\text{C-NMR (400 MHz, CDCl}_3\text{):}\) δ (ppm) 147.7, 140.2, 134.1, 134.0, 130.3, 128.6, 125.2, 48.0.

### 2.6.6 Polymerization of Carbodiimide Monomers

Polymerizations were performed in an MBRAUD UNIlab dry box under a nitrogen atmosphere. Catalyst solution in dry chloroform of a known concentration was added to a clean scintillation vial containing monomer and a clean stir bar. Once the polymerization was complete, the crude polymer would be dissolved in minimum CHCl₃ and precipitated into methanol. The volume ratio of methanol used is 10 to 20:1 methanol / crude polymer solution.
**Poly(N,N'-dibenzyl)carbodiimide Poly-1:** 2.14 g (9.63 mmol, 150 eq.) \(N,N'\)-dibenzylcarbodiimide, 0.0163 g (0.0642 mmol 1.0 eq.) **Cat-1**, 0.67 mL dry CDCl₃.

Yield: 1.55 g (6.97 mmol) off-white solid, 72 %. FTIR (KBr pellet, cm⁻¹): 3080 (w, C-H aryl), 3061 (w, C-H aryl), 3028 (w, C-H aryl), 2972 (m, C-H alkyl), 2899 (m, C-H alkyl), 2843 (m, C-H alkyl), 1649 (s, C=N), 1628 (s, C=N). \(^1\)H-NMR (400 MHz, CDCl₃): δ (ppm) 7.05 – 6.49 (Ar-H, 10H, very broad triplet), 5.41 (benzyl-H, 1H, broad singlet), 4.45 (benzyl-H, 1H, broad singlet), 4.00 (benzyl-H, \(J = 14.8\), 1H, broad doublet), 3.57 (benzyl-H, \(J = 14.8\), 1H, broad doublet).

**Poly(N,N'-di(methoxymethyl)carbodiimide Poly-2:** 0.414 g (3.19 mmol, 158 eq.) \(N,N'\)-di(methoxymethyl)carbodiimide, 0.00512 g (0.0202 mmol, 1.0 eq.) **Cat-1**, and 0.21 mL dry CHCl₃.

Yield: 0.200 g (1.53 mmol) viscous liquid, 48 %. \(^1\)H-NMR (400 MHz, CDCl₃): δ (ppm) 4.80 – 4.20 (4H, broad), 3.80 – 3.40 (2H, broad), 3.40 – 2.80 (4H, broad).
Poly(N,N’-di(4-n-butylbenzyl))carbodiimide Poly-3: 0.23 g (0.69 mmol, 143 eq.)

N,N’-di(4-n-butylbenzyl)carbodiimide, 0.00122 g (0.005 mmol, 1.0 eq.) Cat-1, and 0.5 mL dry CHCl₃.

Yield: 0.16 g (0.47 mmol) off-white solid, 68 %. FTIR (KBr pellet, cm⁻¹): 3014 (w, C-H aryl), 2958 (m, C-H alkyl), 2925 (m, C-H alkyl), 2856 (m, C-H alkyl), 1648 (s, C=N), 1626 (s, C=N). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.17 – 6.20 (Ar-H, 8H, very board), 2.60 – 2.36 (benzyl-H, 4H, board doublet), 1.60 – 1.22 (-CH₂CH₂CH₂CH₃, board doublet), 0.92 (-CH₂CH₂CH₂CH₃, 6H, board).
Poly(N,N'-di(4-fluorobenzyl))carbodiimide Poly-4: 0.94 g (3.65 mmol, 25 eq.)
N,N'-di(4-fluorobenzyl)carbodiimide, 0.038 g (0.150 mmol, 1.0 eq.) Cat-1, and 3.8 mL dry
CHCl₃.

Yield: 0.30 g (1.16 mmol) off-white solid, 32 %. ¹⁹F-NMR (376.3 MHz, CDCl₃): δ (ppm) – 73 (3F, broad), - 111 - - 120 (88F, broad doublet). n = 44, Mₙ = 11,352.

Poly(N,N'-di(4-methoxybenzyl))carbodiimide Poly-5: 0.21 g (0.74 mmol, 130 eq.)
N,N'-di(4-methoxybenzyl)carbodiimide, 1.45 g (0.0057 mmol, 1.0 eq.) Cat-1, and 0.1 mL dry CHCl₃.

Yield: 0.075 g (0.27 mmol) of an off-white solid, 36 %. FTIR (KBr pellet, cm⁻¹): 3057 (w, aryl-H), 2937 (m, alkyl-H), 2900 (m, alkyl-H), 2833 (m, alkyl-H), 1647 (s, C=N), 1612 (s, C=N).
Poly(N-methyl-N'(2-nitrobenzyl))carbodiimide Poly-6: 0.712 g (3.72 mmol, 154 eq.) of N-methyl-N'(2-nitrobenzyl)carbodiimide, 0.0061 mL (0.024 mmol, 1.0 eq.) Cat-1, and 0.25 mL dry CHCl₃.

Yield: 0.387 g (2.00 mmol) off-white solid, 54.3%. FTIR (KBr pellet, cm⁻¹): 3111 (m, aryl-H), 3061 (m, aryl-H), 2916 (m, alkyl-H), 2852 (m, alkyl-H), 1672 (s, C=N), 1637 (s, C=N), 1522 (s, NO₂), 1317 (s, NO₂).

Poly(N-(2-nitrobenzyl)-N'-(propyl)carbodiimide Poly-7: 0.599 g (2.73 mmol, 141 eq.) of N-(2-nitrobenzyl)-N'-(propyl)carbodiimide. 0.0049 g (0.019 mmol, 1.0 eq.), and 0.20 mL dry CHCl₃.

Yield: 0.480 g FTIR (KBr pellet, cm⁻¹): 3111 (m, aryl-H), 3061 (m, aryl-H), 2916 (m, alkyl-H), 2852 (m, alkyl-H), 1672 (s, C=N), 1630 (s, C=N), 1522 (s, NO₂), 1317 (s, NO₂).
Poly(N-hexyl-N’-(2-nitrobenzyl))carbodiimide Poly-8: 0.745 g (2.84 mmol, 147 eq.) N-hexyl-N’-(2-nitrobenzyl)carbodiimide, 0.0049 g (0.019 mmol, 1.0 eq.), and 0.20 mL dry CHCl₃.

Yield: 0.489 g (1.87 mmol) off-white solid, 65.6 %. FTIR (KBr pellet, cm⁻¹): 3111 (m, aryl-H), 3061 (m, aryl-H), 2916 (m, alkyl-H), 2852 (m, alkyl-H), 1672 (s, C=N), 1633 (s, C=N), 1522 (s, NO₂), 1317 (s, NO₂). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.00 – 7.00 (Ar-H, 4H, very board), 1.75 – 0.25 (Alkyl-H, 11H, very board triplet).

2.6.7 Deprotection of Dibenzylated Polycarbodiimide

Polyguanide DePoly-1: To a clean, dry 100 mL glass container 70 mL of CHCl₃ and 17.5 mL of EtOH was added with a magnetic stir bar. To the solvent 0.9760 g (4.4 mmol, 150:1 Cl₃TiOCH₂CF₃) Poly-1 was added and stirred for 20 minutes. One to 2 drops of conc. HCl was added to the solution followed by 1.4640 g (0.1464 g metal on polymer basis) of Pd
on carbon black was added. The glass vessel was placed in a Parr reactor and the H₂ pressure was set to 2 atm (30 psig). The pressure was maintained constant for 24 hours by periodic addition of gas. Heterogeneous catalyst was removed by filtration through diatomaceous earth. The solvent was removed via reduced pressure evaporation; product was extracted with deionized water. Final product was dried to a red solid. Yield: 0.02 g.

2.7 References


15. Lee, H.-S. Asymmetric polymerization initiated by cationic zirconocene complexes possessing chiral counter anions. North Carolina State University, Raleigh, NC, **2006**.


19. Clark, J. B. The synthesis and characterization of ester-bearing polycarbodiimides. North Carolina State University, Raleigh, NC, **2010**.


Chapter 3: Advances in Regioregularity of Polycarbodiimides

3.1 An Odd Development - Synopsis

Regioregularity has been the focus of much work in polymer chemistry over the past few decades, as it has tremendous impact on a material’s physical properties. Ziegler and Natta were awarded the Nobel Prize in Chemistry in 1963 for their work correlating the regioregularity of a system to its physical properties. The elucidation and control of regio-structural isomers has been at the forefront of research into structure-property relationships. Tacticity is a related concept, which describes the relative stereochemical position of chiral centers along the polymer backbone. Tacticity has profound effects on glass transition temperature, $T_g$, and the material’s ability to crystallize.¹

To begin our study of the regioregularity of polycarbodiimides, we focused on the different regioisomers that may result from the non-symmetric carbodiimide monomer (see Figure 3.1 below). Both of these regioisomers may lead to regioregular or regioirregular polymers. Upon polymerization of this non-symmetric monomer, infrared spectroscopy was used as a means of characterization. To date, there is much precedence for using the imine region of polycarbodiimides as an internal handle for the qualitative determination of regioregular/irregular polymers resulting from non-symmetric carbodiimides.
As the development of a fully deprotected polycarbodiimide, polyguanide, was underway a datum regarding an anomalous imine IR stretch of Poly-1, the debenzylated precursor polycarbodiimide, came to light, specifically Poly-1 possessing two imine stretches were only one was expected. As briefly discussed in the previous chapter, the regioregularity of polycarbodiimides are a result of biases in the titanium(IV)-amidinate active complex, steric or electronic, leading to a preferred insertion pathway during propagation. In this section of work, the anomalous Poly-1 imine stretch became the launch point for the search for a direct, unambiguous methodology for the determination of regioregularity and an exploration of their ramifications.

3.2 Polycarbodiimide Helicity

Since the discovery of highly isotactic, helical polypropylene by Natta et al. in the 1950s\(^2\), chemists have synthesized and studied many different types of helical polymers and their properties. Independent of scientific and academic interests, this helical motif is of interest to the world at large, due to its resemblance to naturally-occurring biopolymers, such

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**Figure 3.1:** Two possible regioisomers from non-symmetric carbodiimide.
as polypeptides, proteins, and DNA. Polycarbodiimide possesses several levels or layers of chirality and function. An in-depth review of their hierarchical chirality has been recently published and it is recommended that the reader to refer to this manuscript. Below is a brief summary of a review on the helical asymmetry of polycarbodiimides.

3.2.1 Helical Asymmetry

Polycarbodiimides can be viewed as a poly(amidines), however this term is generally not used in order to minimize confusion with polymers of other architectures containing amidines. An example of a completely unsubstituted polycarbodiimide, polyguanide (structure shown in Figure 3.2a), illustrates this basic amidine repeat unit. Looking down the backbone along the z-axis direction of polyguanide, it is expected to be planar (as seen in Chapter 1). Once pendent groups are added, the backbone planarity is disrupted to accommodate the steric bulk. These groups introduce a dihedral angle (θ), which is a function of the size of pendent group. This out of plane rotation continues at each monomer unit and as a result, the helicity of polycarbodiimides is developed. An example of this is shown below. Molecular modeling calculations of an N,N’-dimethyl polycarbodiimide results in a dihedral angle of 60° and 6 repeat units per 360° rotation down the z-axis (see Figure 3.2b).
There are several ways to bias the helix to develop an excess single screw-sense: configurationally chiral pendent groups can be attached, followed by annealing to achieve a thermodynamically preferred state. Also, the chiral catalyst can be used to kinetically lock in the helical bias, or the use of a chiral small molecule, i.e., chiral acids, that can interact with and influence the direction of the helix. A generic structure of the polymer is shown in Figure 3.3, indicating the possible rotations of the main chain and pendent groups. Synchronous rotation of these groups simultaneously is believed to result in helix inversion.

Figure 3.2: a) polyguanide, b) polycarbodiimide with main chain rotation ($\theta$).

Figure 3.3: Main chain bond rotations ($\theta$), pendent group rotations ($\Omega$, $\Psi$), and imine inversion ($\Phi$). (This figure has been adapted from previously referenced literature.)$^3$
3.3 Indirect Regioregularity Detection in Polycarbodiimides

3.3.1 Origin of Regioregularity

The helicity and regioregularity of polycarbodiimides are directly tied to the polymer microstructure. A deeper understanding of the structure-property relationships of the microstructure and regioregularity and their effects on reversal dynamic optical activity\(^4\), \(^5\) and liquid crystalline properites\(^6\) has been an ongoing topic of investigation in the Novak Group. It is important to note that regioregularity (or regioirregularity) discussed and explored here is strictly in the context of non-symmetric carbodiimide monomers \((R_1 \neq R_2)\), specifically alkyl/aryl monomers; symmetric carbodiimides by definition, can only polymerize regioregular polymers. Determining the regioregularity would shed light on three matters, (1) is an aryl/alkyl polycarbodiimide regioregular (one regioisomer) or regioirregular (two regioisomers)? and if so, what is the ratio of these products? (2) into which insertion pathways does carbodiimide monomer insert into the titanium(IV)-amidinate active chain end, i.e., regioisomer A, B, or both (Figure 3.4)? (3) and is the imine stretch observed by IR an acceptable diagnostic tool for regiostructural determination?
To answer these questions, isotopic labeling experiments were conducted using nitrogen-15 enriched polycarbodiimides.

3.3.2 Early Attempts at Determining Regioregularity

From the very first successful polymerization of a carbodiimide monomer, Goodwin and Novak were aware of regioregularity and its importance in determining regioisomer. In these early endeavors, thermal decomposition of polycarbodiimides were analyzed using gas chromatography in tandem with mass spectrometry. As reported by Robinson and also observed here, polycarbodiimides have fairly low ceiling temperatures, which when reached, begin to depolymerization back to starting monomers. The pathway of this depolymerization is thought to occur by way of random homolytic cleavage of the backbone C–N bond which is continued by radical unzipping (see Figure 3.5).
Figure 3.5: The thermal decomposition of a symmetric polycarbodiimide. First a C–N bond homolytically cleaves followed by a cascade or unzipping of the polymer backbone returning the polymer to the starting monomer.5

In the case of symmetric monomers, there are no biases present along the backbone carbon-nitrogen bonds, therefore homolytic cleavage of the backbone occurs randomly. This depolymerization can only produce one monomer. While with polymers of non-symmetric monomers, the backbone carbon-nitrogen bonds are not equivalent leading to a couple of pathways available for homolytic cleavage and ultimately the possibility of three monomer products, the original non-symmetric monomer and two metathesis products (see Figure 3.6).
Although much of this work has remained unpublished, this approach for determining regioregularity has served as an internal reference. Recently, Kennemur in his doctoral work revisited this mode of analysis, and, concluded that the propensity for the monomers to metathesize consequently precluded this methodology as primary evidence and identification of regioisomers.\textsuperscript{5}

Nevertheless, the necessity for regioisomer assignment and the limitations found with thermal decomposition to the development of a regioisomer detection strategy using infrared spectroscopy, which was verified independently with \textsuperscript{13}C-NMR by Lu.\textsuperscript{9} In this work, Lu

\textit{Figure 3.6:} The thermal decomposition of a non-symmetric polycarbodiimide giving rise to three potential monomer products.\textsuperscript{5}
synthesized and studied a series of chiral and achiral polycarbodiimides and carefully collected their imine, C=N, stretch values. A portion of this study has been included in Table 3.1.

**Table 3.1:** Polymers of two symmetric and a non-symmetric monomer, a di-alkyl polycarbodiimide **Poly-20**, a di-aryl polycarbodiimide **Poly-21**, and a N-(n-hexyl)-N’-phenyl polycarbodiimide **Poly-12**; including imine stretch and $^{13}$C-NMR signals of select carbons. (Adapted from Yujie Lu’s dissertation)\(^9\)

<table>
<thead>
<tr>
<th></th>
<th>Imine (cm(^{-1}))</th>
<th>$^{13}$C-NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Poly-20</strong></td>
<td>1644</td>
<td>(a) 48.7, (b) 32.2</td>
</tr>
<tr>
<td><strong>Poly-21</strong></td>
<td>1665</td>
<td>-</td>
</tr>
<tr>
<td><strong>Poly-12</strong></td>
<td>1624</td>
<td>(c) 47.3</td>
</tr>
</tbody>
</table>

Starting with the symmetric monomers, a di-n-hexyl (**Poly-20**) with an imine stretch of 1644 cm\(^{-1}\) and a di(4-n-butylphenyl) (**Poly-21**) at 1665 cm\(^{-1}\), the possible imine stretch reference values were ascertained. Both these polymers are by definition regioregular and therefore all imines are configurationally equivalent and provide clear differences between alkyl and aryl imine substitution. From here polymers of non-symmetric monomers were
studied, of particular interest was Polycarbox-11, N-(n-hexyl)-N'-phenyl polycarbodiimide, which has a lower imine stretch at 1624 cm\(^{-1}\) than the two reference points. The assignment of the alkyl, namely n-hexyl, in the imine position was done independently by qualitative \(^{13}\)C-NMR of Polycarbox-12 and Polycarbox-20. In Polycarbox-12 the carbon-13 signals for the methylene carbons attached to the nitrogen backbone were 48.7 ppm and 32.3 ppm; leading to the assignment of the more down field carbon attached to the sp\(^2\) nitrogen. Using the IR imine stretch became a common methodology for rationalizing the presence or absence of a regiorregular structure.

3.3.3 Application of Infrared Spectroscopy to Regioregularity Determination

From this initial work by Lu, the thorough inspection of the imine IR stretch region, 1670 to 1620 cm\(^{-1}\), became a standard method for interpreting, albeit qualitatively, the polycarbodiimide regioregularity in recent years.\(^4\), \(^5\), \(^10\)-\(^15\) As this protocol was expanded to polycarbodiimide on the whole, polymers exhibiting one imine stretch were deemed as regiorregular, much like Polycarbox-12, while polycarbodiimides with two stretches were categorized as regioirregular. Moreover, as a general rule, polymers from non-symmetric aryl/alkyl carbodiimides with an imine stretch in the 1640s are believed to correspond to the aromatic ring attached directly to the imine nitrogen, whereas a stretch in the 1620s corresponds to an aliphatic group.

Returning to Polycarbox-1, the anomalous polycarbodiimide, the appearance of two imine stretches related to a symmetric polycarbodiimide as not been previously reported. When comparing the imine stretch of Polycarbox-1 against Polycarbox-20 (Figure 3.5), the 1642 cm\(^{-1}\) stretch
matches closely with the 1644 cm\(^{-1}\) of the di-n-hexyl polymer, which is understandable, i.e., both polymers have sp\(^3\) hybridized carbons attached to the imine nitrogen. However, the emergence of a 1626 cm\(^{-1}\) stretch suggests other vibrational modes are present relating to the imine, which coincides with the accepted aryl-imine stretch. By extending the length of the methylene linker to ethylene, this anomalous stretch is not present in Poly-9 with a return to a single dialkyl-like imine stretch of 1645 cm\(^{-1}\). Likewise, the \(^1\)H-NMR spectra of Poly-9 reveals a loss of up field shifted aromatic hydrogen and ethylene signals, i.e., the anisotropy is significantly lessened.

![Infrared spectra of Poly-1, Poly-9, and Poly-20](image)

**Figure 3.7:** Infrared spectra of Poly-1, Poly-9, and Poly-20. With the addition of one methylene group the 1626 cm\(^{-1}\) disappears on Poly-9.
This behavior points to a uniqueness of having dibenzyl groups on both the amine and imine of the backbone. While the 1645 cm\(^{-1}\) is associated with the expected C=N-alkyl stretch; experiments were undertaken to elucidated the origin of this 1626 cm\(^{-1}\) peak.

![Infrared spectra of Poly 22, Poly-23, and Poly-24](image)

Figure 3.8: Infrared spectra of Poly 22, Poly-23, and Poly-24.\(^5\) With the addition of one methylene group the 1626 cm\(^{-1}\) absorbance disappears.

The experiments involved the polymerization of non-symmetric carbodiimide monomers composed of alkyl/benzyl (Poly-22) and aryl/benzyl (Poly-23) pendant groups. \(N\)-(n-hexyl)-\(N\)'-(benzyl)carbodiimide was polymerized with Cat-2, originally developed for mono-debenzylation, als also presented two distinct imine stretches at 1654 and 1637 cm\(^{-1}\)
respectfully. The shift of both stretches to higher frequency by approximately 10 cm\(^{-1}\) is not immediately explainable. Furthermore, there is no electronic bias during propagation so both regioisomers should be present at equal portions. Moving to aryl/benzyl polymer (Poly-23), polymerized with Cat-1, only one predominate stretch is present indicating one regioisomer, but it should be pointed out that the anomalous stretch of 1626 cm\(^{-1}\) may simply coincide with the 1624 cm\(^{-1}\) present in aryl/alkyl polycarbodiimides and buried underneath. The behavior of two imine stretches also can be found in analog polymers such as Poly-24 with a methylnaphthyl pendent group.

![Infrared spectra of Poly-6 and Poly-8](image)

**Figure 3.9:** Infrared spectra of Poly-6 and Poly-8. A non-symmetric alkyl/benzyl also shows unusual two imine peaks with frequency shifted to higher frequency compared to Poly-1.

Other related polymers such as Poly-6 and Poly-8, from the mono-debenzylation studies, also displayed two imine stretches. Much like Poly-21, the signals are shift to higher
frequency by 10 cm\(^{-1}\) while Poly-6 shows a larger shift to 1672 cm\(^{-1}\). From these studies a pattern begins to emerge which presents us with a much more complicated and scientifically rich picture. Beyond regioregularity, the imine stretch appears effected by the nature of the pendent groups far beyond simply their chemical identity or position.

3.3.4 Solvent Effects on Infrared Spectra of a Dibenzylated Polymer

A main thrust of recent polycarbodiimide studies involving reversible, dynamic optical activity which is greatly affected by temperature and solvent, commonly referred to as a ‘switching’ phenomenon.\(^{4,5,12,16}\) Kennemur, continuing the work begun by Tang et al., studied the governing forces behind this optical phenomenon. \(N\)-(1-naphthyl)-\(N'\)-(n-octadecyl) polycarbodiimide (Poly-25) is the archetype which has received the most attention in recent years. Much like a dibenzylated polycarbodiimide, Poly-25, also shows two IR imine stretches. Based on previous examples, the two absorptions arise from regioregularity in the microstructure of the polymer.
Figure 3.10: Infrared spectra of Poly-25, \( N-(1\text{-naphthyl})-N'\text{-octadecyl polycarbodiimide}.\)

Now let us step back a moment and consider the different methods for collecting IR spectra. The conventional methods employed with polycarbodiimides involve KBr salt pellets or a solvent cast thin film. For Poly-25 and related polymers most IR spectra were collected from the drying of a polymer solution of chloroform on a KBr salt plate. While the benzylated polymer IR spectra collection used KBr salt pellets mainly as a result of poor solubility. In order to ensure proper comparison Poly-3, the alkylated dibenzyl polymer, was dissolved in chloroform and THF and cast on a salt plate. The resulting spectra showed intensity changes in the imine region along with minor shifts. Also, the spectra contained the emergence of new stretching modes by the appearance of new peaks in the fingerprint region. In Figure 3.12, Poly-3 IR spectra were collected by way of KBr pellet which is a solvent free
method, however the last solvent Poly-3 was exposed to was methanol, a very poor solvent for polycarbodiimides, during the purification and work up. Following drying, the conformations are locked in place revealing augmented IR spectra.

Figure 3.11: Infrared spectra of Poly-3 dry and casted from THF and CHCl₃.
3.3.5 Variable-Temperature Infrared Spectroscopy

A final IR study that was conducted by Kennemur on Poly-25 and Poly-20 involving variable temperature solution IR was undertaken.\textsuperscript{17} In these studies the polymers were dissolved in chloroform in a 20 mL scintillation vial and analyzed with an ATR IR probe by Mettler Toledo.

![Variable Temperature Infrared Spectra of Poly-25 in CHCl₃](image)

**Figure 3.12**: Variable temperature infrared spectra of Poly-25 in CHCl₃. The peak at 1645 cm\(^{-1}\) reversibly disappears and reappears as a function of temperature.\textsuperscript{17}

Immediately the observation of 1645 cm\(^{-1}\) stretch significantly disappears at lower temperature is evident in Figure 3.12. The experiment has been repeated and verified using a conventional transmittance IR with a variable length sample chamber fitted with a plastic coil connected to a cooling/heating bath. Symmetric polycarbodiimides, which do not have
reversible optical activity, such as Poly-1 and Poly-20 also, do not show changes in the infrared spectra as a function of temperature in solution.

3.3.6 Preliminary Conclusions

The imine region of the infrared spectrum for polycarbodiimides is significantly rich with information. In addition, solvent and temperature having profound effects on the intensity and presence of the stretches. However, the assignment of regioisomers strictly from these imine stretches may be misleading and requires further reexamination.

3.4 Directly Resolving Regioregularity of Polycarbodiimides

Regioregularity assignment remains an important structural element in the analysis of polycarbodiimides. Without this knowledge, investigations into high order phenomena such as the ‘switching’ behavior of polyaromatic polycarbodiimides are significantly complicated. A direct and unambiguous strategy is outlined here for non-symmetry polycarbodiimides.

3.4.1 Use of NMR for Stereoregularity Determination

Nuclear magnetic resonance has been employed for decades as a primary instrument for determining sequential distribution of stereoisomeric repeat units along the polymer backbone.\(^1\), \(^18\) Primarily, carbon-13 NMR has been heavily utilized for the study of conformational sensitive polymer microstructures. Minute differences in tacticity and
structural placement can be observed in the carbon-13 spectrum and supported by calculations.\textsuperscript{18,19}

### 3.4.2 Nitrogen-15 Isotopic Labeling

Although \textsuperscript{13}C-NMR is widely used for microstructure determination, the uniqueness of polycarbodiimides impairs its usefulness, i.e., the periodicity and regular structure simplifies the carbon-13 spectra. The carbon of interest, such as the backbone sp\textsuperscript{2} carbon, does not suffer from in-equivalent chemical environments thereby differentiating the regioisomers, moreover they require long relaxation times for adequate data collection. The α-carbons of the pendent groups have been studied by Lu and recently Clark\textsuperscript{14} which show promise but need to be validated. Therefore nitrogen-15 enrichment and NMR experiments were undertaken.

Nitrogen-15 NMR is a seldom used technique in polymer chemistry, however, in the biochemical field nitrogen-15 labeling is done routinely for the study of polypeptides and protein-protein interactions.\textsuperscript{20,21} Borrowing a page from this field, the isotopic enrichment of polycarbodiimides was begun. Before diving head first into this work, a few parameters needed to be established, as they were of importance in verifying the validity of this endeavor. Firstly, let us recap the goal of this nitrogen-15 study: determine and quantify the regioisomers that are present in these polymers. Secondly, for complete enrichment, commercially available pre-enriched amines and isocyanates are available but they are cost
prohibitive. Therefore a synthetic scheme will need to be developed for enrichment from inexpensive starting materials.

3.4.3 Strategies for Nitrogen-15 Enrichment

A synthetic strategy based on the use of 99.8 % $^{15}N$-enriched ammonium chloride as the isotope source was developed. The general synthetic scheme began with $^{15}\text{NH}_4\text{Cl}$ reacting with an acyl chloride to yield an $^{15}N$-amide. The amide was then subjected to Hofmann rearrangement conditions in the presence of methanol to capture the isocyanate as methyl $^{15}N$-carbamate. Unmasking the carbamate was done by acidolysis in refluxing conc. HCl producing the $^{15}N$-amine●HCl. This became a general starting material for the polycarbodiimide synthesis at relatively high overall yields. For di-labeled $^{15}N$-carbodiimides, an $^{15}N$-amine●HCl was allowed to react with thiophosgene to form a $^{15}N$-isothiocyanate, which was immediately reacted with a second mole of $^{15}N$-amine●HCl providing a di-$^{15}N$-labeled thiourea in the presence of a proton scavenger. The thiourea was desulfurized using triphenylphosphine dibromide and triethylamine in DCM.
Scheme 3.1: General Scheme for the synthesis of singly and doubly $^{15}$N labeled carbodiimides: (a) $^{15}$NH$_4$Cl, KOH, DI H$_2$O, DEE; (b) DBU, NBS, Methanol, reflux, 45 min.; (c) conc. HCl, reflux, 12 – 16 hrs; (d) thiophosgene, DCM, NaOH, DIPEA, 0 °C – rt, 12 hrs; (e) R'-15NH$_2$ HCl, DCM, DIPEA, rt, 6 hrs; (f) R'-NCO, Et$_3$N, rt, 6 hrs; (g) PPh$_3$Br$_2$, Et$_3$N, 0 °C – rt, 12 hrs.

Although the reaction scheme is straightforward and works exceptionally well for short alkyl chains and single ring aromatics, it is not universal. The synthesis of the amide worked fairly well for most reactions that were attempted with yields 45 – 90%. The Hofmann Rearrangement was first attempted using the bromine and sodium hydroxide protocol, but these conditions provided low yields and challenging purification owing to halogenated byproduct. The use of hypervalent iodine, such as iodosobenzene in the form of (diacetoxyiodo)benzene, was also investigated and showed promise for these alkyl rearrangements. When applied however, to aryl amides, rapid oxidation of the amine to nitro aryl occurred, which was compounded by low conversion. Therefore, a procedure developed by Huang et al., using NBS and DBU, gave a general plan for the rearrangement.
by trapping the isocyanate intermediate as a methyl carbamate via methanolysis at yields of >
80%. Other alcohols were tried such as tert-butanol, which would provide a t-BOC amine,
but was unsuccessful mainly due to poor solubility of DBU and NBS. Even if the solubility
was not a factor, it was also expected that the poor nucleophilicity of tert-butanol would
severely handicap the reaction. The final synthetic step to the required amine was the
unmasking of the methyl carbamate under strongly acidic conditions. This reaction can also
be done under basic conditions or thermal decomposition to the isocyanate at temperature
greater than 200°C. Ultimately, acidolysis was chosen mainly because the resulting amine
acid salt was convenient to work with. The unmasking of the carbamate was fairly smooth
with one exception; the acidolysis of methyl $^{15}$N-benzylcarbamate to $^{15}$N-benzylamine which
was sluggish and challenging to purify.

3.4.4 Nitrogen-15 Enriched Polycarbodiimides

With nitrogen-15 enriched starting materials in hand, polymers were prepared using
both Cat-1 and Cat-2 for analysis. The generally accepted references for $^{15}$N-NMR reported
are $^{15}$N enriched ammonium chloride at 0.00 ppm, $^{15}$N-nitromethane at 380.2 ppm, and $^{15}$N-
nitric acid at 367.0 ppm. With $^{15}$NH$_4$Cl available to us, it would be logical to use it as a
reference, unfortunately, the enriched salt is not soluble in CDCl$_3$, therefore $^{15}$N-benzamide
was chosen as the reference and set to 0.00 ppm, which is ~100 ppm down field from
$^{15}$NH$_4$Cl.
The first attempt at collecting proton decoupled, nitrogen-15 NMR spectra was not successful. The relaxation time exceeded 30 seconds between pulses, extending data collection to days per sample. Compounding the problem of long NMR runs, the ratios of the resulting signals were not as expected due to differences in the nitrogen relaxation rates. To rectify this, a common and effective relaxation reagent was employed, namely, gadolinium(III) acetylacetonate hydrate, Gd(acac)$_3$, at a concentration of 0.02 M which reduced the relaxation time down to 10 seconds with data acquisition completed in 4 to 6 hours. The collected resonances for imines and amines listed below match closely to small amidine model compounds of varying substitutions.$^{27,28}$

Starting with a di-isotopically labeled $^{15}$N-(n-hexyl)-$^{15}$N'-phenyl polycarbodiimide (Poly-13), it was shown that the non-symmetric aryl/alkyl carbodiimide, polymerized using Cat-1 at a 120:1 monomer to catalyst ratio, indeed produces a regioregular polymer. This regioregularity was evidenced by the appearance of only two signals present in the NMR spectra at 136.4 ppm and 15.5 ppm relative to $^{15}$N-benzamide. Based on model compounds, the signal at 136.4 ppm is assigned to the nitrogen in the imine position and the signal at 15.5 ppm to that of the amide backbone nitrogen. If this polymer was regioirregular, it would be expected that four signals should be present and the ratio of the two pairs would directly indicate the molar ratio of the two isomers. To further confirm these assignments and to determine which groups reside where, mono-labeled monomers were prepared and studied. The next polymer studied was a mono-enriched $N$-(n-hexyl)-$^{15}$N'-phenyl polycarbodiimide (Poly-14) where to nitrogen attached to phenyl group was completely enriched by allowing
$^{15}$N-aniline to react with n-hexyl isocyanate, followed by dehydration using PPh$_3$/Br$_2$ and Et$_3$N. This monomer was then polymerized using Cat-1. The $^{15}$N spectrum of this polymer confirmed the presence of only one regioisomer as evidenced by a single resonance at 136.3 ppm. Importantly, this study also confirmed the regioisomer present has the phenyl group attached to the imine nitrogen. The ramification on the insertion mechanism during polymerization is discussed in section 3.4.6.

**Figure 3.13:** The $^{15}$N-NMR spectra of (R)Poly-14, Poly-13, and Poly-14. With the presence of only two peaks in Poly-13, a completely regioregular polymer is confirmed. Moreover, the assignment of the regioisomer is possible with mono-label Poly-14. The regioregularity appears insensitive to the ligands on the metal center.
Returning to the earlier conclusions about regioregularity assignment of \( N\)-(n-hexyl)-\( N'\)-phenyl polycarbodiimide by IR spectroscopy (alkyl group in the imine position and the aromatic in amide position) we find the opposite is actually present. However, based on IR it was also postulated at that time that such a polymer is completely regioregular, which in fact it is, by the careful inspection of the IR imine region. Furthermore, the imine stretch for the mono- and di-labeled \( N\)-(n-hexyl)-\( N'\)-phenyl polycarbodiimide adds additional weight to the revised regioisomer assignment by displaying an isotope effect on the imine stretch. With the \( ^{15}\)N solely on the aromatic nitrogen, the imine stretch shifts to lower frequency from 1626 cm\(^{-1}\) to 1610 cm\(^{-1}\); this shift is also evident when the both imine and amine nitrogen are enriched, but is not present in the polymer with the \( ^{15}\)N enrichment on the alkyl nitrogen.
Figure 3.14: Infrared spectra of nitrogen-15 enriched polymers (R)Poly-14, Poly-13, and Poly-14.

Up to this point it can be concluded that the achiral trichlorotitanium(IV) 2,2,2-trifluoroethoxide catalyst, Cat-1, produces regioregular polymers. This catalyst is a workhorse of much of the carbodiimide polymerizations when a chiral polymer is not a factor or required (e.g., from protected polycarbodiimides). A second common catalyst, (R)-BINOL-titanium(IV)-diisopropoxide, Cat-2, is often used to bias the stereochemistry of the insertion pathway in order to produce an excess screw-sense. In this case, $^{15}N$-(n-hexyl)-$N'$-phenyl polycarbodiimide was polymerized using Cat-2 at a catalyst loading of 120:1, to yield
(R)Poly-14. In this experiment, the n-hexyl group was chosen as the label site to further confirm and reinforce the regioisomer assignment, but also more practically, $^{15}$N-n-hexylamine HCl has been the most robust of the isotopic labeling routes and was readily scaled up. For the NMR spectra in Figure 3.14, it is clear that (R)Poly-14 is also, highly regioregular and possesses the exact same regioisomer. Therefore the biasing of the helix to a excess screw-sense, using a catalyst with a different ligand set does not adversely affect the polymerization, i.e., the insertion pathway, and hence, the regioregularity.

The next two polymers studied were the anomalous, dibenzylated polycarbodiimide Poly-1 and di(n-hexyl) polycarbodiimide Poly-20. These polymers were prepared from which were nitrogen-15 enriched monomers to yield Poly-11 and Poly-18, respectfully (Figure 3.15). For Poly-11, a completely enriched polymer, there was no expectation of regioirrregularity given that only one regioisomer is possible. However, to preclude any doubts, the nitrogen-15 spectra was collected revealing, as expected, regioirrregularity polymer with an imine at 137.4 ppm and amine at 3.0 ppm. Further experiments were undertaken with Poly-11 which can be found in Section 3.5.2.
Figure 3.15: $^{15}$N-NMR spectra of Poly-11 and Poly-18. Polymers from symmetric monomers must polymerize to completely regioirregular polycarbodiimides.

The dialkyl polymer, Poly-18, was also evaluated but this polymer was only monolabeled. The chemical shifts for the imine and amine nitrogens were shifted up field from Poly-11, pointing to a significant change in the chemical environment. The ratio of imines to amines in Poly-18 is 1:1 emphasizes the fact that the pulse delay of 8 to 12 seconds provides adequate time for both nuclei to relax.

3.4.5 Electronic and Steric Effects on Polymerization

The establishment of a direct methodology to determine the regioregularity of polycarbodiimides allows for the exploration of the affects of electron density and sterics around the active titanium(IV)-amidinate complex during polymerization by observing the resulting regioisomer. The electronic effects were studied first by the synthesis of a series of
$N$-(n-hexyl)-$N'$-phenyl polycarbodiimides with electron withdrawing and donating ring substitution in the para- position.

The first to be examined were strongly electron withdrawing groups such as nitro- and cyano- substituents. Unfortunately, these electron deficient derivatives produced unstable carbodiimides. In the case of para-nitrophenyl, rapid hydrolysis of the monomer back to urea during work up reduced the yield to negligible amounts. While para-cyanophenyl carbodiimide, once purified via column chromatography readily dimerized upon standing, solvent free, at room temperature in a matter of an hour. This was evidenced by the increase in color, viscosity, and the development of an imine stretch as seen in the IR.

The next two para- substituted phenyl, namely 4-chlorophenyl ($\text{Poly-17}$) and 4-methylphenyl ($\text{(R)Poly-16}$) were successfully polymerized, albeit in a sluggish fashion, at a catalyst loading of 120:1. $\text{Poly-17}$ contains a withdrawing while $\text{(R)Poly-16}$ contains a mildly donating substituent. Both $\text{Poly-17}$ and $\text{(R)Poly-16}$ polymerizations suffered from poor yields at 8 % and 23 % respectfully, but the yields are more representative of nature of the polymers than the sluggishness of the reaction. The resulting polymers were fine powders, causing recovery of the product during work up to be troublesome. Disappointingly, these two polymers were insoluble so the regioisomer could not be directly determined via solution NMR. Both imine regions were inspected for regioirregularity. As seen in figure at Figure 3.16, both polymers show one imine stretch at 1628 cm$^{-1}$ which suggests an $N$-(n-hexyl)-$N'$-phenyl polycarbodiimide with the aromatic ring on the imine
nitrogen. Cautiously, it can be suggested that with a mildly donating or withdrawn group on the aromatic ring favors the insertion into the alkyl-N–Ti bond.

![Figure 3.16: Infrared spectra of Poly-17, and (R)Poly-16. N-(n-hexyl)-N’-phenyl polycarbodiimides with mildly withdrawing and donating subsituents appear to provide regioregular polycarbodiimides.](image)

Monomer 15, **M-15**, with the incorporation of a strongly electron donating methoxy group in the para- position of the phenyl group was successfully prepared and polymerized at a catalyst loading of 120:1 using both **Cat-1** and **Cat-2** to produce **Poly-15** and **(R)Poly-15**, respectfully. Like the chloro- and methyl- substituted polycarbodiimides, the methoxy-polymers also suffered from the similar depressed yields of 10 % and 35 %, respectfully. The nitrogen-15 NMR was successfully collected and shows the same regioisomer as previously
observed, i.e., phenyl on the imine nitrogen. Both catalysts appear completely insensitive to the increased electron density at the aromatic nitrogen from the donating methoxy group in the titanium(IV)-amidinate complex. Moreover, a single imine stretch was observed for both polymers at 1617 cm$^{-1}$ and 1618 cm$^{-1}$ for Poly-15 and (R)Poly-15, respectfully.

![Figure 3.17: The $^{15}$N-NMR spectra of (R)Poly-15 and Poly-15. Both polymers are regioregular matching the N-(n-hexyl)-N’-phenyl polycarbodiimide regioisomer, indicating insensitivity to electronic influence.](image)

Moving away from aryl/alkyl non-symmetric polymers, an experiment to study the effects of steric hindrance on monomer insertion mechanism was also undertaken. It is already known that steric bulk located at the $\alpha$-carbon will have a effect on monomer insertion into the titanium(IV)-amidinate complex. What was not confirmed were the effects
further removed from the complex. To address this query, a non-symmetric $^{15}\text{N}-(\text{n-hexyl})-N'-(\text{n-propyl})$ polycarbodiimide (Poly-18) was prepared using Cat-1 at a 120:1 catalyst loading. The pendent groups, n-hexyl and n-propyl, have essentially the same $A$ value of 1.79 kcal/mol$^{29}$ (the literature value for ethyl) so there is no significant steric difference, hence a regioirregular polymer is expected. From Figure 3.18, Poly-18 is in fact a regioirregular polymer with a ratio of n-hexyl groups in the imine and amine position of 1:1. The experiment suggests that steric effects beyond the $\gamma$-carbon play no role in monomer insertion mechanism.

![Figure 3.18: The $^{15}$N-NMR spectra of Poly-18 and Poly-19. Both dialkyl polymers are completely regioirregular independent of alkyl chain length.](image)

3.4.6 Ramifications of Established Regioisomer of Aryl/Alkyl Polymers

With the establishment of regioregularity assignment, a more clear understanding of the insertion step of the carbodiimide into the active titanium(IV)-amidinate complex can be had. From these studies, both Cat-1, an achiral catalyst, and Cat-2, a chiral BINOL catalyst,
are essentially the same with regard to monomer insertion. The titanium(IV)-amidinate complex appears to be insensitive to increased electron density while, regrettably, strong electron withdrawing groups could not be evaluated. Nevertheless, a few conclusions can be drawn with regard to electron effects on the titanium(IV)-amidinate complex (see Figure 3.19).

Firstly, the alkyl in the amine position suggests that the propagating chain end is predominately, if not exclusively, located on the alkyl nitrogen. Recalling the view of the titanium(IV)-amidinate complex as effectively an anionic propagation chain end may be of help here. The electron density of the anion is concentrated at the alkyl nitrogen and therefore interacting with the electron deficit metal center over resonating with the amidinate. At the titanium(IV)-amidinate complex resonance of aromatic with the nitrogen is possible therefore electron density on the aromatic side of the titanium(IV)-amidinate complex is diluted into the ring nullifying the aromatic nitrogen nucleophilicity when in competition with an alkyl nitrogen. Moreover, the nucleophilicity of the alkyl nitrogen is significantly higher than the aromatic nitrogen which, even with a strongly donating group, such as the methoxy- from Poly-15 and (R)Poly-15, was not sufficient to overcome the alkyl nitrogen’s nucleophilicity. So, even if the strongly electron withdrawing polymers were successfully polymerized, the resulting regioisomer would likely match the regioisomer presently assigned. Moreover, additional evidence of this in-balance in nucleophilicity can be directly observed with the polymerization of an aryl/alkyl monomer requiring nominally a day to reach solidification versus an aryl/aryl symmetric monomer requiring days.
In addition to the electron donating/withdrawing nature of substituent on the aromatic ring, there are steric considerations. The $A$ value, in respect to cyclohexane, for a benzene ring is 2.8 kcal/mol while an ethyl group is 1.8 kcal/mol (a substitute value for n-hexyl). The difference in steric size is 1.0 kcal/mol which translates to a ratio of equilibrium constants, $K$, favoring the alkyl-N-Ti(IV) insertion bond 5:1 over the aryl-N-Ti(IV).

3.5 Miscellaneous Studies

This section will cover some studies involving isotope enriched polymers that do not necessarily fit as part of the regioregularity studies, but are noteworthy for inclusion.

3.5.1 Infrared Isotope Effect on a Dibenzylated Polymer

During the course of nitrogen-15 isotopic enrichment of polycarbodiimides several polymers were attempted and deemed redundant, i.e., a mono-labeled polymer provides
equivalent information on regioregularity as a di-labeled polymer. In this case the IR spectrum for a mono-labeled dibenzyl polymer (Poly-10) and di-label (Poly-11) were inspected. As it has been detailed in this manuscript, Poly-1 has an unusual imine stretch profile with two imine stretches present. When the polymer is partially nitrogen-15 enriched, the isotope effects shift the frequency from 1642 cm\(^{-1}\) to 1635 cm\(^{-1}\) which has been observed with a di-n-hexyl, partially enriched polymer Poly-18. The 1624 cm\(^{-1}\) stretch may still be present but just beneath the isotope affected stretch. Additional unusual imine behavior presences itself when both nitrogens are \(^{15}\)N enriched; the imine once again shifts to a predominate 1624 cm\(^{-1}\) stretch.

Figure 3.20: Infrared spectra of Poly-1, Poly-10, and Poly-11. The isotope effect on the imine group is evident with both the mono- and di-labeled dibenzylated polycarbodiimides.
3.5.2 Deprotection of a Nitrogen-15 Enriched Polymer

With a nitrogen-15 enriched dibenzyalted polymer, it was obvious that debenzylation should be undertaken. Therefore nitrogen-15 NMR was attempted on an enriched polyguanide using the Gd(acac)$_3$ relaxation reagent. Unfortunately, no spectral data were successfully collected via solution NMR. The addition of the relaxation reagent appeared to have complexed with the debenzylated polymer as observed by the development of a reddish color upon addition. The color was not present in any of the other studied polycarbodiimides.

Solid state CP/MS $^{15}$N-NMR of pyrolyzed polymer was also attempted with the assistance of Dr. Alex Nevzorov. Regrettably, data collection was unsuccessful, mainly due to the small sampling, 10 mg, that would require days of data acquisition to elucidate signal was not practical. The experiment should be reattempted once it is further optimized.

3.6 Conclusions

The importance of regioregularity assignment of polycarbodiimides cannot be oversold. Physical properties such as crystallization, packing in concentrated solution, i.e., cholesteric liquid crystal solutions, and higher chiro-optical phenomenon are all tied to the connectivity and relative position of pendent groups. To date, the regioregularity was indirectly observed using $^{13}$C-NMR and infrared spectroscopy with limited success. However, unambiguous assignment was still not possible. With the outlined finding in this manuscript several conclusions may now be made: (1) the imine region of the IR spectrum
for polycarbodiimides contain diagnostic regioisomer information may be misleading, (2) polycarbodiimide from non-symmetric aryl/alkyl monomers, when polymerized produce exclusively one regioisomer composed of the aryl attached to the imine group, (3) the insertion pathway into the active titanium(IV)-amidinate complex appears to be insensitive to choice of titanium(IV) catalyst, Cat-1 or Cat-2, (4) the insertion pathway also appears insensitive to electronic effects from the aromatic ring, donating or mildly withdrawing, (5) polymers from non-symmetric, dialkyl monomers do not sterically bias the insertion pathway when the point of non-symmetry is beyond the γ-carbon, (6) and finally, outlined here is a robust and cost effective strategy for global regioisomer assessment of polycarbodiimides via nitrogen-15 enrichment.

3.7 Experimental Section

3.7.1 Materials

All materials were purchased from Sigma-Aldrich and used as is without further purification unless stated. Solvents and materials used for the synthesis of organotitanium(IV) catalysts and polymerizations of carbodiimides were distilled, degassed, and stored over molecular sieves prior to use. Common laboratory supplies were purchased from the NCSU Chemistry Stockroom and used as is.
3.7.2 Instrumentation

$^1$H- and $^{13}$C-NMR spectroscopy was performed on a Mercury 300 or 400 spectrometer using deuterated solvents, while $^{15}$N-NMR spectroscopy was exclusively performed on a Mercury 400. Internal standards for $^1$H-NMR using CDCl$_3$ was tetramethylsilane $\delta = 0.00$ ppm and residual DMSO$_{d6}$ solvent $\delta = 2.50$ ppm. For $^{13}$C-NMR, CDCl$_3$ and DMSO$_{d6}$ used the residual solvent $\delta = 77.23$ ppm and ($\delta = 39.51$ ppm) respectfully. External standard of $^{15}$N-benzamide set to $\delta = 0.00$ ppm was used for $^{15}$N-NMR. Infrared spectral data was collected using a Jasco FT/IR-410 Infrared Spectrophotometer (Easton, MD).

3.7.3 Synthesis of Titanium(IV) Catalyst

Synthesis of titanium(IV) catalyst was accomplishment and confirmed by following a procedure previously reported in literature.

$\text{O} \quad \text{O} \quad \text{Ti} \quad \text{O} \quad \text{O}$

(R)-BINOL-titanium(IV)-diisopropoxide$^{30}$ Cat-2: 98% Yield. $^1$H NMR (300 MHz, CDCl$_3$ stored over molecular sieves) $\delta$ (ppm): 1.06 (d, 12H), 4.49 (m, 2H), 6.75 (d, 2H), 7.15 (d, 2H), 7.34 (m, 4H), 7.46 (d, 2H), 7.86 (d, 2H).
3.7.4 Synthesis of Nitrogen-15 Labeled Reagents

The synthesis of enriched amide via amidation with $^{15}\text{NH}_4\text{Cl}$\textsuperscript{22}, carbamates via Hofmann Rearrangement\textsuperscript{23}, and amine HCl salts by way of acidolysis has been previously reported and adapted for Nitrogen-15 isotope enrichment in this work.

$^{15}$N-Benzamide L-1: To a 250 ml round-bottom 40 ml of deionized water and 1.79 g (32.9 mmol, 1 eq.) of $^{15}\text{NH}_4\text{Cl}$ was added with a stir bar; agitation was started long enough to dissolve salt and then turned off. Ethyl ether was added (100 ml) to the aqueous phase and allowed to settle to form a bilayer followed by gentle addition of 7.61 ml (9.21 g, 65.7 mmol, 2.0 eq.) of benzoyl chloride. The bilayer was cooled to 0 °C with an ice bath. A solution of 11.06 g (197.1 mmol, 6.0 eq.) of KOH in 30 ml deionized water was chilled then added to the aqueous phase through the organic phase using a glass pipette. The bilayer was left undisturbed for 10 minutes followed by 10 minutes of mild stirring. The reaction was warmed to room temperature and aggressively stirred for 30 minutes. The organic phase was washed with 50 ml of saturated sodium chloride solution and set aside. Additional product was extracted with ethyl ether (3 X 100 ml) from the aqueous phase and combined. The combined organic phase was dried with sodium sulfate and solvent was removed via reduced pressure evaporation. Solids were washed with brine to remove any remaining benzoate.
Yield: 1.31 g (10.8 mmol) white crystals, 66%. FTIR (KBr pellet, cm⁻¹): 3356 (s, ¹⁵N-H), 3188 (s, ¹⁵N-H), 3060 (m, aryl-H), 1653 (s, C=O), 1576 (s, C=C). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (Ar-H, J = 14.0 Hz, 2H, dt), 7.57 – 7.43 (Ar-H, 2H, m). 6.18 (¹⁵N-H, J₁⁵N-₁H = 72 Hz, 2H, d), 5.89 (¹⁵N-H, J₁⁵N-₁H = 72 Hz, 2H, d). ¹³C-NMR (100 MHz, CDCl₃): 169.9, 133.6, 132.2, 128.8, 127.5. ¹⁵N-NMR (40.5 MHz, CDCl₃): δ (ppm) 0.00. HRMS-ESI: M_{theoretical} = 123.0571, M_{sample} = 123.0569, ΔM = -0.2 mmass units (-1.6 ppm), C₇H₇¹⁵NO.

¹⁵N-Heptanamide L-2: Employing the same procedure as L-1. 75 ml of deionized water, 4.19 g (76.80 mmol, 1 eq.) of ¹⁵NH₄Cl, 150 ml Ethyl ether, 23.78 ml (153.61 mmol, 2.0 eq.) heptanoyl chloride, and a solution of 25.9 g (460.8 mmol, 6.0 eq.) KOH in 40 ml deionized water.

Yield: 7.47 g (57.4 mmol) white crystals, 74.7%. FTIR (KBr pellet, cm⁻¹): 3356 (s, ¹⁵N-H str), 3188 (s, ¹⁵N-H str), 2956 (m, C-H alkyl), 2937 (m, C-H alkyl), 2870 (m, C-H alkyl), 1653 (s, C=O), 1633 (w, ¹⁵N-H bend). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 5.57 (¹⁵N-H, J₁⁵N-₁H = 88 Hz, 1H, d), 5.46 (¹⁵N-H, J₁⁵N-₁H = 88 Hz, 1H, d), 2.22 (-CH₂CH₂(CH₂)₃CH₃, J = 8.0 Hz, 2H, t), 1.64 (-CH₂CH₂(CH₂)₃CH₃, J = 7.2 Hz, 2H, p), 1.38 – 1.30 (-CH₂CH₂(CH₂)₃CH₃, 6H, m), 0.89 (-CH₂CH₂(CH₂)₃CH₃, J = 7.2 Hz, 3H, t). ¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 176.0 (J₁⁵N-₁³C = 12.9 Hz), 36.1 (J₁⁵N-₁³C = 33.0 Hz), 31.7, 29.1,
25.7, 22.7, 14.2. $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 6.38. HRMS-ESI: $M_{\text{theoretical}} = 131.1197$, $M_{\text{sample}} = 131.1198$, $\Delta M = 0.1$ mmass units (0.7 ppm), C$_7$H$_{15}$N$_{15}$O.

$^{15}$N-2-Phenylacetamide L-3: Employing the same procedure as L-1. 40 ml of deionized water, 1.44 g (26.5 mmol, 1 eq.) $^{15}$NH$_4$Cl, 150 ml ethyl ether, 7.00 ml (8.18g, 52.9 mmol, 2.0 eq.) 2-phenylacetyl chloride, and a solution of 8.90 g (158.7 mmol, 6.0 eq.) of KOH in 20 ml deionized water.

Yield: 3.51 g (25.8 mmol) white crystals, 97.5 %. FTIR (KBr pellet, cm$^{-1}$): 3348 (s, $^{15}$N-H), 3172 (s, $^{15}$N-H), 3060 (w, aryl-H), 2918 (w, alkyl-H), 1705 (s, C=O), 1496 (w, C=C). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.38 – 7.26 (Ar-H, 5H, m), 6.08 ($^{15}$N-H, $J_{15N-1H} = 89.2$ Hz, $J_{1H-1H} = 3.2$ Hz, 1H, dd), 5.43 ($^{15}$N-H, $J_{15N-1H} = 89.2$ Hz, $J_{1H-1H} = 2.8$ Hz, 1H, dd), 3.58 (benzyl-H, 2H, s). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 174.2 ($J_{15N-13C} = 15.2$ Hz), 134.9, 129.6, 129.3, 128.7, 127.7, 43.4 ($J_{15N-13C} = 8.4$ Hz). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 8.55. HRMS-ESI: $M_{\text{theoretical}} = 137.0733$, $M_{\text{sample}} = 137.0731$, $\Delta M = -0.2$ mmass units (-1.4 ppm), C$_8$H$_9$N$_{15}$O.

Methyl $^{15}$N-phenylcarbamate L-4: To a 1 L round-bottomed flask 500 ml of methanol, a magnetic stir bar, 2.57 g (21.0 mmol, 1 eq) benzamide, and 3.75 g (21.0 mmol, 1
eq) N-bromosuccinimide (NBS) was added. The flask was placed in an oil bath, stirring was started and 7.14 ml (7.27 g, 47.8 mmol, 2.27 eq) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The reaction was refluxed for 15 minutes at which point a second addition of 3.75 g (21.0 mmol, 1 eq) NBS was added slowly into the reaction, upon addition there is violent foaming that quickly subsides. The reflux was allowed to continue for an additional 30 minutes. The solvent is removed by reduced pressure evaporation and the residue is dissolved in 400 mL of ethyl acetate. The organic solution is washed with 6 N HCl (2 × 75 ml), followed by 1.0 N NaOH (2 × 75 ml), saturated brine (2 X 50 ml), and finally dried over sodium sulfate. The solvent is removed by reduced pressure evaporation and the crude product purified by flash column chromatography (silica gel, ethyl acetate/hexane (1:1)). Final purification done by crystallizing from hexanes.

Yield: 2.12 g (14.0 mmol) of a white crystals, 78 %. FTIR (KBr pellet, cm⁻¹): 3296 (s, $^{15}$N-H), 3126 (w, aryl-H), 3061 (m, aryl-H), 2952 (m, alkyl-H), 1709 (s, C=O), 1599 (m, C=C). $^1$H-NMR (400 MHz, DMSO$_{d6}$): δ (ppm) 9.64 ($^{15}$N-H, $J_{^{15}N-1H} = 91.2$ Hz, 1H, d), 7.45 (Ar-H, $J = 8.0$ Hz, 2H, d), 7.27 (Ar-H, $J = 7.6$ Hz, 2H, t), 6.98 (Ar-H, $J = 7.2$ Hz, 2H, t), 3.66 (-CH$_3$, 3H, s). $^{13}$C-NMR (100 MHz, DMSO$_{d6}$): δ (ppm) 153.9 ($J_{^{15}N-13C} = 26.5$ Hz), 139.1 ($J_{^{15}N-13C} = 15.2$ Hz), 128.8, 122.4, 118.1, 51.6. $^{15}$N-NMR (40.5 MHz, CDCl$_3$): δ (ppm) 7.1. HRMS-ESI: $M_{\text{theoretical}} = 153.0676$, $M_{\text{sample}} = 153.0698$, ΔM = 2.2 mmass units (14.4 ppm), C$_8$H$_9$$^{15}$NO$_2$. 
Methyl $^{15}$N-hexylcarbamate L-5: Employing the same procedure as L-4. 1.5 L of methanol, 7.00 g (53.8 mmol, 1 eq.) $^{15}$N-heptanamide, 19.14 g (107.6 mmol, 2.0 eq.) NBS, and 18.25 ml (18.6 g, 122.1 mmol, 2.27 eq.) DBU.

Yield: 5.38 g (33.8 mmol) of a pale liquid, 62 %. FTIR (KBr pellet, cm$^{-1}$): 3333 (m, $^{15}$N-H), 2929 (m, alkyl-H), 2860 (m, alkyl-H), 1701 (s, C=O). $^1$H-NMR (400 MHz, DMSO$_{d6}$): $\delta$ (ppm) 7.08 ($^{15}$N-H, $J_{^{15}N-1H} = 92.0$ Hz, $J_{1H-1H} = 5.6$ Hz, 1H, dt), 3.50 (-CH$_3$, 3H, s), 2.95 (-CH$_2$(CH$_2$)$_4$CH$_3$, $J = 6.4$ Hz, 2H, pentet), 1.39 – 1.23 (-CH$_2$(CH$_2$)$_4$CH$_3$, 8H, m), 0.86 (-CH$_2$(CH$_2$)$_4$CH$_3$, $J = 7.2$ Hz, 3H, t). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 156.6 ($J_{^{15}N-13C} = 26.5$ Hz), 51.0, 40.2 ($J_{^{15}N-13C} = 10.6$ Hz), 31.0, 29.4, 25.9, 22.1, 13.9. $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) – 13.2. HRMS-ESI: $M_{\text{theoretical}} = 161.1302$, $M_{\text{sample}} = 161.1298$, $\Delta M = -0.4$ mmass units (-2.48 ppm), C$_8$H$_{17}$N$_2$O$_2$.

Methyl $^{15}$N-benzylcarbamate L-6: Employing the same procedure as L-4. 1.3 L of methanol, 3.37 g (24.8 mmol, 1.0 eq) $^{15}$N-2-Phenylacetamide, 8.82 g (49.6 mmol, 1.0 eq) NBS, and 8.40 ml (8.55 g, 56.2 mmol, 2.27 eq) DBU.

Yield: 3.34 g (20.1 mmol) of clear oil, 81 %. FTIR (KBr pellet, cm$^{-1}$): 3365 (s, $^{15}$N-H), 3086 (w, aryl-H), 3062 (w, aryl-H), 3030 (m, aryl-H), 2952 (m, alkyl-H), 1705 (s, C=O),
1454 (m, C=C aryl). $^1$H-NMR (400 MHz, DMSO$_{d6}$): $\delta$ (ppm) 7.69 ($^{15}$N-H, $J_{^{15}N-^{1}H} = 92.8$ Hz, $J_{^{1}H-^{1}H} = 6.4$ Hz, 1H, dt), 7.31 (Ar-H, $J = 7.6$ Hz 2H, td), 7.23 (Ar-H, $J = 7.6$ Hz, 2H, t). 4.17 (benzyl-H, $J = 6.4$ Hz, 2H, d), 3.54 (-CH$_3$, 3H, s). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 156.9 ($J_{^{15}N-^{13}C} = 26.6$ Hz), 139.8, 128.3, 127.0, 126.8, 51.4, 43.8 ($J_{^{15}N-^{13}C} = 12.2$ Hz). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) -11.56. HRMS-ESI: $M_{\text{theoretical}} = 167.0833$, $M_{\text{sample}} = 167.0832$, $\Delta M = -0.1$ mmass units (-0.6 ppm), C$_9$H$_{11}^{15}$NO$_2$.

$^{15}$N-Aniline hydrochloride L-7: To a 250 mL round bottom flask 1.64 g (10.78 mmol) of methyl $^{15}$N-hexylcarbamate was added with a stir bar. To the solid 50 mL of conc. HCl was added and set to reflux for 12 hours. Following the reflux, the acid was neutralized with saturated solution of K$_2$CO$_3$ to a pH of about 2. The aqueous solution was washed with ethyl acetate to extract unreacted materials and the aqueous solution concentrated to a crude solid. Ethanol was added to extract the product from the crude mixture of salts and inorganic solids were filtered. The product was recovered by removing the ethanol reduced pressure evaporation and drying under high vacuum.

Yield 0.58 g (4.44 mmol) of a yellow solid, 41.0 %. $^1$H-NMR (400 MHz, DMSO$_{d6}$): $\delta$ (ppm) 10.43 ($^{15}$N-H, 3H, b), 7.48 (Ar-H, $J = 7.6$ Hz, 2H, td), 7.41 – 7.38 (Ar-H, 3H, m). $^{13}$C-NMR (100 MHz, DMSO$_{d6}$): $\delta$ (ppm) 132.1 ($J_{^{15}N-^{13}C} = 8.4$ Hz), 129.7 ($J_{^{15}N-^{13}C} = 1.5$ Hz),
127.8, 123.2. HRMS-ESI: $M_{\text{theoretical}} = 95.0622, M_{\text{sample}} = 95.0625, \Delta M = 0.3$ mmass units (3.1 ppm), $C_6H_7^{15}N$. 

![15NH2 HCl]

$^{15}N$-(1-hexylamine) hydrochloride L-8: To a 250 mL round bottom flask 5.00 g (31.21 mmol) of methyl $^{15}N$-hexylcarbamate was added with a stir bar. To the solid 50 mL of conc. HCl was added and set to reflux for 16 hours. Following the reflux, the acid was neutralized with saturated solution of $K_2CO_3$ to a pH of about 2. The aqueous solution was washed with ethyl acetate to extract unreacted materials and the aqueous solution concentrated to a crude solid. Ethanol was added to extract the product from the crude mixture of salts and inorganic solids were filtered. The product was recovered by removing the ethanol reduced pressure evaporation and drying under high vacuum.

Yield 2.64 g (26.3 mmol) of a white solid, 84 %. $^1H$-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 8.19 ($^{15}N$-H, $J_{^{15}N-1H} = 73$ Hz, 3H, d), 5.46 ($^{15}N$-H, $J_{^{15}N-1H} = 88$ Hz, 1H, d), 2.22 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, $J = 8.0$ Hz, 2H, t), 1.64 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, $J = 7.2$ Hz, 2H, p), 1.38 – 1.30 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, 6H, m), 0.89 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, $J = 7.2$ Hz, 3H, t). $^{13}C$-NMR (100 MHz, CDCl$_3$): 40.1 ($J_{^{15}N-13C} = 4.6$ Hz), 31.3, 27.7, 26.4, 22.6, 14.1. $^{15}N$-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) – 50.1. HRMS-ESI: $M_{\text{theoretical}} = 103.1258, M_{\text{sample}} = 103.1242, \Delta M = 0.4$ mmass units (3.8 ppm), $C_6H_{15}^{15}N$. 

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3.7.5 General Procedure for the Preparation of Ureas and Thioureas

The synthesis of ureas and thiourea were conducted following two general procedures: Symmetric ureas were generated by the addition of amine into solution of CDI at a 1:2 molar ratio to the anime in 150 mL of DCM at room temperature. In the cases when anime salts were used, the amine salt was pre-dissolved in DCM with triethylamine at a 3 molar equivalents based on the amine, then added to the CDI solution. Typically the reaction was allowed to stir overnight or 12 hours at room temperature at which point the solvent was removed via reduced pressure evaporation and the crude product was crystallized from boiling ethanol. The purified urea was dried under high vacuum. If the imidzole byproduct persists, the urea was redissolved in DCM and washed with a brine solution, dried with sodium sulfate, and purified, *vide supra*. For non-symmetric ureas and thioureas are generally prepared following the same procedure as symmetric ureas with the CDI being replaced with an isocyanate or isothiocyanate.

![Chemical structure](image)

*N,N*-di(2-phenylethyl)urea U-10: Following outline procedure for symmetric ureas.

150 mL of DCM, 3.02 g (18.6 mmol, 1.0 eq) of CDI, and 4.52 g (37.3 mmol, 2.0 eq) of 2-phenylethylamine.

Yield: 3.51 g (13.10 mmol) large, white crystals, 70.2 %. FTIR (KBr pellet, cm\(^{-1}\)):

3338 (s, N-H), 3088 (w, aryl-H), 3061 (w, aryl-H), 3026 (w, aryl-H), 2933 (m, alkyl-H),
$\delta$ (ppm) 7.29 (Ar-\(H\), \(J = 6.4\) Hz, 4H, td), 7.21 – 7.17 (Ar-\(H\), 6H, m), 5.88 (N-\(H\), \(J = 5.2\) Hz, 2H, t), 3.21 (Ar-CH\(_2\)CH\(_2\)-N, \(J = 6.8\) Hz, 4H, qd), 2.66 (Ar-CH\(_2\)CH\(_2\)-N, \(J = 7.6\) Hz, 4H, t). \(^{13}\)C-NMR (100 MHz, DMSO\(_{d6}\)): \(\delta\) (ppm) 157.9, 139.8, 128.7, 128.3, 125.9, 40.9, 36.2.

\(^{15}\)N-hexyl-\(^{15}\)N-phenylthiourea U-12: A 100 ml round-bottom containing 15 mL of dry DCM, 1.83 mL (2.75 g, 23.9 mmol, 3 eq.) thiophosgene, and stir bar was cooled in a ice bath. To the vessel, a solution of 1.04 g (8.0 mmol, 1.0 eq.) \(^{15}\)N-aniline HCl, 1.39 mL (1.03 g, 8.0 mmol, 1.0 eq.) DIPEA, and 10 mL of DCM was added slowly, followed by 0.96 g (23.9 mmol, 3.0 eq.) of finely crushed NaOH. The reaction was allowed to warm to room temperature and react overnight. The solvent and excess thiophosgene was vacuum striped and the isothiocyanate was purified via column chromatography (25 hexane:1 DMC). Without further purification, the solvent was removed and the isothiocyanate was redissolved in DCM. To the reaction vessel, a solution of 1.10 g (8.0 mmol, 1.0 eq.) \(^{15}\)N-hexylamine HCl, 2.78 mL (2.06 g, 15.9 mmol, 2.0 eq.) DIPEA, and 10 mL of DCM was added and stirred at room temperature for 4 hours. The thiourea was purified by column chrom. (50 ethyl acetate: 50 hexane) and dried under high vacuum.

Yield: 1.24 g (5.2 mmol) yellow solid, 65.6 %. FTIR (KBr pellet, cm\(^{-1}\)): 3232 (s, \(^{15}\)N-H str), 3064 (s, aryl-H), 2948 (m, alkyl-H), 2923 (m, alkyl-H), 1599 (m, C=C), 1537 (s, C=S). \(^{1}\)H-NMR (400 MHz, DMSO\(_{d6}\)): \(\delta\) (ppm) 7.74 (\(^{15}\)N-H, \(J_{N-H} = 94.8\) Hz, 1H, d), 7.45 (Ar-
H, \( J = 8.4 \text{ Hz}, \ 2\text{H, td})\), 7.32 (Ar-H, \( J = 6.4 \text{ Hz}, \ 1\text{H, td})\), 7.20 (Ar-H, \( J = 7.6 \text{ Hz}, \ 2\text{H, dd})\), 6.01 (\(^{15}\text{N}-\text{H}, \ J_{\text{N-H}} = 88.4 \text{ Hz}, \ 1\text{H, d})\), 3.62 (-CH\text{\textsubscript{2}}CH\text{\textsubscript{2}}(\text{CH}\text{\textsubscript{2}})\text{CH}_{3}, \ J = 7.2 \text{ Hz}, \ 2\text{H, t})\). \(^{13}\text{C}-\text{NMR}\ (75 \text{ MHz, DMSO\textsubscript{d}_6})\): \( \delta \) (ppm) 180.2 (\( \text{J}_{\text{C-N}} = 15.7 \text{ Hz}, \ J_{\text{C-N}} = 16.6 \text{ Hz})\), 139.4 (\( \text{J}_{\text{15N-13C}} = 15.1 \text{ Hz})\), 128.6, 124.0, 122.9, 43.9 (\( \text{J}_{\text{15N-13C}} = 11.4 \text{ Hz})\), 31.0, 28.4, 26.1, 22.1, 14.0. \(^{15}\text{N}-\text{NMR}\ (40.5 \text{ MHz, CDCl}_3): \delta \) (ppm): 29.3, 18.9. \ HRMS-ESI: \( M_{\text{theroretical}} = 239.1361\), \( M_{\text{sample}} = 239.1351\), \( \Delta M = -1.0 \text{ mmass units (-}4.18 \text{ ppm})\), \( \text{C}_{13}\text{H}_{20}\text{^{15}\text{N}}_{2}\text{S} \).

\[ \begin{align*}
\text{\textbf{\(^{15}\text{N,}^{\text{N'}}\text{-Dibenzylurea U-13}:\)} Due to the challenging purification of the \(^{15}\text{N}-\text{benzylamine, carbamate deprotected was immediately followed by urea synthesis. To a 250 mL round bottom flask 3.20 g (19.3 mmol) of methyl \(^{15}\text{N}-\text{benzylcarbamate was added with a stir bar. To the solid 50 mL of conc. HCl was added and set to reflux for 16 hours. Following the reflux, the acid was neutralized with saturated solution of K}_2\text{CO}_3 to a pH of about 2. The aqueous solution was washed with ethyl acetate to extract unreacted materials and the aqueous solution concentrated to a crude solid. Ethanol was added to extract the product from the crude mixture of salts and inorganic solids were filtered. The product was recovered by removing the ethanol reduced pressure evaporation and drying under high vacuum. Yielding 2.7 g of crude material which was redissolved in 150 mL of DCM 0.79 mL (0.83 g, 6.22 mmol) of benzyl isocyanate, and 2.07 mL (1.57 g, 15.6 mmol) of triethylamine.} \end{align*} \]
Yield: 0.58 g (2.39 mmol) white crystals, 12%. FTIR (KBr pellet, cm\(^{-1}\)): 3317 (s, \(^{15}\)N-H), 3087 (s, aryl-H), 3057 (s, aryl-H), 3030 (s, aryl-H), 2922 (m, alkyl-H), 2873 (m, alkyl-H), 1626 (s, C=O), 1568 (m, C=C). \(^1\)H-NMR (300 MHz, DMSO\(_d6\)): \(\delta\) (ppm): 7.33 – 7.22 (Ar-H, 10H, m), 6.45 (N-H, \(J = 6.0\) Hz, 1H, t), 6.45 (\(^{15}\)N-H, \(J_{^{15}\text{N}-\text{H}} = 89.4\) Hz, \(J_{\text{H-H}} = 15.0\) Hz, 1H, tt), 4.23 (benzyl-H, \(J = 6.0\) Hz, 4H, d). \(^{13}\)C-NMR (75 MHz, DMSO\(_d6\)): \(\delta\) (ppm) 158.1 (\(J_{^{15}\text{N}-\text{C}} = 19.1\) Hz), 140.9, 128.2, 127.0, 126.6, 43.0 (\(J_{^{15}\text{N}-^{13}\text{C}} = 11.3\) Hz). \(^{15}\)N-NMR (40.5 MHz, CDCl\(_3\)): \(\delta\) (ppm) -10.9. HRMS-ESI: \(M_{\text{theoretical}} = 242.1306\), \(M_{\text{sample}} = 242.1297\), \(\Delta M = -0.9\) mmass units (-3.72 ppm), \(C_{15}H_{16}^{15}\)NNO.

\(^{15}\)N,\(^{15}\)N'-Dibenzylurea U-13: Following the same procedure and scale as employed for U-13 for the carbamate deprotected followed by symmetric urea synthesis protocol. 1.35 g (8.32 mmol) of CDI and 5.80 mL (4.30 g, 33.3 mmol) of DIPEA.

Yield: 1.00 g (4.12 mmol) white crystals, 11%. FTIR (KBr pellet, cm\(^{-1}\)): 3311 (s, \(^{15}\)N-H), 3086 (s, aryl-H), 3062 (s, aryl-H), 3030 (s, aryl-H), 2922 (m, alkyl-H), 2875 (m, alkyl-H), 1624 (s, C=O), 1562 (m, C=C).

\(^{15}\)N-hexyl-\(^{15}\)N'-phenylurea U-14: Following outline procedure for non-symmetric ureas. 50 mL of CHCl\(_3\), 0.68 g (4.90 mmol, 1.0 eq) of \(^{15}\)N-(1-hexylamine) hydrochloride,
0.64 mL (0.700 g, 5.88 mmol, 1.2 eq) phenyl isocyanate, and 1.30 mL (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.

Yield: 0.71 g (3.22 mmol) white crystals, 66 %. FTIR (KBr pellet, cm⁻¹): 3325 (s, N-H), 3037 (w, aryl-H), 2958 (m, alkyl-H), 2927 (m, alkyl-H), 2854 (m, alkyl-H), 1635 (s, C=O), 1597 (m, C=C). ¹H-NMR (400 MHz, DMSO⁺): δ (ppm) 8.67 (N-H, 1H, s), 7.36 (Ar-H, J = 8.0 Hz, 2H, dd), 7.20 (Ar-H, J = 7.2 Hz, 2H, td), 6.67 (Ar-H, J = 7.6 Hz, 2H, td), 6.01 (¹⁵N-H, J₁₅N-H = 89.2 Hz, J₁₅N-H = 5.6 Hz, 1H, dt), 3.06 (-CH₂CH₂(CH₂)₃CH₃, J = 6.0 Hz, 2H, t), 1.41 (-CH₂CH₂(CH₂)₃CH₃, 2H, m), 1.27 (-CH₂CH₂(CH₂)₃CH₃, 6H, m), 0.87 (-CH₂CH₂(CH₂)₃CH₃, J = 6.4 Hz, 3H, m). ¹³C-NMR (100 MHz, DMSO⁺): δ (ppm) 155.1 (J₁₅N-¹³C = 20.4 Hz), 140.6, 128.6, 120.9, 117.5, 93.9, 31.0, 29.7, 26.1, 22.1. ¹⁵N-NMR (40.5 MHz, CDCl₃): δ (ppm): -9.6. HRMS-ESI: M theoretical = 222.1619, M sample = 222.1619, ΔM = 0 m mass units (0 ppm), C₁₃H₂₀¹⁵NNO.

\[ \text{N-hexyl-}^{15}\text{N'-phenylurea U-15: Following outline procedure for non-symmetric ureas. 150 mL of CHCl₃, 1.49 g (1.49 mmol, 1.1 eq) of 1-hexyl isocyanate, 0.97 mL (1.00g, 10.62 mmol, 1.0 eq) }^{15}\text{N-aniline.} \]

Yield: 1.20 g (5.42 mmol) white crystals, 51 %. FTIR (KBr pellet, cm⁻¹): 3334 (s, N-H), 3302 (s, N-H), 3037 (w, aryl-H), 2958 (m, alkyl-H), 2929 (m, alkyl-H), 2854 (m, alkyl-H), 1633 (s, C=O), 1595 (m, C=C). ¹H-NMR (400 MHz, DMSO⁺): δ (ppm) 8.37 (¹⁵N-H, J₁₅N-H = 88.0 Hz, 1H, d), 7.37 (Ar-H, J = 6.8 Hz, 2H, dd), 7.22 (Ar-H, J = 7.2 Hz, 2H, t), 6.87
(Ar-H, $J = 7.2$ Hz, 2H, t), 6.10 (N-H, $J = 5.6$ Hz, 1H, t), 3.06 ($-CH_2CH_2(CH_2)_3CH_3$, $J = 6.0$ Hz, 2H, q), 1.41 ($-CH_2CH_2(CH_2)_3CH_3$, 2H, m), 1.28 ($-CH_2CH_2(CH_2)_3CH_3$, 6H, m), 0.87 ($-CH_2CH_2(CH_2)_3CH_3$, $J = 6.8$ Hz, 3H, t). $^{13}$C-NMR (75 MHz, DMSO$_{d6}$): $\delta$ (ppm) 155.2 ($J_{15N-13C} = 19.7$ Hz), 140.6 ($J_{15N-13C} = 15.7$ Hz), 128.6, 120.9, 117.5, 39.1, 31.2, 29.8, 26.1, 22.1, 14.0. $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 7.4. HRMS-ESI: $M_{theoretical} = 222.1619$, $M_{sample} = 222.1616$, $\Delta M = -0.3$ mmass units (-1.35 ppm), C$_{13}$H$_{20}$$^{15}$NNO.

$^{15}$N-hexyl-$N'$-(4-methoxyphenyl)thiourea U-16: Following outline procedure for non-symmetric ureas. 50 mL of CHCl$_3$, 0.68 g (4.90 mmol, 1.0 eq) of $^{15}$N-(1-hexylamine) hydrochloride, 0.81 mL (0.97 g, 5.88 mmol, 1.2 eq) 4-methoxy isothiocyanate, and 1.30 mL, (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.

Yield: 0.50 g (1.88 mmol) white crystals, 38 %. FTIR (KBr pellet, cm$^{-1}$): 3257 (s, N-H), 3176 (s, N-H), 3055 (s, aryl-H), 2958 (m, alkyl-H), 2929 (m, alkyl-H), 2856 (m, alkyl-H), 1608 (m, C=C), 1543 (s, C=S). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.47 (N-H, 1H, s), 7.13 (Ar-H, $J = 6.4$ Hz, 2H, dd), 6.96 (Ar-H, $J = 5.6$ Hz, 2H, dd), 6.77 ($^{15}$N-H, $J_{15N-H} = 89.6$ Hz, 1H d), 3.838 (-OCH$_3$, 3H, s), 3.59 ($-CH_2CH_2(CH_2)_3CH_3$, 2H, m), 1.59 ($-CH_2CH_2CH_2(CH_2)_2CH_3$, 4H, m) 1.26 ($-CH_2CH_2CH_2(CH_2)_2CH_3$, 6H, m), 0.86 ($-CH_2CH_2CH_2(CH_2)_2CH_3$, $J = 6.8$ Hz, 3H, t). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 18.5.
HRMS-ESI: $M_{\text{theoretical}} = 268.1496$, $M_{\text{sample}} = 268.1494$, $\Delta M = -0.2$ mmass units (-0.75 ppm), $C_{14}H_{22}{^15}NNSO$.

$^{15}N$-hexyl-$N^\prime$-(4-methylphenyl)urea U-17: Following outline procedure for non-symmetric ureas. 50 mL of DCM, 0.68 g (4.90 mmol, 1.0 eq) of $^{15}N$-(1-hexylamine) hydrochloride, 0.75 g (5.88 mmol, 1.2 eq) 4-methylphenyl isocyanate, and 1.30 mL, (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.

Yield: 0.95 g (4.15 mmol) white crystals, 85 %. FTIR (KBr pellet, cm$^{-1}$): 3332 (s, N-H), 3033 (w, aryl-H), 2956 (m, alkyl-H), 2929 (m, alkyl-H), 2856 (m, alkyl-H), 1633 (s, C=O), 1597 (m, C=C). $^1$H-NMR (400 MHz, DMSO$_{d6}$): $\delta$ (ppm) 8.27 (N-H, 1H, s), 7.23 (Ar-H, $J = 8.4$ Hz, 2H, d), 7.00 (Ar-H, $J = 6.8$ Hz, 2H, td), 6.06 ($^{15}N$-H, $J_{N-H} = 88.8$ Hz, $J_{H-H} = 5.6$ Hz, 1H, dt), 3.05 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, $J = 6.4$ Hz, 2H, t), 2.22 (CH$_3$-Ar 3H, s), 1.40 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, 2H, br), 1.27 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, 6H, m), 0.87 (-CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$, $J = 6.4$ Hz. 3H, m). $^{13}$C-NMR (100 MHz, DMSO$_{d6}$): $\delta$ (ppm) 155.1 ($J_{15N-13C} = 20.4$ Hz), 140.6, 128.6, 120.9, 117.5, 93.9, 31.0, 29.7, 26.1, 22.1. $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm): -9.93. HRMS-ESI: $M_{\text{theoretical}} = 236.1775$, $M_{\text{sample}} = 236.1776$, $\Delta M = 0.1$ mmass units (0.42 ppm), $C_{14}H_{22}{^15}NNO$. 

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\textit{\textsuperscript{15}N-hexyl-N'(4-chlorophenyl)}urea U-18: Following outline procedure for non-symmetric ureas. 50 mL of DCM, 0.68 g (4.90 mmol, 1.0 eq) \textit{\textsuperscript{15}N-}(1-hexylamine) hydrochloride, 0.90 g (5.88 mmol, 1.2 eq) 4-chlorophenyl isocyanate, and 1.30 mL, (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.

Yield: 0.73 g (2.86 mmol) white powder, 59 %. FTIR (KBr pellet, cm\textsuperscript{-1}): 3327 (s, N-H), 3087 (w, aryl-H), 2954 (m, alkyl-H), 2931 (m, alkyl-H), 2860 (m, alkyl-H), 1631 (s, C=O), 1591 (m, C=C). \textsuperscript{1}H-NMR (400 MHz, DMSO\textsubscript{d6}): \(\delta\) (ppm) 8.52 (N-H, 1H, s), 7.40 (Ar-H, \(J = 8.0\) Hz, 2H, dd), 7.25 (Ar-H, \(J = 8.0\) Hz, 2H, dd), 6.14 (\textit{\textsuperscript{15}N-H}, \(J_{1\textit{\textsuperscript{15}N}-1\text{H}} = 89.6\) Hz, \(J_{1\text{H}-1\text{H}} = 5.6\) Hz, 1H, dt), 3.06 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, \(J = 6.4\) Hz, 2H, q), 1.41 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, 2H, br), 1.27 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, 6H, m), 0.87 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, \(J = 5.2\) Hz, 3H, t). \textit{\textsuperscript{15}N-NMR} (40.5 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) -8.76. HRMS-ESI: \textit{M}_{\text{theoretical}} = 256.1229, \textit{M}_{\text{sample}} = 256.1227, \Delta \textit{M} = -0.2\) mmass units (-0.78 ppm), C\textsubscript{13}H\textsubscript{19}\textit{\textsuperscript{15}NNO.}

\textit{\textsuperscript{15}N,N'-di(hexyl)}urea U-19: Following outline procedure for non-symmetric ureas. 50 mL of DCM, 0.68 g (4.90 mmol, 1.0 eq) of \textit{\textsuperscript{15}N-}(1-hexylamine) hydrochloride, 0.86 mL (0.75 g, 5.88 mmol, 1.2 eq) 1-hexyl isocyanate, and 1.30 mL, (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.
Yield: 0.95 g (4.15 mmol) white crystals, 85 %. FTIR (KBr pellet, cm⁻¹): 3329 (s, N-H), 2956 (m, alkyl-H), 2929 (m, alkyl-H), 2856 (m, alkyl-H), 1616 (s, C=O). ¹H-NMR (400 MHz, DMSO₆): δ (ppm) 5.69 (N-H, J = 4.0 Hz, 1H, t), 5.69 (¹⁵N-H, J¹⁵N-¹H = 88.4 Hz, J¹H-¹H = 6.0 Hz, 1H, dt), 2.94 (-CH₂(CH₂)₄CH₃, J = 6.8 Hz, 4H, sextet), 1.33 – 1.23 (-CH₂(CH₂)₃CH₃, 16H, m), 0.86 (-CH₂CH₂(CH₂)₃CH₃, J = 6.0 Hz, 6H, t). ¹⁵N-NMR (40.5 MHz, CDCl₃): δ (ppm) – 12.5. HRMS-ESI: M theoretical = 230.2245, M sample = 230.2250, ΔM = 0.5 mmass units (2.17 ppm), C₁₃H₂₈¹⁵NNO.

**¹⁵N-hexyl-N’-propylurea U-20:** Following outline procedure for non-symmetric ureas. 50 mL of DCM, 0.50 g (3.60 mmol, 1.0 eq) ¹⁵N-(1-hexylamine) hydrochloride, 0.41 mL (0.37 g, 4.33 mmol, 1.2 eq) propyl isocyanate, and 1.30 mL, (0.99 g, 9.79 mmol, 2.0 eq.) triethylamine.

Yield: 0.50 g (2.65 mmol) white crystals, 74 %. FTIR (KBr pellet, cm⁻¹): 3329 (s, N-H), 2960 (m, alkyl-H), 2931 (m, alkyl-H), 2860 (m, alkyl-H), 1622 (s, C-0). ¹H-NMR (400 MHz, DMSO₆): δ (ppm) 5.74 (N-H, 1H, s), 5.74 (¹⁵N-H, J¹⁵N-¹H = 88.4 Hz, J¹H-¹H = 4.8 Hz, 1H, dt), 2.92 (N-CH₂- J = 6.4 Hz, 4H, sextet), 1.38 – 1.23 (-CH₂-, 10H, m), 0.87 – 0.79 (-CH₃, 6H, m). ¹³C-NMR (100 MHz, DMSO₆): δ (ppm) 158.0 (J₁⁵N-¹³C = 18.9 Hz), 41.1, 31.1, 30.0, 26.1, 23.3, 22.1, 13.9, 11.4. ¹⁵N-NMR (40.5 MHz, CDCl₃): δ (ppm) -12.6. HRMS-ESI: M theoretical = 188.1775, M sample = 188.1776, ΔM = -0.1 mmass units (-0.53 ppm), C₁₀H₂₂¹⁵NNO.
3.7.6 General Procedure for the Dehydration of Ureas and Thioureas

The dehydration of the ureas and thioureas were generally carried out in the same matter. A dry 250 or 500 mL round bottom flask was charged with 10 to 20 mL of DCM and triphosphine dibromide and cooled in an ice bath and placed under a nitrogen atmosphere. To the cool reaction solution triethylamine was added dropwise. During this addition vapors may form, allow time to dissipate. Once flask is clear of vapors, add urea in two or three portions over one hour and stir 2 to 12 hours. Once reaction is complete extract monomer with pentane or hexanes filtering byproducts. Purify by column chromatography using a 50/50 solution of hexanes and ethyl acetate and pH 7 preconditioned silica gel.

Due to impractically long relaxation times, > 40 seconds, for nitrogen-15 NMR data collection of carbodiimides, even with the assistance of a relaxation reagent, these values were not collected. The chemical shift of carbodiimide, however has been previously reported.31

\[
\begin{align*}
N,N'\text{-di}(2\text{-phenylethyl})\text{carbodiimide M-11:} & \quad 10 \text{ mL of DCM, 4.15 g (9.83 mmol,} \\
& \quad 1.2 \text{ eq.) triphenylphosphine dibromide, 2.72 mL (2.1 g, 20.50 mmol, 2.5 eq.) triethylamine,} \\
& \quad \text{and 2.20 g (8.20 mmol, 1.0 eq.) } N,N'\text{-di}(2\text{-phenylethyl})\text{urea.}
\end{align*}
\]

Yield: 0.85 g (3.38 mmol) of clear liquid, 41.2 %. FTIR (KBr thinfilm, cm\(^{-1}\)): 3086 (w, aryl-H), 3062 (w, aryl-H), 3028 (w, aryl-H), 2943 (m, alkyl-H), 2127 (s, N=C=N), 1603
(m, C=C). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.30 (Ar-H, $J = 7.2$ Hz, 4H, tt), 7.23 – 7.16 (Ar-H, 5H, m), 3.29 (Phenyl-CH$_2$CH$_2$N, $J = 7.6$ Hz, 4H, t), 2.73 (Phenyl-CH$_2$CH$_2$N, $J = 7.6$ Hz, 4H, t). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 140.4, 139.0, 129.0, 128.6, 126.7, 47.8, 37.6.

$q^{15}N,N'$-Dibenzylcarbodiimide M-13: 10 mL of DCM, 1.39 g (3.28 mmol, 1.2 eq.) of triphenylphosphine dibromide, 0.91 mL (0.69 g, 6.84 mmol, 2.5 eq.) triethylamine, and 0.66 g (2.74 mmol, 1.0 eq.) $^{15}N,N'$-dibenzylurea.

Yield: 0.29 g (1.29 mmol) of colorless oil, 47.0 %. $^1$H-NMR (400 MHz, CDCl$_3$): (ppm): 7.34 – 7.26 (Ar-H, 6H, m), 7.21 – 7.19 (Ar-H, 4H, m), 4.31 (benzyl-H, 4H, s).

$^{15}N,^{15}N'$-Dibenzylcarbodiimide M-13: 10 mL of DCM, 1.36 g (3.22 mmol, 1.2 eq.) of triphenylphosphine dibromide, 0.89 mL (0.68 g, 6.71 mmol, 2.5 eq.) triethylamine, and 0.65 g (2.68 mmol, 1.0 eq.) $^{15}N,^{15}N'$-dibenzylurea.
Yield: 0.33 g (1.37 mmol) of colorless oil, 55%. 3086 (w, aryl-H), 3062 (w, aryl-H), 3030 (w, aryl-H), 2918 (m, alkyl-H), 2850 (m, alkyl-H), 2102 (s, $^{15}$N=C=15N), 1605 (m, C=C).

$^{15}$N-hexyl-$^{15}$N'-phenylcarbodiimide M-14: 10 mL of DCM, 1.12 g (2.64 mmol, 1.2 eq.) triphenylphosphine dibromide, 0.73 mL (0.56 g, 5.51 mmol, 2.5 eq.) triethylamine, and 0.49 g (2.20 mmol, 1.0 eq.) $^{15}$N-hexyl-$^{15}$N'-phenylthiourea.

Yield: 0.24 g (1.18 mmol), colorless oil, 54%. FTIR (KBr thinfilm, cm$^{-1}$): 3062 (w, aryl-H), 3030 (w, aryl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 2110 (s, $^{15}$N=C=15N), 1593 (m, C=C).

$^{15}$N-hexyl-$^{15}$N'-phenylcarbodiimide M-15: 10 mL of DCM, 1.60 g (3.79 mmol, 1.2 eq.) triphenylphosphine dibromide, 1.05 mL (0.80 g, 7.91 mmol, 2.5 eq.) triethylamine, and 0.70 g (3.16 mmol, 1.0 eq.) $^{15}$N-hexyl-$^{15}$N'-phenylurea.

Yield: 0.39 g (1.92 mmol), colorless oil, 61%. FTIR (KBr thinfilm, cm$^{-1}$): 3066 (w, aryl-H), 3021 (w, aryl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 2119 (s, N=C=15N), 1593
\textbf{1H-NMR} (300 MHz, CDCl\textsubscript{3}): \( \delta (\text{ppm}) 7.27 \) (Ar-H, \( J = 4.5 \text{ Hz} \), 4H, t), 7.09 (Ar-H, 1H, m), 3.20 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, \( J = 7.2 \text{ Hz} \), 2H, m), 1.47 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, 2H, m), 0.87 (-CH\textsubscript{2}CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, \( J = 5.7 \text{ Hz} \), 3H, t). \textbf{13C-NMR} (100 MHz, CDCl\textsubscript{3}): 141.1 (\( J_{15N-13C} = 7.5 \text{ Hz} \)), 129.5, 124.7, 123.7, 121.6, 47.1, 31.6, 31.5, 26.7, 22.7, 14.2.

\begin{center}
\includegraphics[width=0.2\textwidth]{15N-hexyl-15N'-phenylcarbodiimide.png}
\end{center}

\textbf{\( N \)-hexyl-\( ^{15}N' \)-phenylcarbodiimide M-16}: 10 mL of DCM, 2.29 g (5.42 mmol, 1.2 eq.) triphenylphosphine dibromide, 1.57 mL (1.14 g, 11.30 mmol, 2.5 eq.) triethylamine, and 1.00 g (4.52 mmol, 1.0 eq.) \( N \)-hexyl-\( ^{15}N' \)-phenylurea.

Yield: 0.36 g (1.77 mmol) of clear liquid, 39%. \textbf{FTIR} (KBr thinfilm, cm\textsuperscript{-1}): 3060 (w, aryl-H), 3030 (w, aryl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 2125 (s, \( ^{15}N=C=N \)), 1593 (m, C=C).

\begin{center}
\includegraphics[width=0.2\textwidth]{15N-hexyl-N'-4-methoxyphenyl.png}
\end{center}

\textbf{\( ^{15}N \)-hexyl-\( N' \)-(4-methoxyphenyl)carbodiimide M-17}: 10 mL of DCM, 2.10 g (4.95 mmol, 1.2 eq.) triphenylphosphine dibromide, 1.32 mL (1.00 g, 9.91 mmol, 2.5 eq.) triethylamine, and 1.02 g (3.82 mmol, 1.0 eq.) \( ^{15}N \)-hexyl-\( N' \)-(4-methoxyphenyl)thiourea.
Yield: 0.31 g (1.33 mmol) of clear liquid, 35 %. FTIR (KBr thinfilm, cm\(^{-1}\)): 3033 (w, aryl-H), 2951 (m, alkyl-H), 2931 (m, alkyl-H), 2858 (m, alkyl-H), 2110 (s, \(^{15}\text{N}=\text{C}=\text{N}\)), 1581 (w, C=C). \(^1\text{H}-\text{NMR} \ (400 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 7.01 \ (\text{Ar-H, } J = 4.8 \text{ Hz, } 2\text{H, dd}), \ 6.82 \ (\text{Ar-H, } J = 5.1 \text{ Hz, } 2\text{H, dd}), \ 3.78 \ (-\text{OCH}_3, \ 3\text{H, s}), \ 3.38 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ J = 5.1 \text{ Hz } 2\text{H, m}), \ 1.66 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ 2\text{H, m}), \ 1.30 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ 6\text{H, m}), \ 0.89 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ J = 5.1 \text{ Hz, } 3\text{H, t}). \ ^{13}\text{C}-\text{NMR} \ (100 \text{ MHz, CDCl}_3): \ 156.9, \ 137.2 \ (J_{\text{15N-13C}} = 29.6\text{Hz}), 133.3, \ 124.5, \ 114.8, \ 55.7, \ 47.2, \ 31.6, \ 26.7, \ 22.8, \ 14.2.

\[ \begin{array}{c}
\text{N} \\
\text{C} \\
^{15}\text{N}
\end{array} \]

\(^{15}\text{N}\)-hexyl-\(\text{N'}\)-(4-methylphenyl)carbodiimide M-18: 10 mL of DCM, 1.08 g (2.54 mmol, 1.2 eq.) triphenylphosphine dibromide, 0.71 mL (0.54 g, 5.31 mmol, 2.5 eq.) triethylamine, and 0.50 g (2.12 mmol, 1.0 eq.) \(^{15}\text{N}\)-hexyl-\(\text{N'}\)-(4-methylphenyl)urea.

Yield: 0.21 g (0.98 mmol) of clear liquid, 42 %. FTIR (KBr thinfilm, cm\(^{-1}\)): 3062 (w, aryl-H), 2927 (m, alkyl-H), 2858 (m, alkyl-H), 2109 (s, \(\text{N}=\text{C}=^{15}\text{N}\)), 1576 (m, C=C). \(^1\text{H}-\text{NMR} \ (300 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 7.08 \ (\text{Ar-H, } 2\text{H, m}), \ 6.98 \ (\text{Ar-H, } J = 4.8 \text{ Hz, } 2\text{H, dd}), \ 3.38 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ J = 5.1 \text{ Hz, } 2\text{H, t}), \ 2.31 \ (-\text{CH}_3, \ 3\text{H, s}), \ 1.67 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ 2\text{H, m}), \ 1.42 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ 6\text{H, m}), \ 0.89 \ (-\text{CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3, \ J = 5.1 \text{ Hz, } 3\text{H, t}).

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15\textit{N}-hexyl-\textit{N'}-(4-chlorophenyl)carbodiimide M-19: 10 mL of DCM, 1.39 g (3.28 mmol, 1.2 eq.) triphenylphosphine dibromide, 0.91 mL (0.69 g, 6.84 mmol, 2.5 eq.) triethylamine, and 0.70 g (2.73 mmol, 1.0 eq.) \( 15\textit{N} \)-hexyl-\textit{N'}-(4-chlorophenyl)urea.

Yield: 0.21 g (0.98 mmol) of clear liquid, 42%. FTIR (KBr thinfilm, cm\(^{-1}\)): 3025 (w, aryl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 2127 (s, N=C=\(15\textit{N}\)), 1591 (m, C=C). \(^1\text{H}-\text{NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 7.24 (Ar-H, 2H, m), 7.01 (Ar-H, \(J = 4.5\) Hz, 2H, dd), 3.41 (-\(CH_2CH_2(CH_2)_3CH_3\), \(J = 6.9\) Hz, 2H, t), 1.66 (-\(CH_2CH_2(CH_2)_3CH_3\), 2H, m), 1.32 (-\(CH_2CH_2(CH_2)_3CH_3\), 6H, m), 0.88 (-\(CH_2CH_2(CH_2)_3CH_3\), \(J = 6.6\) Hz 3H, t).

\(15\textit{N},\textit{N'}\)-di(hexyl)carbodiimide M-20: 10 mL of DCM, 2.10 g (4.98 mmol, 1.2 eq.) triphenylphosphine dibromide, 1.38 mL (1.05 g, 10.38 mmol, 2.5 eq.) triethylamine, and 0.95 g (4.15 mmol, 1.0 eq.) \(15\textit{N}\)-hexyl-\textit{N'}-hexylurea.

Yield: 0.21 g (0.98 mmol) of clear liquid, 42%. FTIR (KBr thinfilm, cm\(^{-1}\)): 2951 (m, alkyl-H), 2925 (m, alkyl-H), 2925 (m, alkyl-H), 2117 (s, N=C=\(15\textit{N}\)). \(^1\text{H}-\text{NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 3.20 (-\(CH_2CH_2(CH_2)_3CH_3\), \(J = 6.8\) Hz, 4H, t), 1.38 – 1.21 (-\(CH_2(CH_2)_4CH_3\),
16H, m), 0.90 (-CH₂CH₂(CH₂)₃CH₃, J = 7.2 Hz. 6H, t). ¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 137.4 (J₁₅N-₁₃C = 9.9 Hz), 47.0, 31.6, 29.9, 26.7, 22.8, 14.2.

³¹⁵N-hexyl-N'-propylcarbodiimide M-21: 10 mL of DCM, 1.24 g (2.95 mmol, 1.2 eq.) triphenylphosphine dibromide, 0.82 mL (0.62 g, 6.14 mmol, 2.5 eq.) triethylamine, and 0.46 g (2.46 mmol, 1.0 eq.) ³¹⁵N-hexyl-N'-propylurea.

Yield: 0.21 g (0.98 mmol) of clear liquid, 42 %. FTIR (KBr thinfilm, cm⁻¹): 2954 (m, alkyl-H), 2931 (m, alkyl-H), 2862 (m, alkyl-H), 2119 (s, N=C=³¹⁵N).

3.7.7 Polymerization of Carbodiimides

Polymerizations were performed in an MBRAUD UNIlab dry box under a nitrogen atmosphere. Catalyst solution in dry chloroform of a known concentration was added to a clean scillation vial containing monomer and a stir bar. Once the polymerization was complete, the crude polymer would be dissolved in minimum CHCl₃ and precipitated into methanol. The volume ratio of methanol used is 10 to 20:1 methanol to crude polymer solution.
Poly(N,N'-di-(2-phenylethyl))carbodiimide Poly-9: 0.85 g (3.38 mmol, 172 eq.) N,N'-di(2-phenylethyl)carbodiimide, 5.0 mg (0.0197 mmol, 1.0 eq.) Cat-1, and 1.00 mL dry CDCl₃.

Yield: 0.44 g (1.77 mmol) off-white solid, 52 %. FTIR (KBr pellet, cm⁻¹): 3334 (s, N-H), 3302 (s, N-H), 3037 (w, aryl-H), 2958 (m, alkyl-H), 2929 (m, alkyl-H), 2854 (m, alkyl-H), 1633 (s, C=O), 1595 (m, C=C). ^H-NMR (300 MHz, CDCl₃): δ (ppm) 7.30 – 6.75 (Ar-H, 10H, board multiplet), 3.58 – 2.27 (CH₂, 8H, very board triplet).

Poly(^15N,N'-dibenzyl)carbodiimide Poly-10: 0.288 g (1.29 mmol, 150 eq.) ^15N,N'-dibenzylcarbodiimide, 0.00218 g (0.0085 mmol 1.0 eq.) of Cat-1, and 0.80 mL dry CDCl₃.

Yield: 0.155 g (0.69 mmol) off-white solid, 54 %. FTIR (KBr pellet, cm⁻¹): 3060 (m, aryl-H), 3028 (m, aryl-H), 2958 (m, alkyl-H), 2920 (m, alkyl-H), 2848 (m, alkyl-H), 1635 (s,
C=N). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.05 – 6.49 (Ar-H, 10H, very broad triplet), 5.41 (benzyl-H, 1H, broad singlet), 4.45 (benzyl-H, 1H, broad singlet), 4.00 (benzyl-H, $J$ = 14.8, 1H, broad doublet), 3.57 (benzyl-H, $J$ = 14.8, 1H, broad doublet). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 137.4 ($^{15}$N=C, 1N), 3.0 ($^{15}$N–C, 1N).

![Poly($^{15}$N,$^{15}$N'-dibenzyl)carbodiimide Poly-11: 0.33 g (1.37 mmol, 150 eq.) $^{15}$N,$^{15}$N'-dibenzylcarbodiimide, 4.0 g (0.0158 mmol, 1.0 eq.) of Cat-1, and 0.50 mL dry CDCl$_3$. Yield: 0.21 g (0.94 mmol) off-white solid, 63 %. FTIR (KBr pellet, cm$^{-1}$): 3060 (m, aryl-H), 3028 (m, aryl-H), 2958 (m, alkyl-H), 2920 (m, alkyl-H), 2848 (m, alkyl-H), 1635 (s, C=N). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.05 – 6.49 (Ar-H, 10H, very broad triplet), 5.41 (benzyl-H, 1H, broad singlet), 4.43 (benzyl-H, 1H, broad singlet), 3.98 (benzyl-H, 1H, broad doublet), 3.59 (benzyl-H, broad doublet). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 137.4 ($^{15}$N=C, 1N), 3.0 ($^{15}$N–C, 1N).
Poly(\textsuperscript{15}N-hexyl-\textsuperscript{15}N'-phenyl)carbodiimide Poly-\textbf{13}: 0.144 g (0.705 mmol, 120 eq.), \textsuperscript{15}N-hexyl-\textsuperscript{15}N'-phenylcarbodiimide, 1.5 mg (0.006 mmol 1.0 eq.) of 2,2,2-trifluoroethoxytrichloro titanate, and 0.50 mL dry CDCl\textsubscript{3}.

FTIR (KBr pellet, cm\textsuperscript{-1}): 3059 (w, aryl-H), 3016 (w, aryl-H), 2954 (m, alkyl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 1612 (s, C=N), 1587 (m, C=C). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) 6.60 (Ar-H, 4H, very broad doublet), 3.64 (Ar-O-CH\textsubscript{3}, 3H, board singlet), 1.58 – 0.40 (Alkyl-H, 13H, very board). \textsuperscript{15}N-NMR (40.5 MHz, CDCl\textsubscript{3}): \(\delta\) (ppm) 136.4 (\textsuperscript{15}N=C, 1N), 15.5 (\textsuperscript{15}N–C, 1N).

Poly(\textsuperscript{15}N-hexyl-\textsuperscript{15}N'-phenyl)carbodiimide Poly-\textbf{14}: 0/36 g (1.77 mmol, 150 eq.) \textsuperscript{15}N-hexyl-\textsuperscript{15}N'-phenylcarbodiimide, 3.00 mg (0.0118 mmol 1.0 eq.) \textbf{Cat-1}, and 1.10 mL dry CDCl\textsubscript{3}.

Yield: 0.22 g (1.07 mmol) off-white solid, 60 %. FTIR (KBr pellet, cm\textsuperscript{-1}): 3059 (w, aryl-H), 3022 (w, aryl-H), 2954 (m, alkyl-H), 2927 (m, alkyl-H), 2858 (m, alkyl-H), 1610 (s,
C=N), 1585 (m, C=C). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 6.80 (Ar-H, 5H, board doublet), 1.58 – 0.40 (Alkyl-H, 13H, very board). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 137.3 ($^{15}$N=C).

(R)-Poly($^{15}$N-hexyl-N’-phenyl)carbodiimide (R)Poly-14: 0.391 g (1.92 mmol, 120 eq.) $^{15}$N-hexyl-N’-phenylcarbodiimide, 7.21 mg (0.016 mmol 1.0 eq.) Cat-2, and 1.83 mL dry CDCl$_3$.

Yield: 0.221 g (1.09 mmol) off-yellow solid, 57%. FTIR (KBr pellet, cm$^{-1}$): 3059 (w, aryl-H), 3018 (w, aryl-H), 2954 (m, alkyl-H), 2927 (m, alkyl-H), 2858 (m, alkyl-H), 1626 (s, C=N), 1589 (m, C=C$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 6.60 (Ar-H, 4H, very board doublet), 3.64 (Ar-O-CH$_3$, 3H, board singlet), 1.58 – 0.40 (Alkyl-H, 13H, very board). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 15.4 ($^{15}$N–C).

Poly($^{15}$N-hexyl-N’-(4-methoxyphenyl)carbodiimide Poly-15: 0.15 g (0.63 mmol, 119 eq.) $^{15}$N-hexyl-N’-(4-methoxyphenyl)carbodiimide, 1.33 mg (0.0053 mmol 1.0 eq.) Cat-1, and 0.49 mL dry CDCl$_3$. 

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Yield: 16 mg (0.067 mmol) off-white solid, 10 %. FTIR (KBr pellet, cm\(^{-1}\)): 3039 (w, aryl-H), 2929 (m, alkyl-H), 2856 (m, alkyl-H), 1617 (s, C=N), 1576 (m, C=C). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 6.60 (Ar-H, 4H, very board doublet), 3.64 (Ar-O-CH\(_3\), 3H, board singlet), 1.58 – 0.40 (Alkyl-H, 13H, very board). \(^{15}\)N-NMR (40.5 MHz, CDCl\(_3\)): \(\delta\) (ppm) 15.2 (\(^{15}\)N–C).

(R)-Poly\(^{15}\)N-hexyl-N’-(4-methoxylphenyl)carbodiimide (R)Poly-15: 0.16 g (0.70 mmol, 121 eq.) \(^{15}\)N-hexyl-N’-(4-methoxyphenyl)carbodiimide, 2.64 mg (0.0058 mmol 1.0 eq.) Cat-2, and 0.69 mL dry CDCl\(_3\).

Yield: 57 mg (0.242 mmol) off-white solid, 35 %. FTIR (KBr pellet, cm\(^{-1}\)): 3030 (w, aryl-H), 2952 (m, alkyl-H), 2931 (m, alkyl-H), 2856 (m, alkyl-H), 1618 (s, C=N), 1576 (m, C=C). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 6.60 (Ar-H, 4H, very board doublet), 3.64 (Ar-O-CH\(_3\), 3H, board singlet), 1.58 – 0.40 (Alkyl-H, 13H, very board). \(^{15}\)N-NMR (40.5 MHz, CDCl\(_3\)): \(\delta\) (ppm) 15.0 (\(^{15}\)N–C).
(R)-Poly(15N-hexyl-N’-(4-methylphenyl))carbodiimide (R)Poly-16: 93.2 mg (0.429 mmol, 120 eq.) 15N-hexyl-N’-(4-methylphenyl)carbodiimide, 1.6 mg (0.0036 mmol 1.0 eq.), and 0.42 mL dry CHCl₃.

Yield: 21 mg (0.097 mmol) yellow solid, 23 %. FTIR (KBr pellet, cm⁻¹): 3047 (w, aryl-H), 3022 (w, aryl-H), 2954 (m, alkyl-H), 2925 (m, alkyl-H), 2858 (m, alkyl-H), 1628 (s, C=N), 1606 (m, C=C).

Poly(15N-hexyl-N’-(4-chlorophenyl))carbodiimide Poly-17: 0.158 g (0.576 mmol, 120 eq.) 15N-hexyl-N’-(4-chlorophenyl)carbodiimide, 1.4 mg (0.0055 mmol 1.0 eq.) Cat-1, and 0.52 mL dry CHCl₃.

Yield: 12 mg (0.052 mmol) white solid, 8 %. FTIR (KBr pellet, cm⁻¹): 3047 (w, aryl-H), 3022 (w, aryl-H), 2954 (m, alkyl-H), 2925 (m, alkyl-H), 2858 (m, alkyl-H), 1628 (s, C=N), 1589 (m, C=C).
**Poly($^{15}$N-hexyl-$^{15}$N’-hexyl)carbodiimide Poly-18:** 0.49 g (2.32 mmol, 120 eq.) $^{15}$N-hexyl-$^{15}$N’-hexyl)carbodiimide, 4.9 mg (0.0194 mmol, 1.0 eq.) of **Cat-1** and 1.79 mL dry CDCl$_3$.

Yield: 0.13 g (0.617 mmol) white solid, 27 %. FTIR (KBr pellet, cm$^{-1}$): 2956 (m, alkyl-H), 2927 (m, alkyl-H), 2856 (m, alkyl-H), 1637 (s, C=N). $^1$H-NMR (300 MHz, CDCl$_3$): δ (ppm) 4.10 (2H, board), 3.13 (2H, board singlet), 1.30 (12H, board doublet), 0.88 (6H, board singlet). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): δ (ppm) 132.9 ($^{15}$N=C, 1N), 1.7 ($^{15}$N–C, 1N).
Poly($^{15}$N-hexyl-$N'$-propyl)carbodiimide Poly-19: 19.2 mg (0.113 mmol, 120 eq.) $^{15}$N-hexyl-$N'$-propylcarbodiimide, 0.2 mg (0.0001 mmol 1.0 eq.) of Cat-1, and 0.10 mL dry CHCl$_3$.

Yield: 10 mg (0.05 mmol) white solid, 53 %. FTIR (KBr pellet, cm$^{-1}$): 2958 (m, alkyl-H), 2929 (m, alkyl-H), 2858 (m, alkyl-H), 1637 (s, C=N). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 3.14 (4H, broad), 1.30 (10H, very broad doublet) 0.89 (16H, broad singlet). $^{15}$N-NMR (40.5 MHz, CDCl$_3$): $\delta$ (ppm) 133.5 ($^{15}$N=C, 1N), 2.0 ($^{15}$N–C, 1N).

(R)-Poly($N$-hexyl-$N'$-benzyl)carbodiimide Poly-22: 0.69 g (3.21 mmol, 97 eq.) $N$-hexyl-$N'$-benzyl)carbodiimide, and 15 mg (0.059 mmol 1.0 eq.) of Cat-2, solvent free.
Yield: 0.32 g (1.48 mmol) yellow solid, 55 %. FTIR (KBr pellet, cm\(^{-1}\)): 3083 (w, aryl-H), 3058 (m, aryl-H), 3027 (m, aryl-H), 2955 (m, alkyl-H), 2927 (m, alkyl-H), 2857 (m, alkyl-H), 1654 (s, C=N), 1637 (s, C=N), 1583 (m, C=C).

**Poly(\text{N-(4-n-butylphenyl)-N' benzyl})carbodiimide Poly-23:** 2.96 g (11.22 mmol, 118 eq.) N-(4-n-butylphenyl)-N'-benzyl)carbodiimide, and 24.0 mg (0.095 mmol 1.0 eq.) of **Cat-1**, solvent free.

Yield: 1.98 grams (7.71 mmol) white solid, 55 %. FTIR (KBr pellet, cm\(^{-1}\)): 3061 (m, aryl-H), 3031 (m, aryl-H), 2955 (s, alkyl-H), 2927 (s, alkyl-H), 2857 (s, alkyl-H), 1625 (s, C=N), 1601 (m, C=C).

### 3.8 References


Chapter 4: Biofilm Inhibitors Covalently Tethered to Polymer Materials

4.1 Bacterial Biofilms

A departure from polyguanide and polycarbodiimide research, studies were also undertaken on the covalent tethering of biofilm inhibitors to polymer surfaces. This chapter is focused on the development and validation of polymers, of medical relevance, which inhibit \textit{Acinetobacter baumannii} from forming biofilms by the use of Oroidin derived additives. This work was done in collaboration with the Melander Group at North Carolina State University, Raleigh, NC.

4.1.1 Introduction

Over three quarters of the microbial infections are associated with bacterial biofilms.\textsuperscript{1} Biofilms, communities of surface attached microorganisms encased in robust extra-cellular matrices,\textsuperscript{2} are a serious threat to public health, in particular individuals whom rely on indwelling medical devices (IMD).\textsuperscript{3} Of this vulnerable population, 4.5 in every 100 admissions of hospital patients being infected with gram-negative bacteria originating from biofilms.\textsuperscript{4} Compounding the humanitarian impact, there is a significant financial consequences associated with biofilm infections. It is estimated that the cost associated with fighting biofilm infections in the US which can be in excess of $5 billion annually (2010). IMD-associated infections are tenacious given their 1000-fold increased resistance to antibiotics over the bacteria in the platonic state.\textsuperscript{5} In most cases, the effective course of action is replacement of the IMD which poses a new set of risks for the patient (e.g., replacement of
a heart valve). Of these biofilm-induced infections, *Acinetobacter baumannii*, gram-negative bacteria, is becoming one of the more aggressive bacterial infections associated with IMD.\(^6\)

4.1.2 Anti-biofilm Inhibitors Derived from Oroidin

Oroidin has been the focus and inspiration as a scaffold for the development of biofilm inhibitor research in the Melander Group\(^7\) and has since garnered some attention of scientific community at large.\(^8\)

![Figure 4.1: Oroidin scaffold.](image)

Oroidin is a class of marine alkaloids isolated from the marine sponges, and from that natural product motif, thorough structure-property relationship analysis was done to determine and exploit the specific sites and functional groups of biology activity.\(^9\)\(^-\)\(^12\)

4.1.3 Biomaterials in Medical Applications

The use of polymer and composite materials, natural or man-made, in the human body dates back to early civilization.\(^13\) The ancient Egyptians were known to replace facial organs with artificial materials as found in Egyptian mummies. Many of these materials only fulfilled the most basic of needs of the times. Through the centuries of human development these biomaterials garnered more widespread use and modernation.\(^14\) Medicine practiced
today utilizes a wide range of biomaterials in virtually all aspects of health and beauty. Of particular interest in this text is the use of biomaterials for indwelling medical devices (IMD) and implants, such as heart stints, pacemakers, catheters, contact lenses, to name a few. To tackle these applications, scientists in the medical and materials fields have developed a large arsenal of composite biomaterials such as poly(meth)acrylate, polysiloxanes, polyurethanes, polycarbonates, glass fibers, and carbon fibers. Combinations of biomaterials are used to maximize physical properties as appropriate for the application, structural, and biological compatibility, i.e., flexible poly(2-hydroxyethyl) methacrylate with polysiloxane co-polymers for contact lens while carbon fibers and poly(methylmethacrylate) are used for rigid bone plates. The critical factors for choosing the appropriate biomaterial is a multileveled scheme based on physical property considerations in order of most important down: 1) chemical characteristics such as bulk properties, yield strength, tensile strength, density, etc, 2) adhesion and surface topology, 3) biofunctionality, i.e., bioinert versus bioactive, and 4) processing and fabrication. Few biomaterials fulfill all the requirements, therefore combinations of polymers and composites are common place.

4.2 Covalent Tethering of Biofilm Inhibitor

In recent years there has been some progress in understanding and eradicating bacterial biofilms from IMD surfaces. A few of the recent strategies implemented in addressing this issue include the incorporation of antimicrobial compounds such as silver salts or quaternary ammonium salts to the surface of the IMD,\textsuperscript{15, 16} and the impregnation of
antibiotics into the devices for delayed release while in use.\textsuperscript{17} Both of these methods have suffered from short-term efficacy mainly due to their mode of action, i.e., prevention of biofilm formation but way of bacterial death, as the bacterial residue promotes further biofilm formation. We selected from the family of Oroidin derivatives developed by Melander et al., a potent \textit{Acinetobacter baumannii} biofilm inhibitor 2-aminimidazole alkyne, 1, which has an IC\textsubscript{50} of 13 \(\mu\)M. From there we attempted to covalently link 2 to a polymer surface.

![Figure 4.2: Anti-biofilm inhibitor 2-aminimidazole alkyne 1, methacrylate functional 2.](image)

We are targeting polymers presently being used in the medical field for IMD. In this work, we elected to focus on a combination of polyurethane/polymethacrylate co-polymers. The polyurethane diisocyanate prepolymer (\(M_n \sim 2000\)) was first functionalize with methacrylate end groups to allow it to act as a crosslinker with the methacrylate co-monomers, 3. Next, the biofilm inhibitor 1 was further functionalized via alkyne/azide (Click) cyclization with an azide possessing a methacrylate tail to be used as a co-monomer in a UV-initiated photo-polymerization. The alteration of 1 to 2 had minimal impact on the IC\textsubscript{50} value, IC\textsubscript{50} 13 vs. 16 \(\mu\)M, against \textit{Acinetobacter baumannii}. 

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Crosslinked polymer films possessing 2 in concentrations 0.4 to 8.1 wt.% (3-co-2) were prepared, via UV photo-polymerization, and studied. The balance of the formulation composed of isobornyl methacrylate monomer and 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-propyl)ketone at 2.0 wt. % as the photoinitiator. It was found that at under 0.8 wt. % 2 there was no significant biofilm reduction but at the higher concentrations the biofilm formation was reduced as seen in Figure 4.4.

**Table 4.1:** Formulations of photo-polymerization polymer films.

<table>
<thead>
<tr>
<th></th>
<th>Control: 3 and 3-co-4</th>
<th>3-co-2 and 3-co-4-co-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isobornyl methacrylate</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Photoinitiator</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Photoinitiator: 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-propyl)ketone
Figure 4.4: Polymer strips (from left to right), Control, L₁ 8.1%, L₂ 4.1%, L₃ 1.7%, L₄ 0.8%, and L₅ 0.4% of 2 in 3-co-2. For simplicity, the nomenclature here denotes –co– for photocrosslinked samples and –blend– for blended prepolymer samples.

There was significant phase separation of the 2 deriving from the heterogeneity of the formulation. The 2-aminoimidazole subunit of 1/2 is quite polar in contrast to the relatively non-polar isobornyl methacrylate and the polyurethane methacrylate oligomer 3. This phase separation during preparation and photocuring proved to be problematic (vide infra). From these preliminary results it can be reported that the activity of this class of biofilm inhibitors is not adversely affected or compromised when rendered immobile by covalently tethering to a surface. Therefore, the next step is to quantitatively explore this phenomenon with a 4.0 wt. % concentration of 2 in polymer films, with different crosslinkers and crosslink densities.

With this active co-polymer (3-co-2) in hand we proceeded to quantify activity and determine the leachablility of 2 from 3-co-2 and quantify any resulting loss of activity. A
control crosslinked co-polymer and 3-co-2 were soaked in DI water for 24 hours to remove any loose material from the surface. Following this soak, 3-co-2 inhibited biofilm formation up to 80 % when compared to the control. The leaching study was expanded to include 2 weeks in DI water and 24 hours in methanol. Unfortunately, these samples both demonstrated a significant loss in bioactivity. The materials extracted from the methanol presoak were determined to be low molecular weight compounds with crosslinked solids identified as mainly homopolymer of 2 by IR. Homo-polymerization of 2 is believed to be caused by the phase separation of the prepolymer and 2 during polymerization leading to low copolymerization. In order to compensate for the phase separation and prevent loss of activity from leaching, the crosslink density of the 3-co-2 need to be increased. Hence, the crosslinker, 4, (Figure 4.3) was prepared and utilized in conjunction with 3. Introduction of 4 was accomplished by the addition of 30 mol % excess toluene diisocyanate during the polyurethane methacrylate synthesis of 3. The residual isocyanate units were capped by 2-hydroxyethyl methacrylate. The crosslinker 4 is a common and expected byproduct when synthesizing 3 as seen in the SEC curves in Figure 4.5. The concentration of 4 varies from batch to batch, but by increasing the ratio of isocyanate and therefore the methacrylate present, increases 4 in concentration. As a consequence of this alteration, the Mn, Mw, and polydispersity are all decreased for the polyurethane methacrylate oligomer, 3-blend-4, by decreasing the chain extension. The resulting photocured polymer films, 3-co-4-co-2, inhibited biofilm formation of 74% following 2 weeks leaching study in DI water at 25 °C, 72% following 24 hours in methanol at 25 °C, and 80% following 24 hours in hexane at 25
°C when compared to the control. As a control experiment, 3-co-4-blend-1 was prepared with 1, the biofilm inhibitor without the methacrylate tether. The alkyne functional inhibitor was formulated and photo-polymerized in the same ratios as used for 3-co-4-co-2. Following 24 hours leaching studies in DI water, 3-co-4-blend-1 inhibited biofilm formation with an activity of 83 % suggesting short immersions in water cannot extract 1, however, all bioactivity was lost when 3-co-4-blend-1 was exposed to methanol.

Figure 4.5: GPC curves for 3 (left) and 3-blend-4 (right). Both 3 and 3-blend-4 contain 4 as a byproduct of synthesis of a polyurethane methacrylate.* denote residual solvents.
Next, Scanning Electron Microscope (SEM) imagining of the control and 3-co-4-co-2 was employed. Following bacterial exposure for 24 hours at 37 °C and crosslinking of the biofilm using glutaric aldehyde and ethanol; the presence of 2 in 3-co-4-co-2 is clearly visible in Figure 4.6. In addition, there appears to be no topologic defects observed between the control and 3-co-4-co-2 as a result of bacterial exposure and biofilm inhibition.

![SEM images](image)

**Figure 4.6:** SEM images. **A.** Control polymer, 3-co-4, exposed to bacteria for 24 hours; **B.** 3-co-4-co-2 exposed to bacteria 24 hours.

Verifying the presence of 2 on the surface of 3-co-4-co-2 was first attempted with the use of solid state CP/MS 13C-NMR. The concentration of 2 was increased to 10 wt. % to maximize the sensitivity of the carbon-13 detection. There were no detectable differences in the 13C-NMR spectra of polymer films with or without 2. Next X-ray photoelectron spectroscopy (XPS) was attempted to confirm the present of 2 on the surface of the polymer film. The surface of the control and 3-co-4-co-2 contained carbon (1s), nitrogen (1s), and
oxygen (1s), however there was a noticeable increase in the content of nitrogen (from 1 to 7%) while a decrease of oxygen (from 24 to 18%), relative to the 3-co-4 control sample. Furthermore, in line with increasing concentrations of 2, there was an emergence of 1% chloride (2p) on the surface attributed to the hydrochloride salt of the 2-aminomidazole head. From these results it can be concluded that there is a disproportionate concentration of 2 present at the polymer surface relative to the expected of a well distributed system of 4.0 wt. %. This is consistent with the surface active polar 2 (the active biofilm inhibitor) reorganizing to concentrate at the air-surface interface.
Figure 4.7: XPS Spectra of 3-co-4 (control) and 3-co-4-co-2 (sample).
4.3 Conclusions

The biofilm inhibitors based on Oroidin derivatives show vast fluctuations in activity with seemingly modest structural change. With this backdrop, we have shown that it is possible to modify the Oroidin derivatives in such a way as to incorporate polymerizable groups and incorporate these active components within a polymer without compromising their bioactivity. Moreover, biofilm formation of Acinetobacter baumannii was inhibited up to 73% compared to the control that lacked the inhibitor. Losses in bioactivity activity due to leaching were overcome by increasing the crosslink density of the matrix without significantly changing the physical properties of the polymer. $3\text{-co-}4\text{-co-}2$ provides a resilient, bio-relevant polymer resistant to biofilm formulation even after exposure to polar and apolar solvents. These studies also reinforce the importance of covalently tethering the bioactive component, 2, to the polymeric substrate (in this case through copolymerization of methacrylate side-chains). Without covalent bonding, comparable materials with blended 1 will stand short durations exposed to water (24 hours) but lose their activity when exposed to methanol.
4.4 Experimental

4.4.1 Materials

All reagents, monomers and prepolymer were purchased from Sigma-Aldrich and used without further purification, unless otherwise stated. Dr. Lingling Peng of the Melander Group synthesized and supplied the active compounds 1 and 2.

4.4.2 Instrumentation

The photo-polymerization was accomplished using a Hanovia 450 W broadband UV-lamp (Fairfield, NJ). Scanning Electron Microscope images were obtained using a JEOL 6400F Field Emission SEM and the X-ray photoelectron spectra using a Riber XPS, both of which are housed at the North Carolina State University Analytical Instrumentation Facility. Infrared spectral data was collected using a Jasco FT/IR-410 Infrared Spectrophotometer (Easton, MD). Molecular weight and polydispersity was collected size exclusion chromatography (SEC) utilizing a high pressure pump set at 1.5 mL/min (~600 psi) HPLC Grade THF, Waters LC Spectrophotometer UV detector Lambda-Max Model 481, a single Jordi-Gel DVB 1000A column fitted with a guard column, and a Linear Chart Recorder located at the Gorman Group. The SEC was calibrated against polystyrene standards.
4.4.3 Synthesis of Prepolymers

Polyurethane Methacrylate Oligomer (3): Prior to starting reaction, poly(tetrahydrofuran) polyether polyol was placed in an 80 °C oven for two hours to facilitate use. To a clean, dry 250 mL three neck round bottom flask, 50 mL toluene was added with a magnetic stir bar, fitted thermometer, and placed over an oil bath. The reaction vessel was connected to a nitrogen stream and to the solution 11.9 mL (14.5 g, 166.1 mmol, 2.0 eq.) of 2,4-toluene diisocyanate was added via a syringe. In one addition 84.6 g (83.0 mmol, 1.0 eq.) of melted poly(tetrahydrofuran) polyether polyol is added to reaction mixture in one addition. The reaction solution was heated to 80 °C; once the reaction temperature reached 60 °C, 110 mg (1000 ppm based on the polyol) of 1,4-diazabicyclo[2.2.2]octane (DABCO) was added to catalyze the reaction, this resulted an immediate increase in temperature to 80 °C. Following two hours at 80 °C, the solution was air cooled to 60 °C and the remaining reagents were added; 10.8 g (83.0 mmol, 1.0 eq.) of 2-hydroxyethyl methacrylate and 50 mg (500 ppm based on the oligomer) 4-methoxyphenol. The reaction was kept at 60 °C and covered with aluminum foil to block ambient light for an additional 8 hours. Toluene was removed via reduced pressure evaporation followed by 2 hours under high vacuum.

Yield: 86 g of a clear, viscous liquid, quantitative yield. FTIR (thinfilm, cm⁻¹): 3302 (s, N-H), 3024 (s, aryl-H), 2941(s, alkyl-H), 2858 (s, alkyl-H), 1728 (s, C=O), 1535(s, C=C). GPC: Mₙ = 4703, Mₘ = 9436, PDI = 2.000.
Polyurethane Methacrylate Oligomer (3-blend-4): Following the same procedure as 3: 10.0 mL (12.1 g, 69.5 mmol, 2.2 eq.) of 2,4-toluene diisocyanate, 64.3 g (31.6 mmol, 1 eq.) of poly(tetrahydrofuran) polyether polyol, 86 mg (1000 ppm based on the polyol) of 1,4-diazabicyclo[2.2.2]octane (DABCO), 9.9 g (75.8 mmol, 1.2 eq.) of 2-hydroxyethyl methacrylate, and 43 mg (500 ppm based on the oligomer) 4-methoxyphenol.

Yield: 86 g of a yellow, viscous liquid, quantitative yield. FTIR (thin film, cm\(^{-1}\)):

4.4.4 Photo-polymerization Polymer Films

Polymerization procedure: The polymer films were prepared by thoroughly mixing the components in a 20 mL vial followed by degassing under vacuum (20 in Hg) for two hours. Care must be taken not allow extended periods of time under vacuum which may lead to auto-polymerization. Once degassed, formulation was poured on clean, smooth aluminum foil attached to the bottom of an inverted, glass Petri dish. A second clean, glass Petri dish wish placed on top of the viscous formulation to form a laminated film. The second Petri dish was placed at an in such a way to minimize or completely prevent the formation of air pockets in the laminate. The set up was placed under a 450 W, submersion broad-spectrum UV lamp for 6 minutes for photo-polymerization. The polymerized film was immediately removed by peeling the aluminum foil from one side followed by removing the film from the glass.
4.4.5 X-ray Photoelectron Spectroscopy

**Sample preparation:** polymer films were soaked in deionized water for 24 hours at ambient temperature followed by drying under high vacuum prior to experiment.

4.4.6 Scanning Electron Microscope

**Sample preparation:** Follow bacterial incubation, polymer films were gentle rinsed with a phosphate buffered saline solution then affixed to the polymer surface using 2.5 v/v % solution of gulatric aldehyde in phosphate buffered saline for one hour at room temperature. The polymer films, now with crosslinked biofilms, was dehydrated with 2 mL an aqueous ethanol solution in a stepwise fashion of increasing ethanol concentration for 5 to 10 minutes each at concentrations of 30, 50, 70, 95, and 100%. The washed samples were dried under high vacuum overnight prior to study.
4.5 References


APPENDIX
APPENDIX A: $^{15}$N-NMR Spectra of Reagents

Note: $^{15}$N-NMR spectra of compounds that were used but were not included in the main text.
\(^{15}\text{N-\hspace{1pt}Benzamide L-1}\) (set reference to 0.00 ppm)
$^{15}$N-Heptanamide L-2
$^{15}$N-2-Phenylacetamide L-3

Pulse Sequence: c2pul
Solvent: CC15
Ambient temperature
File: X207-60_phenylacetamide_15N
Mercury-400DS "ncumerc400"

Relax. delay 2.000 sec
Pulse 54.0 degrees
Acq. time 0.928 sec
Width 20000.0 Hz
Windowing on

Observe N15, 39.548177 MHz
Decouple H1, 494.137144 MHz
Power 84 dB
Continuous on

WALTZ-16 modulated

Data Processing
Line broadening 1.0 Hz
FI size 32K
Total time 5 min, 48 sec
Methyl $^{15}$N-phenylcarbamate L-4

Parameters:
- Solvent: CDCl$_3$
- Temperature: Ambient
- Spectral width: 25000 Hz
- ppm range: 300 to -180
- Total time: 50 min, 22 sec

**Diagram:**
A graph showing a single peak at around 7 ppm.
Methyl $^{15}$N-hexylcarbamate L-5
Methyl $^{15}N$-benzylcarbamate L-6
$^{15}$N-(1-hexylamine) hydrochloride L-8
$^{15}$N-hexyl-$^{15}$N-phenylthiourea U-12
$^{15}N,N'$-Dibenzylurea U-13
$^{15}$N-hexyl-$N'$-phenylurea U-14
N-hexyl-15N'-phenylurea U-15
$^{15}$N-hexyl-$N'$-(4-methoxyphenyl)thiourea U-16
$^{15}N$-hexyl-$N'$-(4-methylphenyl)urea U-17
15\textsuperscript{N}-hexyl-\textsuperscript{N'}-(4-chlorophenyl)urea U-18
$^{15}N,N'\text{-di(hexyl)urea U-19}$

- Pulse Sequence: z2pul
- Solvent: CDC13
- Ambient temperature: Mercury-400BB
- Relax. delay 2.000 sec
- Pulse 54.0 degrees
- Acq. time 0.088 sec
- # of scans 64
- # of repetitions
- records 4096, 46.5442399 MHz
- DECUPLER H1, 409.1371451 MHz
- Power 0.1 dB
- Resolution on
- WALTZ-16 modulated
- DATA PROCESSING
  - Line broadening 8.0 Hz
  - FT time 25246
  - Total time 5 min, 40 sec
$^{15}$N-hexyl-N'-propylurea U-20

XJ07-31_15N-hexyl-N-propylurea_15N
Pulse Sequence: s2p3
Solvent: CDCl3
Ambient temperature
Resonance $^{15}$N-hexyl-N-propylurea_15N
Mercury-300BB "nucmerc08"
Relax. delay 2.000 sec
Pulse 8.0 degree
Avg. time 5.500 sec
Width 10000.0 Hz
64 repetitions
Observe N15, 40.692399 MHz
Decoupler H1, 460.137641 MHz
Power 44 dB
Continuously on
SEFT C-13 modulated
B1 offset 8.0 Hz
Line broadening 8.0 Hz
FF size 32/64
Total time 5 min, 45 sec