Chiral Influence on Synthetic Molecules

DISSEPTION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy
in the Graduate School of The Ohio State University

By

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ABSTRACT

Reported are the studies on chiral influence on synthetic molecules such as azobenzene containing oligomers, benzophenone derivatives, and 1, 4, 5, 8-perylenetetracarboxylic acid diimides. Amino acids and other simple, low-cost chiral inducers were used as readily available sources of asymmetric induction. The design of the folded azobenzene oligomer originated from the concept that the architecture of the meta- substituted aromatic groups would force the molecule to assemble into a helix. The stability of this helical formation would be assisted by both \( \pi-\pi \) stacking and hydrogen bonding. The resulting oligomer exists in two enantiomeric helical forms. It was hypothesized that a small chiral perturbation placed at a specific point at the end of the oligomer would then be amplified throughout the length of the entire molecule creating a preference for one-handed sense of the helix over the other antipode. This theory was proven through the use of circular dichroism (CD) spectra. The chiral oligomers were synthesized in two and four turn variants and the induced chirality increased by more than two times with this increase in length. The oligomer was determined to be right-handed or \( P \) sense. This conclusion was reached through interpretation of the CD spectra, computer assisted molecular modeling, calculated CD’s, and through collaboration with Christopher M. Hadad’s research group.
Benzophenone was envisioned as a ligand in asymmetric catalysis. Benzophenone is a chiral-racemic molecule that exists in two enantiomeric, propeller-like forms. It was proposed that after the benzophenone scaffold was appended with a pair of phosphine atoms it can act as a ligand in transition metal catalysis. The ketone moiety could then be manipulated with a chiral amine to form an imine and then this handed perturbation could be amplified through the molecule. The induced chirality would subsequently transfer to the active site of the metal catalyst. Favorable hydrogen bonding interactions the assist in stabilizing the catalyst in its preferred handed form. A benefit of this ligand would be the modularity granted to the catalyst by changing the identity or handedness of the amino acid used for induction. It was observed via CD that the identity of the amine employed had a great effect on the resulting signal and therefore the chiral environment of the pre-catalyst.

Finally, the self-assembly of several one-dimensional nanostructures comprised of 1, 4, 5, 8-perylenetetracarboxylic acid diimides with various imide groups was studied. The imides were altered from simple alkyl chains or several combinations of protected lysine to form amphiphiles and bola-amphiphiles. Perylene was selected because of its many opto-electronic properties that are frequently exploited in intermolecular charge transfer. It was observed through various analytical techniques that the perylene diimides strongly assembled in numerous solvent conditions with the exception of 2,2,2-trifluoroethanol (TFE).
DEDICATION

To the bosses, advisors, and professors and colleagues from my past and present:
For remaining patient, challenging me with different thoughts and ideas, allowing me to
grow and mature at my own rate, reminding me to remain humble, and that cooler heads
will always prevail.

To my parents and the people of West Virginia:
For showing me that some of the most intelligent, talented, skilled, thoughtful, and
resourceful individuals didn’t obtain those traits in the classroom.
ACKNOWLEDGMENTS

I would not have been able to survive in graduate school, let alone succeed without the constant (positive) criticism of Amanda Hofacker. Working next to her was a crash-course in the right and wrong ways to conduct research. There have been many graduate and undergraduate students that have experienced her teachings through me.

I’d like to thank Kazuhiko Mitsui for his constant helpful discussions regarding chemistry; I truly appreciated our informal group meetings. He would always take time out of his day to devise solutions to other group members’ problems. It was not uncommon for him to consider a problem for days to try and help solve some of our difficulties.

Adam Hickernell, Dustin Grieves, and Dan Wilburn of The Science Logic provided me with good times and a great distraction while playing with them. I wish all graduate students could know the relief of redirecting some of their energy and frustration to a place outside of work.

My fellow graduate students here at Ohio State (those in Parquette group and those that weren’t) were a constant source of inspiration, motivation, commiseration, entertainment, and relief and must be recognized for their help. Because of them, graduate school was a blast—if it only weren’t burdened with all that work.
Lastly, I’d like to thank Jon. Without a shadow of a doubt I could not have been able to work for anyone else in graduate school. His patience and understanding is otherworldly. I can only imagine how differently life would have turned out if I had approached another professor with some of the problems and concerns that I brought to Jon. I will miss having a boss that can be helpful and knowledgeable but also can joke around.
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Research Publications


FIELDS OF STUDY

Major Field: Chemistry
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<td>------------</td>
</tr>
<tr>
<td>α</td>
<td>alpha</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
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<td>Ala</td>
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</tr>
<tr>
<td>Alloc</td>
<td>allyloxy carbonyl</td>
</tr>
<tr>
<td>Anal.</td>
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</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>b</td>
<td>broad (IR and NMR)</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary-butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>C or $^{13}$C</td>
<td>carbon</td>
</tr>
<tr>
<td>°C</td>
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</tr>
<tr>
<td>calc.</td>
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<tr>
<td>CCl₄</td>
<td>carbontetrachloride</td>
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CD    circular dichroism
CDCl₃  deuterated chloroform
CH₂Cl₂  dichloromethane/methylene chloride
CHCl₃  chloroform
CH₃CN  acetonitrile
(COCl)₂  oxalyl chloride
δ    chemical shift in parts per million downfield from tetramethylsilane
d    doublet (spectra); day(s)
DABCO  1,4-diazabicyclo[2.2.2]octane
DCM   dichloromethane/methylene chloride
DIPEA  N,N-diisopropylethylamine
DMAP  4-(N,N-dimethylamino)pyridine
DMF   N,N-dimethylformamide
DMSO  dimethylsulfoxide
dpp   diphenyl phosphine
dppe  1,2-bis(diphenylphosphino)ethane
dppp  1,2-bis(diphenylphosphino)propane
ee    enantiomeric excess
EI    electron impact
eq.   equivalent
ES    electrospray
Et    ethyl
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<thead>
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<td>Et₃N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethyl alcohol</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>H or ^1^H</td>
<td>proton</td>
</tr>
<tr>
<td>H₂</td>
<td>hydrogen</td>
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<td>h</td>
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</tr>
<tr>
<td>Hg</td>
<td>mercury</td>
</tr>
<tr>
<td>HNO₃</td>
<td>nitric acid</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz (NMR)</td>
</tr>
<tr>
<td>k</td>
<td>kilo</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>L</td>
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<tr>
<td>LiAlH₄</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>lit.</td>
<td>literature</td>
</tr>
<tr>
<td>m</td>
<td>milli; meter(s); multiplet (NMR)</td>
</tr>
<tr>
<td>µ</td>
<td>micro</td>
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</table>
M  moles per liter
MALDI  matrix assisted laser desorption ionization
Me  methyl
MeOH  methyl alcohol
MgSO₄  magnesium sulfate
MHz  megahertz
min  minute(s)
mol  mole(s)
MOM  methoxy-methyl
mp  melting point
MS  mass spectrometry; molecular sieves
m/z  charge to mass ratio
NaH  sodium hydride
NBS  N'-bromosuccinimide
nm  nanometer(s)
NMR  nuclear magnetic resonance
OAc  acetate
Obsd  observed
p  para
Pd-C  palladium on carbon
Pd(PPh₃)₄  tetrakistriphenylphosphine palladium
Ph  phenyl
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<td>PPh₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR); second(s)</td>
</tr>
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<td>SOCl₂</td>
<td>thionyl chloride</td>
</tr>
<tr>
<td>t</td>
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<tr>
<td>t</td>
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<td>TBS</td>
<td>t-butyldimethylsilyl</td>
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<td>triethylsilyl</td>
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<tr>
<td>TMS-Cl</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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</tbody>
</table>
CHAPTER 1

CHIRAL INDUCTION IN SYNTHETIC HELICAL OLIGOMERS

1.1 Introduction

Synthetic chemical systems that adopt folded geometries are of interest because they can be designed to mimic bio-macromolecules such as the form and function of proteins.\textsuperscript{1,2} There has been much focus on the topic of chiral folded oligomers.\textsuperscript{3} Their specifically handed, well-defined secondary structure could possibly be used for asymmetric catalysis or other sophisticated chemical functions such as chiral recognition and self-assembly.\textsuperscript{4} Folding has been induced via various methods such as solvophobicity,\textsuperscript{5} aromatic stacking,\textsuperscript{6} metal coordination,\textsuperscript{7} and intramolecular coordination\textsuperscript{8} among others.

The various techniques to introduce asymmetry to synthetic systems can include the use of chiral guests\textsuperscript{9} or chiral groups placed on the internals\textsuperscript{10} or the periphery\textsuperscript{11} of the molecule or as a side chain.\textsuperscript{12} Additionally, chirality can be introduced from a single point source or be used in a repeat unit of short oligomers. The ability to control the chirality of these supramolecular molecules is novel in the creation of biomimetic molecules.\textsuperscript{13}
1.2 Methods of Chiral Induction

1.2.1 Chirality Introduction via Host/Guest Interactions

The Moore group has synthesized an achiral hydrophobic phenylene ethynylene oligomer that folds in polar organic solvents. In nonpolar organic solvents, the molecule is denatured and adopts a random, unfolded state. The oligomer folds due to the meta-linkage between the aromatic groups producing a favorable cyclical geometry combined with solvophobic conditions stemming from hydrophobic aromatic groups appended by hydrophilic end groups. In the absence of chiral information, the oligomer exists in both right and left-handed helical antipodes. A chiral guest was designed to fit into the interior of the oligomer; upon its introduction, the handedness is imparted to the overall structure as viewed by circular dichroism (CD) spectra (Figure 1.1). The highest binding affinities were achieved when the host oligomer was matched perfectly in size with the chiral guest rod (Figure 1.2). In later studies, it was discovered the addition of HCl to form the piperazinium dihydrochloride salt increased the binding affinity of the oligomers.
In an example of dynamic combinatorial chemistry, Moore has also utilized his oligomer scaffold to explore the use of templation in driving self-assembly.\cite{Moore2015}
Several varying lengths of his phenylene ethynylene oligomer, all functionalized with a terminal imine residue, were allowed to equilibrate under favorable metathesis conditions. In the absence of a template, the reaction results in a mixture of oligomers of varying lengths (Figure 1.4b), however when the template was introduced, a single isomer dominates the products (Figure 1.4c). The results of the binding assays were studied via high performance liquid chromatography (HPLC).
1.2.2 Chirality in Repeat Units of an Oligomer

A facile method for the introduction of handedness to an oligomer is to attach the chiral residue to the repeat unit of the oligomer; doing so insures that the monomer chirality is expressed explicitly throughout the molecule.\textsuperscript{16} This technique should direct favorable interactions between the bulky chiral substituents further reinforcing the stability of the resultant structure.\textsuperscript{17} As illustrated in Figure 1.5, the Moore group again utilized their phenylene ethynylene oligomer by appending the repeat units with an optically active poly-ether chain.\textsuperscript{18}

\begin{figure}
\centering
\includegraphics{figure1.4.png}
\caption{HPLC traces after the metathesis reactions (a) in CHCl\textsubscript{3}, (b) in CH\textsubscript{3}CN and (c) in CH\textsubscript{3}CN in the presence of piperazine binding ligand}
\end{figure}
The researchers related that the introduction of the chiral methyl group did not destabilize the resulting helix in relation to the control compound that possessed the same chain length dependence properties as the chiral analog.

Yokozawa used a similar technique in the synthesis of helical polymers consisting of a $N$-alkylated poly($p$-benzamide) scaffold (Figure 1.6). The dynamic polymers readily interconvert between two helical antipodes and a chiral influence results in a shift toward the more preferred geometry. The researchers hypothesized the driving force behind helix formation is the cis- conformation of the amide bonds that comprise the backbone of the polymer and $\pi$-$\pi$ stacking between aromatic monomers. X-ray crystallography confirmed the helical nature of the polymer in the solid state and temperature-dependant CD spectra confirmed helicity in solution.

This work relates two important requirements: a flexible backbone to allow the different twist-senses of a helix to equilibrate towards the more energetically desirable state; and that even a small chiral source is sufficient for the amount of chiral induction that can be amplified through cooperative interactions.
1.2.3 Chirality at Core

2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) is a axially chiral compound that is capable of existing in one of two stable enantiomeric rotomers.\textsuperscript{10} Due to steric constraints, the interconversion between the two helical antipodes is energetically disfavored under normal reaction conditions. Turning again to the phenylene ethynylene system, Moore functionalized the central portion of the molecule with a ether functionalized binaphthyl unit at the 7 and 7' positions.\textsuperscript{20}

By varying the lengths of the phenylene ethynylene oligomer on either side of the BINAP, unit the researchers determined that the greatest amount of chirality was expressed when the binaphthyl unit was located at the absolute center of the chain where length of both side groups were equal (n = n, Figure 1.7) as opposed to placement closer to one end of the oligomer.
Later, the Moore group substituted their BINAP inducer for a tartaric acid residue placed at the center of their flexible phenylene ethynylene oligomer. They found that
by varying the protecting groups on the central alcohol residues, they could affect the extent of chirality expressed in the helix. The larger trimethyl silyl groups resulted in an increase in CD signal in relation to the smaller methyl or ketal groups (Figure 1.9). In this example, steric bulk is the force that drives the helical bias to one diastereomeric form.

![Figure 1.9: Moore’s internally chiral phenylene acetylene oligomer](image1.png)

![Figure 1.10: CD Spectra in acetonitrile of compounds in Figure 1.9](image2.png)
1.2.4 Chirality at Periphery

Huc was able to create an amphipathic oligomer comprised of amides of various aromatic amino acids. Quinoline monomer units directed intramolecular hydrogen bonding between adjacent amide groups to further impel helix formation (Figure 1.11). Polar ether side chains were introduced to further facilitate folding in polar solvents in an attempt to grant solubility under biological conditions while additionally shielding the hydrophobic quinoline moiety from the polar solvent environment. The researchers were able to confirm the helical nature in the solid phase by the use of X-ray crystallography and by various $^1$H-NMR techniques in solution phase.

![Figure 1.11: Huc’s amphipathic aromatic amino acid oligomer](image)

Huc continued work on his oligo-quinoline scaffold with the introduction of a chiral group at the end of the oligomer chain (Figure 1.12). The chiral information for his system originated from a single point source at the periphery of the molecule and through coordinatively coupled equilibria, propagated throughout the oligomer’s length. Figure
1.13 illustrates the presence of chirality as viewed by the CD spectra in the solution phase.

Due to energetic constraints, a crystal originating of the predominant diastereomeric form could not be obtained. The crystals contained both right handed and left handed diastereomers regardless of the optical purity of the inducer; this unfortunate consequence originates from the tendency of right and left handed oligomers to co-crystallize in centro-symmetric packing.12,23-26

Figure 1.12: Huc’s various chiral quinoline oligomers
The ability to assign a particular helical handedness resulting from a specific enantiomer of the chiral inducer of a folded oligomer is quite difficult. As a novel solution, Huc synthesized a racemic analog allowing the two enantiomers to co-crystallize thereby specifically deducing the handedness of the synthesized oligomers specific to the stereoisomer of chiral perturbation used (Figure 1.14).27
Chen has also generated a chiral oligoamide helix with a small, terminally appended inducer. Additionally, the researchers were able to transition the secondary structure from a random coil to a specifically handed foldamer through changing the pH (Figure 1.15). With the addition of triflic acid the phenanthroline nitrogens become protonated and interrupt the intramolecular hydrogen bonding by the rotation of adjacent groups.
This rotation results in the irregular introduction of steric bulk in the area of the folded oligomers. A titration experiment was monitored via CD spectroscopy to characterize the denaturation and the helical structure was characterized by \textsuperscript{1}H-NMR and 2D NOESY. (Figure 1.16).

Figure 1.15: Denaturing chiral oligomide foldamer

Figure 1.16: Chiral oligomide foldamer
Light as stimuli to induce changes in synthetic molecules has several advantages such as the absence of invasive changes in solvent, pH, concentration, or the use of other additives. Azobenzene as a specific means to alter the physical properties of synthetic molecules is the focus of much attention because of the functionality’s response to mild external stimuli and full reversibility between the trans- and cis- isomers. This trait, in particular, can be exploited in devices for reusable binary data storage by possessing both an off and on (0 and 1) state or for control of light-harvesting.
The Wang group has reported a folded bi-aryl compound containing a chiral imide whose handedness was controlled via the isomerization of a sterically congested azobenzene unit (Figure 1.18, left). Isomerization of the azobenzene to the Z isomer with 340 nm light places the steric bulk of the two phenyl rings away from each other. The result is a stable form of the opposite helical antipode. The lifetime of both forms was not reported.

Recently Haberhauer has related a bridged macrocycle that utilized azobenzene as a reversible switch for chirality.\textsuperscript{32} Azobenzene exists in two different enantiomeric forms while in its cis- conformer (Figure 1.20). Through irradiation with circularly polarized light, the researchers were able to obtain only one form of the two possible cis- isomers. As this unit was appended to a large chiral cyclic imidazole containing peptide, isomerization back to the stable trans- form is suppressed. The ability to repress this
back isomerization is important to the retention of data when azobenzenes are used in memory devices.

![Haberhauer’s Chirality Switch](image)

**Figure 1.19:** Haberhauer’s Chirality Switch

![Light-induced switching](image)

**Figure 1.20:** Light-induced switching of azobenzene (bidirectional) and of the chiral azobenzene derivative (unidirectional).

In another use of BINAP has a chiral inducer, Takaishi has appended a BINAP unit with azobenzene joined by an ether linkage (Figure 1.21). With isomerization of
azobenzene, the BINAP units changed their dihedral angle. The researchers were unable to completely reverse the chirality of the BINAP moiety.

Figure 1.21: Takaishi’s chiral BINAP switch

Figure 1.22: (a, b) CD spectra (c, d) Absorption spectra after 365 nm irradiation (blue solid and dashed lines), after 436 nm irradiation (red solid and dashed lines)
1.3 Azobenzenes Incorporated into Oligomers

The creation of materials responsive to external stimuli is central to understanding how to control the secondary structure of supramolecular architectures and mimic the behavior of natural systems. The Hecht group synthesized a Moore-type phenylene ethynylene oligomer containing a single azobenzene residue (Figure 1.23, left).\textsuperscript{34,35} The authors hypothesized that when irradiated with UV light, the central azobenzene bond would be disrupted resulting in a fully unfolded state.

![Figure 1.23: Hecht’s chiral azobenzene containing oligomer (left). Changes in the CD spectra with exposure to UV light (right).](image)

Chirality was introduced to the compound by the central triethylene glycol units that were appended with a handed methyl group. As can be viewed in the CD spectra in Figure 1.23 (right), the chiral oligomer experiences very little change when the molecule is irradiated with UV light. This lack of conformational movement was also supported
by the lack of significant changes in the UV spectra (Figure 1.24, inset). The authors were unable to reason why the proposed method for folding and unfolding did not function as designed; a possible explanation for this drawback is discussed below.

The Parquette group has synthesized a folded oligomer consisting of alternating pyridinedicarboxamide/$m$-(phenylazo)azobenzene subunits (Figures 1.25 and 1.26).\textsuperscript{36} The forces that drive the folding ($\pi-\pi$ stacking, meta-connectivity, and intramolecular hydrogen bonding) will be discussed in more detail the following chapter. The oligomer’s folded state was revealed by NOE spectroscopy and anisotropic field shifts in $^1$H-NMR (Figure 1.27). As the length of the molecule grows, the signals for the internal protons are increasingly shifted up-field due to shielding by the aromatic rings of the helix within the folded portion of the oligomer.
The forces that dictate folding are very strong; unfortunately, they also lead to several unforeseen effects. As chain length increases, the amount of isomerization ($E \rightarrow Z$) of the internal azobenzene bonds decreases. This lack of isomerization is due to the stability of the folded oligomer from $\pi-\pi$ interactions and hydrogen bonding. Therefore
isomerization of the azo bonds does not disrupt the helix and result in a globally unfolded state. Additionally, the molecule does not exist in a fully unfolded state in any given solvent or temperature conditions. The stability of the helix morphology results in this resilience to denaturation. This reduction in internal isomerization is a design element that will be exploited in the next chapter.

Figure 1.28: Determination of helical interconversion barrier of four-turn oligomer

An important piece of evidence of the molecule’s folded geometry is illustrated in Figure 1.28. As the temperature of a solution of the four-turn oligomer is decreased, the Cbz- methylene peak as observed by $^1$H-NMR transition from a singlet into a pair of doublets. The reason for this phenomenon is these protons experience different
environments in different handed forms and become diasterotopic. As the barrier to interconversion between the right and left-handed helical antipodes slows, one proton points to the interior of either the $M$ or $P$ helix, and the other points away. As a consequence of this observation, it is hypothesized that chiral information could be placed at this key methylene position and could impart a handed influence. This asymmetric induction would then be propagated throughout the molecule. These design elements will be explored in the next chapter.

1.4 Conclusions

Chiral induction can originate from many sources. The rational design, synthesis, study, and application of these synthetic systems are important in furthering the understanding of the operation of biological processes. Currently the ability to mimic the high degree of complexity associated with natural systems is unattainable, however the recent developments in the field of chiral induction in synthetic systems are an important means to elucidate nature’s mysteries. With these tools, a chemist could solve the energy crisis by synthesizing more efficient light harvesting systems; designing smarter pharmaceuticals capable of controlled release; or in environmentally friendly synthetic materials.
1.5 References


CHAPTER 2

PHOTOMODULATED CHIRAL INDUCTION IN HELICAL AZOBENZENE OLIGOMERS


2.1 Introduction

The design of supramolecular structures that mimic the folding and dynamics of biological molecules has emerged as a promising strategy to combine structure with function in abiotic systems. Molecular helices are ubiquitous in natural systems and has served as the inspiration for numerous strategies to induce helicity in synthetic oligomers.

Helical systems provide the potential to amplify weak or small chiral influences via coupled equilibria that propagate local perturbations throughout the helical backbone resulting in the predominance of a single helical sense. This type of chiral amplification necessitates the molecule has a dynamic nature with infrequent, highly mobile helical reversal points that interconvert the helical antipodes. The ability of such dynamic systems to amplify small chiral perturbations appears to be a general phenomenon among fluxional helical oligomers, polymers, and supramolecular assemblies. This chapter relates that helical oligomers composed of alternating
pyridine-2,6-dicarboxamides and \( m \)-(phenylazo) azobenzenes adopt a preferred helical sense upon attachment of L-alanine at the terminal positions. Irradiation with 350 nm light induces a predominant \( E \rightarrow Z \) photoisomerization of the terminal azo linkages, which decouples the helix and terminal interactions in a manner that suppresses chiral amplification.

### 2.2 Folded Oligomers

#### 2.2.1 Research Design

Earlier work in our group described a series of oligomers composed of repeating azobenzene chromophores exhibiting conformational properties ideally suited to permit the induction of a helical handedness.\(^{36}\) Particularly, the oligomer exists in two enantiomeric helical forms. These oligomers adopt remarkably stable helical conformations lacking an observable unfolded state in both polar and nonpolar media. However, NMR line shape studies indicated a highly dynamic equilibrium interconverting the \( M \) and \( P \) helical antipodes with energetic barriers ranging from 11.1 to 13.8 kcal/mol for two- and four-turn helices, respectively.

#### 2.2.2 Computational Design

Replica-exchange molecular dynamics (REMD)\(^{56}\) simulations suggest that helical exchange proceeds via intermediates composed of right- and left-handed segments separated by helical reversal points, which circumvents the need to access any fully unfolded states (Figure 2.1). Details of the REMD experiments are \textit{vida infra}. The nature of this helical exchange resembles the stepwise unfolding process attributed to related oligoamide foldamers\(^{17,57}\) and helical polymers.\(^{46,47}\)
Previously, we observed that the methylene protons, Ha and Hb, in Cbz-protected oligomers (A) exhibited chemical shifts differing by ca. 0.5 ppm at –37 °C (Figure 2.2). This difference emerged from the disparity in anisotropic shifting caused by the positioning of one methylene proton toward and the other away from the helix backbone. Therefore one could hypothesize that capping the terminal amines with a small chiral influence such as Cbz-L-alanine would place a stereogenic center at approximately this position. The orientation of the methyl and hydrogen groups relative to the helix backbone on this carbon would then differentiate the stabilities of the M and P helical forms (Figure 2.2). This theory was supported by Monte Carlo conformational searching of two-turn helix 2a, which indicated an energetic preference for a P helical form, thereby positioning the methyl group away from the helical backbone based on steric interactions.
2.3 Results and Discussion

The UV-vis spectra of oligomers 1a-3b shown in Figure 2.3 feature a strong absorption at ca. 385 nm corresponding to a $\pi \rightarrow \pi^*$ transition of the azobenzene chromophore. Additionally, a weak $n \rightarrow \pi^*$ transition broadened over the 450-490 nm range, typical of $E$-azobenzene chromophores, is also present in the spectra. Bis-azo oligomer 1a ((Cbz-L-Ala)$_2$(N=N)$_2$) is too short to adopt a helical conformation and, therefore, did not exhibit any observable circular dichroism (CD) transitions above 200 nm (Figure 2.4). In contrast, two-turn oligomer 2a ((Cbz-L-Ala)$_2$(N=N)$_4$) displayed negative CD bands at 320 and 477 nm, and an intense positive band at 407 nm. The presence of the CD transitions in this region of the spectrum indicates the induction of a preferred sense of helicity in the azobenzene oligomer. The four-turn oligomer 3a ((Cbz-L-Ala)$_2$(N=N)$_8$) also exhibited these CD bands with intensities greater than two-fold that
of 2a, as might be expected based on the difference in the number of azobenzene chromophores. This nonlinear enhancement of the CD intensity for 3a, compared with 2a, indicates a more efficient amplification of the terminal chiral influences. This analysis is confirmed by overlaying the UV spectra’s of 2a and 3a.

Figure 2.3: Helical oligomers 1a-3b
Figure 2.4: Molar CD spectra of oligomers 1a-3b and UV-vis spectra of 3a in MeCN at −10 °C.
Figure 2.5: Comparison of the experimental CD spectrum of oligomer 3a (black) and predicted CD spectra of 3a (RI-BP86/TZVP in orange, B3LYP/SV(P) in blue, and BHLYP/SV(P) in red), calculated for geometries optimized at the respective levels of theory.
The UV-vis and CD spectra of the optimized geometry of oligomers 2a and 3a were calculated using time-dependent density functional theory (TD-DFT) at the RI-BP86/TZVP, B3LYP/SV(P), and BH&HLYP/SV(P)\textsuperscript{59-63} levels of theory (Figures 2.5 and 2.6).\textsuperscript{64-71} The resulting spectra were uniformly blue-shifted by 0.5, 0.1, and -0.55 eV, respectively, and a 0.3 eV Gaussian line broadening was applied to each excitation.

Figure 2.6: Comparison of the experimental CD spectrum of oligomer 2a (black) and predicted CD spectra of 2a (RI-BP86/TZVP in orange, B3LYP/SV(P) in red, and BHLYP/SV(P) in blue), calculated for geometries optimized at the respective levels of theory.
The prediction of CD spectra has only recently been applied to the analysis of conformations of large molecules, and our protocol mirrors that utilized successfully elsewhere. Oligomers 2a and 3a are ideal candidates for CD calculations because, as suggested by the REMD studies, the $M$ and $P$ helical forms interconvert without experiencing a fully unfolded state. Hence, the calculated CD spectra of a static $M$ or $P$ helix would qualitatively reproduce the features of an experimental spectrum. The agreement between the simulated spectra and experiment was fairly good, with the B3LYP spectrum most closely matching experiment. The qualitative properties of the spectrum and, in particular, the trough at $\sim 475$ nm and the peak at $\sim 400$ nm were reproduced; however, the trough at 340 nm shows significantly more negative polarization in the calculated spectra. The BH&HLYP and RI-BP86 spectra show larger deviations than the B3LYP spectrum, suggesting that the latter has the proper amount of inclusion of Fock-exchange.

Additionally, it should be noted that the geometries optimized using hybrid DFT most closely resemble the crystal structure, with RI-BP86 over estimating the spacing between the helical turns. (Figure 2.7)
The calculated spectra most closely resemble the experimental spectrum of the 4-turn oligomer 3a, particularly in the region around 320-370 nm, compared with the 2-turn oligomer 2a (Figures 2.5 and 2.6). The B3LYP spectrum, in particular, matches exceptionally well. As the CD spectra were calculated using static, helical structures, it is reasonable that they might resemble the experimental spectrum of the very strongly biased oligomer 3a more closely than that of 2a. Although oligomers 2a and 3a differ in
length, the molecule’s chromophores are identical only differing in overall length and the excited-state properties are therefore are presumably similar. With the multiple levels of theory employed, including the generally more accurate hybrid DFT methods, and a clear similarity with the spectrum of oligomer 3a, the calculated CD spectra strongly support the conclusion that the P helical sense is present in the experimental oligomers. Further, it suggests that the difference in experimental CD spectra is the result of changes in the helical bias (Figure 2.8 and Table 2.1). The data from these calculations is located in Appendix B.
Figure 2.8: Raw CD and UV-vis spectra calculated for azobenzene 2a as well as a total spectrum with a 0.3 eV Gaussian broadening. Both are blue-shifted by 0.5 eV from the calculated energies. The excitations with the largest contribution to the CD spectrum are labeled accordingly.
A large decrease in the amplitude of the CD spectrum was observed for four-turn oligomer 3b ((H₂N-L-Ala)₂(N=N)₈), which lacked the terminal Cbz groups (Figure 2.9). To explore the impact of the terminal groups on the extent of helical bias, we varied the nature of the acyl groups in analogs of the two-turn oligomer 2a. The intensity of the CD band at 407 nm was highest for 2a, lowest for amino-terminated 2b and generally increased as the acyl group became more electron-withdrawing (Figure 2.8). The source of this effect is likely due to a stabilizing hydrogen bond between the NH–CO and another donor group that is enhanced by electron withdrawing groups or a favorable π-
stacking effect between electron-rich and electron-poor aromatic rings as seen in Figure 2.2. However, the exact nature of this interaction remains to be determined.

![Graph showing CD spectra of 2a–2e (MeCN, −10 °C)](image)

**Figure 2.9:** Effect of terminal group: CD spectra of 2a – 2e (MeCN, −10 °C)

Previously, we observed that $E \rightarrow Z$ photoisomerization of the azo bonds within the helix was progressively suppressed with increasing oligomer length. Conversely, the azo bonds at the termini of the helices experienced *ca. 40% isomerization to the Z form in both the two-turn and four-turn oligomers. Accordingly, irradiation of the oligomers
induces $E \rightarrow Z$ isomerization mainly at the terminal positions without disruption of the helical structure (Figure 2.11). Irradiating the two- and four-turn oligomers, 2a and 3a, with 350 nm radiation afforded a photostationary state within 10 min exhibiting significantly diminished CD spectra (Figure 2.10). The decrease in helical bias induced by exposure to light emerges from isomerization of the terminal azo linkages that displaces the controlling stereogenic center of the Cbz-L-Ala group from the helix backbone (Figure 2.11).
Figure 2.10: CD spectra in CH$_3$CN at –10 °C before (solid lines) and after (dashed lines) irradiation with 350 nm light
**Figure 2.11**: Predominant isomerization of terminal azo linkages decreases chiral induction.
2.4 Synthesis

The strategy towards the target oligomers 2a and 3a is significantly different from the prior procedure.\textsuperscript{36} Previously, a dimerization/deprotection/protection scheme was employed. The current strategy utilizes step-wise elongation so that as the molecule gradually becomes large enough to fold over itself in a helical form, the impact of chiral induction can be studied spectroscopically. Additionally, for the molecules that are incapable of folding, one can observe the lack of a signal in the CD insuring that no linear dichroism signals would be mistakenly attributed to chiral induction. An additional
benefit of this strategy is to serve as a test to determine if solid phase techniques are useful in the future to generate molecules of longer length.

To join the multiple azobenzene moieties together, pyridine 2,6-dicarboxamide was chosen for synthetic ease and stability granted to the oligomer: this linkage allows for a syn-syn conformation due to hydrogen bonding of the amide protons with the central pyridine nitrogen in conjunction with electrostatic interactions between the two carbonyls reinforcing a compact helical bias (Figure 2.12). Additionally, because of electrostatic interactions of the amines, the azo system also prefers a syn-syn conformation (Figure 2.13). The pyridine dicarboxamides grant the ability to dimerize azobenzene units or desymmetrize the molecule.

Figure 2.12: Syn-Syn preference of bis-azo diamine DFT calculations (kcal/mol)

Figure 2.13: Syn-Syn preference of 2,6-pyridine dicarboxamides DFT calculations (kcal/mol)
The synthesis began with the attachment of Cbz-alanine to the azo system in a one to two stoichiometry. The peptide coupling reagent HATU (\(O\)-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) is used for this step because of its high efficiency, mild reaction conditions, and very low tendency to racemize the chiral amino acids to grant compound 1b (Figure 2.14).\textsuperscript{76,77} To form the symmetrical model compound 1a, the HATU/Cbz-alanine coupling step is only varied in stoichiometry.

![Structure of peptide coupling reagent HATU](image)

\textbf{Figure 2.14:} Structure of peptide coupling reagent HATU

Molecule 1b then was dimerized with half an equivalent of 2,6-pyridine diacyl chloride to yield two-turn oligomer 2a. Following deprotection of the terminal Cbz-groups with TFA/thioanisole in DCM, the terminal alanine amines can be derivatized with various acyl groups to study the effect they have on oligomer stability.

The four-turn oligomer 3a was not synthesized via traditional deprotection/dimerization elongation methods from the two-turn oligomer 2a; instead it was generated linearly. The synthesis began by the coupling of compound 1b with 2-allyloxycarbonyl-6-pyridine-carboxylic acid chloride followed by deprotection of the allyl ester. The resultant acid was subsequently coupled with achiral azo compound 8 to
yield two-turn oligomer 9. The fluorenylmethyl group of the mono-alanine two-turn oligomer was deprotected with piperidine in DMF to give 2g. Finally, 2g then was dimerized with pyridine diacyl chloride to yield the four-turn oligomer 3a. Finally, deprotection of 3a with TFA/thioanisole with EtOAc as the solvent gave chiral, four-turn terminal amine 3b.

2.5 Conclusions

In conclusion, appending Cbz-L-alanine to the terminal position of azobenzene oligomers biases the twist-sense of their helical structures. Comparison of the experimental and computationally predicted CD spectra indicates the presence of a P helical bias. Molecular modeling studies suggest that that the energetic benefit of projecting the methyl group of L-alanine away from the helix backbone produces the P helical bias. Exposure to 350 nm light suppresses chiral induction within the helical structure by inducing isomerization of the terminal azo linkages, which orients the chiral terminal groups away from the helix.

2.6 Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 1600 instrument. $^1$H NMR were recorded at 400 MHz and $^{13}$C NMR spectra at 100 MHz on a Bruker DPX-250 or a DPX-400 instrument as indicated. Circular dichroism (CD) measurements were carried out on an Aviv 202 CD spectrometer, using optical grade solvents and quartz glass cuvettes with a 10 mm path length. Electrospray mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. MALDI-TOF spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All
starting materials were used as supplied from commercial suppliers unless otherwise noted. All reactions were carried out under a N₂ atmosphere unless otherwise noted. Dimethylformamide (DMF) was dried by distillation from MgSO₄; Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride. All melting points were recorded in glass capillaries and are uncorrected. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents.

**Abbreviations:** HATU = N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate; DIEA = N-ethyl-N-(1-methylethyl)-2-propanamine; DMF = N,N-dimethyl formamide; Cbz = carbobenzyloxy-; FMOC-L-Ala-OH = Nα-(9-fluorenlymethoxycarbonyl)-L-alanine; TFA = trifluoroacetic acid.

![Chemical structure of Oligomer 1a](image_url)

**Oligomer 1a (Cbz-L-Ala)₂(N=N)₂.** 2-[3-(2-amino-phenylazo)-phenylazo] aniline⁷ (0.50 g, 1.58 mmol, 1.0 equiv) was dissolved in 20 mL of dry CH₂Cl₂ with 4 Å molecular sieves. A mixture of Cbz-L-Ala-OH (740 mg, 3.32 mmol, 2.1 equiv), HATU (1.077 g, 2.84 mmol, 1.8 equiv), DIEA (0.610 mL, 460 mg, 3.54 mmol, 2.24 equiv) and 20 mL of DMF was prepared and stirred for 1 h at ambient temperature. The mixture was then
added dropwise over a period of 15 min. to the CH$_2$Cl$_2$ solution of the diamine. The resulting mixture was allowed to slowly come to rt over 36 h. The sieves were removed by filtration using small portions of EtOAc and MeOH. This solution was evaporated to a red oil by Kügelrohr distillation (0.001 mm Hg), which was further purified using column chromatography (CH$_2$Cl$_2$). 688.2 mg (60 % yield). Mp 186-189 °C (CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, DMSO, 70 °C) $\delta$ 10.39 (s, 2H), 8.60 (s, 1H), 8.47 (d, $J= 8$Hz, 2H), 8.14 (d, $J= 8$Hz, 2H), 7.84 (d, $J= 8$Hz, 2H), 7.66 (m, 3H), 7.58 (t, $J= Hz$, 2H), 7.24 (m, 10H), 5.07 (d, $J= 12.8$Hz, 2H), 4.96 (d, $J= 12.8$Hz, 2H), 4.42 (pent, $J = 7$Hz, 2H), 1.43 (d, $J= 7$Hz, 6H). $^{13}$C NMR (100 MHz, DMSO, 70 °C) $\delta$ 171.9, 153.5, 140.6, 137.1, 136.9, 133.4, 128.6, 127.9, 124.6, 118.7, 66.2, 17.8. IR (CH$_2$Cl$_2$) 1710, 1615, 1520, 1220 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 749.0 (calcd. for C$_{40}$H$_{37}$N$_7$NaO$_6$ 749.2).

Oligomer 1b (Cbz-L-Ala)(N=N)$_2$NH$_2$ 2-[3-(2-amino-phenylazo)-phenylazo] aniline (1.0 g, 3.16 mmol, 1.1 equiv) was dissolved in 14 mL of dry CH$_2$Cl$_2$ with 4 Å molecular sieves. The solution was stirred for 1 h at 0 °C and concurrently sonicated to facilitate dissolution. A mixture of Cbz-L-Ala-OH (640 mg, 2.89 mmol, 1.0 equiv), HATU (980 mg, 2.58 mmol, 0.9 equiv) DIEA (0.600 mL, 450 mg, 3.48 mmol, 1.21 equiv) and 14 mL of DMF was prepared and stirred for 1 h under nitrogen in a flask containing 4 Å
activated sieves. This activated acid mixture was added dropwise over a period of 15 min to a solution of the diamine. After the addition was complete, the solution was allowed to slowly come to rt over 21 h. Filtration was used to remove the sieves and the solution was washed with small portions of EtOAc and MeOH. The DMF was removed in vacuo to a red oil. The oil was further purified by column chromatography (CH$_2$Cl$_2$) affording 1b as a red solid 694.5 mg (47 % yield). Mp 153-155 °C (CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$) δ 10.61 (bs, 1H), 8.74 (d, J= 7.2Hz 1H), 8.42 (bs, 1H), 8.03 (d, J= 7.2Hz, 2H), 7.97 (d, J= 7.2Hz, 1H), 7.90 (d, J= 7.2Hz, 1H), 7.64 (t, J= 7.2Hz, 1H), 7.55 (t, J= 7.2Hz, 1H), 7.28 (m, 5H), 6.89 (td, J= 1.2, 8Hz, 1H) 6.83 (dd, J= 1.2, 8Hz, 1H), 6.05 (bs, 2H), 5.56 (bs, 1H), 5.19 (d, J= 12Hz, 2H), 5.06 (d, J= 12Hz, 2H), 4.51 (m, 1H), 1.60 (d, J= 7.2Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.5, 151.2, 138.2, 137.1, 136.9, 133.4, 130.0, 128.6, 128.0, 127.9, 127.6, 124.6, 124.0, 118.7, 67.3. IR (CH$_2$Cl$_2$) 2989, 1700, 1619, 1524, 1216 cm$^{-1}$. HRMS (MALDI) m/z [Na]$^+$ 544.4 (calcd. for C$_{29}$H$_{27}$N$_7$O$_3$Na 544.2).

**Oligomer 2a (Cbz-L-Ala)$_2$(N=N)$_4$.** Compound 1b (100 mg, 0.20 mmol, 2 equiv) was dissolved in 1 mL of pyridine, and stirred for 1 h at 0 °C. Pyridine-2,6-dicarbonyl chloride (17 mg, 0.10 mmol, 1.0 equiv) was suspended in 2 mL each of THF and CH$_2$Cl$_2$
then added to the solution of the 1b. After stirring at rt for 6 h, the solution was poured into 250 mL of sat. aq. sodium chloride and 250 mL CH₂Cl₂. The organic layer was separated and sequentially washed with 250 mL of 1 M H₂SO₄, 250 mL 0.5 M sodium bicarbonate, and 250 mL sat. aq. sodium chloride. The organic layer was then dried over MgSO₄ and evaporated. The resulting orange residue was purified via column chromatography with CH₂Cl₂ → 10:1 CH₂Cl₂:EtOAc to give 50 mg (50 % yield) as an orange solid. Mp 123-125 °C (CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 11.27 (s, 2H), 10.40 (s, 2H), 8.72 (d, J= 8Hz, 2H) 8.52 (d, J= 8Hz, 2H), 8.45 (d, J= 7.76Hz, 2H), 8.07 (m, 3H), 7.76 (d, J= 8Hz, 2H), 7.53 (m, 6H), 7.39 (d, J= 8Hz, 2H), 7.28 (m, 14H), 7.06 (td, J= 1.2, 8Hz, 2H), 6.97 (td, J= 1.2, 8Hz, 2H), 5.43 (bs, 2H), 5.03 (d, J= 10Hz, 2H), 4.93 (d, J= 10Hz, 2H), 4.38 (pent, J= 8Hz, 2H), 1.53 (d, J= 7.08Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 161.0, 152.9, 152.3, 149.7, 139.6, 139.1, 138.9, 136.32, 135.9, 135.8, 133.3, 129.3, 128.5, 128.2, 128.0, 125.7, 123.9, 123.4, 121.2, 120.3, 119.9, 117.7, 67.2. IR (CH₂Cl₂) 3348, 1688, 1595, 1519, 1440, 1313, 1292 cm⁻¹. HRMS (MALDI) m/z [Na]⁺ 1196.6 (calcd. for C₆₅H₅₅N₁₅O₈Na 1196.4).

**Oligomer 2b (NH₂-L-Ala)₂(N=N)₄.** Oligomer 2a, (50.8 mg, 0.043 mmol, 1.0 equiv) was treated with thioanisole (256 µL, 268.8 mg, 2.165 mmol, 50 equiv). This mixture was
cooled to 0 °C with stirring and TFA (889 μL, 1.3 g, 11.69 mmol, 270 equiv) was added and the reaction immediately turned black. The solution was allowed to stir for an additional 3 h and was then poured into 20 mL of cold EtOAc and the resultant mixture was washed with 20 mL of 5% aq. NaHCO₃. The organic layer was separated, dried (MgSO₄), and evaporated to a black oil. The oil was then purified by column chromatography in CH₂Cl₂ → 99:1 CH₂Cl₂:MeOH to afford 36.6 mg of 2b as a red powder (93.4 % yield.) Mp 100 °C dec (CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 11.75 (s, 2H), 11.40 (s, 2H), 8.73 (d, J= 8Hz, 2H), 8.54 (d, J= 8Hz, 2H), 8.47 (d, J= 8Hz, 2H), 8.19 (t, 1H), 8.13 (s, 2H), 7.79 (dd, J= 1.2, 8Hz, 2H), 7.61 (d, J= 8Hz, 2H), 7.56 (t, 2H), 7.47 (d, J= 8Hz, 2H), 7.37 (t, 2H), 7.32 (dd, J= 1.2, 8Hz, 2H), 7.24 (t, 2H), 7.13 (t, J= 8Hz, 2H), 7.00 (t, 2H), 3.50 (sextet, J= 8Hz, 2H), 1.40 (d, J= 6.8Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 160.9, 153.2, 152.9, 139.6, 139.3, 137.0, 136.3, 133.5, 132.9, 129.2, 125.8, 125.2, 123.5, 123.5, 120.2, 120.0, 118.1, 117.9, 115.5, 51.8, 21.8. IR (CH₂Cl₂) 3337, 1696, 1593, 1521, 1436, 1301 cm⁻¹. HRMS (MALDI) m/z [Na]⁺ 928.1 (calcd. for C₄₉H₄₃N₁₅O₄Na 928.3).

Oligomer 2c (p-NO₂-C₆H₄CO-L-Ala)₂(N=N)₄. Oligomer 2b (20.1 mg, 0.02 mmol, 1.0 equiv) was dissolved in 400 μL pyridine and DMAP (5 mg, 0.045 mmol) was added.
The resulting solution was added dropwise to p-nitrobenzoyl chloride (38.9 mg, 0.180 mmol, 8.2 equiv) in 1 mL CH₂Cl₂. After 2h, the reaction was poured into 200 mL of water and washed with an equal volume of CH₂Cl₂. The organic layer was separated, dried (MgSO₄), and purified by column chromatography with CH₂Cl₂ → 99:1 CH₂Cl₂:MeOH to afford 19.6 mg (73%) as an orange residue. Mp 105-110 °C (CH₂Cl₂).

^1H NMR (400 MHz, CDCl₃) δ 11.85 (s, 2H) 10.46 (s, 2H), 8.67 (d, J= 8Hz, 2H), 8.58 (d, J= 8Hz, 2H), 8.52 (d, J= 8Hz, 2H), 8.21 (t, J= 8Hz, 1H), 8.19, (d, J= 8Hz, 2H), 8.13 (s, 2H), 7.88 (d, J= 8Hz, 2H), 7.81 (dd, J= 1.6, 8 Hz, 2H), 7.68 (d, J= 8Hz, 2H) 7.55 (t, J= 8Hz, 2H), 7.46, (d, J= 8Hz, 2H), 7.40 (t, J= 8Hz, 2H), 7.23 (t, J= 8Hz, 2H), 7.15 (d, J=8Hz, 2H), 7.05 (d, J= 8Hz, 4H), 6.87 (d, J= 8Hz, 2H), 6.87 (d, J= 8Hz, 4H), 4.72 (pent, J= 8Hz, 2H) 1.59 (d, J= 3Hz, 6H). ^13C NMR (100 MHz, CDCl₃) δ 162.8, 155.0, 150.8, 147.2, 143.5, 141.2, 140.0, 137.8, 136.5, 131.5, 130.2 129.0, 127.8, 123.8, 119.0, 113.0, 60.2, 29.6. IR (CH₂Cl₂) 3344, 2927, 2358, 1693, 1596, 1524 cm⁻¹. HRMS (MALDI) m/z [Na]⁺ 1226.3 (calcd. for C₆₃H₄₉N₁₇O₁₀Na 1226.3).

![Oligomer](image)

**Oligomer 2d (p-MeO-C₆H₄CO-L-Ala)_2(N=N)_4.** Oligomer 2b (21.1 mg, 0.023 mmol, 1.0 equiv) was charged with p-anisoyl chloride (10 mg, 0.05 mmol, 2.1 equiv) with 5.0 mg of DMAP in 400 μL of dry pyridine. After 6 h, 300 mL of water was added and the mixture
was extracted with CH$_2$Cl$_2$ (300 mL). The organic layer were separated, dried (MgSO$_4$), and evaporated to afford an orange solid. Column chromatography (5:1 hexanes:EtOAc afforded 26 mg of an orange solid (100%). Mp 240-242 °C (hexanes:EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) δ 11.9 (s, 2H), 10.47, (s, 2H), 8.70 (d, $J=8$Hz, 2H), 8.58 (d, $J=8$Hz, 1H), 8.56 (d, $J=8$Hz, 1H), 8.21 (t, $J=8$Hz, 1H), 8.18 (bs, 2H), 7.79 (dd, $J=1.6$Hz, 8Hz, 2H), 7.77 (d, $J=8$Hz, 4H), 7.67 (d, $J=8$Hz, 2H), 7.55 (t, $J=8$Hz, 2H), 7.49 (d, $J=8$Hz, 2H), 7.38 (dd, $J=1.6$, 8Hz, 2H), 7.33 (t, $J=8$Hz, 2H), 7.26 (t, $J=6$Hz, 4H), 7.16 (m, 6H), 6.99 (t, $J=8$Hz, 2H), 4.80 (pent, $J=8$Hz, 2H), 4.45 (bs, 2H), 3.81 (s, 6H), 1.59 (d, $J=6$Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 163.0, 156.3, 151.2, 143.1, 140.2, 137.8, 137.6, 136.2, 128.9, 127.8, 127.6, 125.4, 114.0, 113.8, 102.5, 100.0, 87.2, 68.7, 55.4, 31.0, 29.7. IR (CH$_2$Cl$_2$) 3333, 2922, 1693, 1596, 1510 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 1196.2 (calcd. for C$_{65}$H$_{55}$N$_{15}$O$_8$Na 1196.4).

**Oligomer 2e (CF$_3$CO-L-Ala)$_2$(N=N)$_4$.** Oligomer 2b (15 mg, 0.017 mmol, 1.0 equiv) was dissolved in 100 µL pyridine and trifluoroacetic anhydride (13 µL, 17.4 mg, 0.083 mmol, 5.0 equiv) was added to the solution. After 15 min, the mixture was evaporated to a brown solid and co-evaporated three times with 100 mL dry CH$_2$Cl$_2$. Column chromatography in CH$_2$Cl$_2$ → 99:1 CH$_2$Cl$_2$:MeOH afforded 7 mg of orange residue
Oligomer 2f (CH₃CO-L-Ala)$_2$(N=N)$_4$. Oligomer 2b (12.4 mg, 0.0137 mmol, 1.0 equiv) was dissolved in 400 µL dry pyridine and DMAP (2.0 mg) and acetic anhydride (6.5 µL, 7.0 mg, 0.068 mmol, 5.0 equiv) were added. After 6h, 300 mL of water were added and the mixture was extracted with 50 mL CH₂Cl₂. The organic layer was then washed with 50 mL each of 1.0 M H₂SO₄, 0.5 M NaHCO₃, and water. The organic layer was then dried and evaporated and placed on a column (CH₂Cl₂ → 99:1 CH₂Cl₂:MeOH) to afford 10 mg of the orange product (74 % yield). Mp 150 °C dec (CH₂Cl₂). $^1$H NMR (400 MHz, CDCl₃) δ 11.89 (s, 2H), 10.29 (s, 2H), 8.68 (d, J= 7.6Hz, 2H), 8.61 (d, J= 7.6Hz, 2H), 8.54 (d, J= 7.6Hz, 2H), 8.21 (t, 1H), 8.16 (bs, 2H), 7.80 (dd, J= 1.6, 8Hz, 2H), 7.69, (d,
$J = 7.6\text{Hz, 2H}$, $7.55 \text{ (t, 2H)}$, $7.50 \text{ (d, } J= 8\text{Hz, 2H)}$, $7.43 \text{ (dd, } J= 1.2, 8.4\text{Hz, 2H)}$, $7.38 \text{ (t, 2H)}$, $7.23 \text{ (t, 2H)}$, $7.20 \text{ (t, } J= 8\text{Hz 2H)}$, $7.04 \text{ (d, } J= 8\text{Hz 2H)}$, $6.15 \text{ (d, } J= 8\text{Hz 2H)}$, $4.61 \text{ (pent, 2H)}$, $1.99 \text{ (s, 6H)}$, $1.50 \text{ (d, } J= 7.2\text{Hz 6H)}$. $^{13}\text{C NMR (100 MHz, CDCl}_3\) \delta 162.5, 155.2, 151.8, 142.9, 140.1, 137.6, 136.9, 136.5, 129.5, 128.5, 127.5, 127.3, 125.2, 114.0, 113.2, 101.9, 101.1, 88.0, 65.2, 33.1, 30.7. IR (CH$_2$Cl$_2$) 3323, 1694, 1595, 1520 cm$^{-1}$. IR (CH$_2$Cl$_2$) 3330, 2920, 1695, 1596, 1510 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 1012.2 (calcd. for C$_{53}$H$_{47}$N$_{15}$O$_6$Na 1012.3).

![2-Allyloxy carbonyl-6-pyridine-carboxylic acid](image)

**2-Allyloxy carbonyl-6-pyridine-carboxylic acid.** The diacid chloride (5.9 g, 0.029 mol, 1.0 equiv) was dissolved in 100 mL CH$_2$Cl$_2$. To this solution, a mix of 3 mL of pyridine, (814 mg, 0.0058 mol, 0.2 equiv), and 2.0 mL allyl alcohol (2.86 g, 0.0493 mol, 1.7 equiv) was added dropwise over 15 min. The mixture was allowed to react for an additional 5 min. The reaction was then poured into a separatory funnel containing 250 mL of 0.5 M sodium bicarbonate and extracted three times with an equal volume of chloroform. The aqueous layer was then acidified to pH 1 with 1M sulfuric acid and extracted three times more with chloroform. This second extraction was concentrated to yield 3.66 g (61% yield). Mp 104-105 °C (CH$_2$Cl$_2$). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 10.9 (bs, 1H), 8.44(dd, $J= 1.6, 12.4\text{Hz, 1H})$, 8.39 (dd, $J= 1.6, 12.4\text{Hz, 1H}$), 8.15 (t, $J= 7.6\text{Hz, 1H}$), 6.08 (dtd, $J= 6, 10.5, 16.5\text{Hz, 1H}$), 5.48 (dd, $J= 4.8, 17.2, 2\text{H}$), 4.94 (d, $J= 4.8 \text{Hz, 2H}$) $^{13}$C NMR (100
MHz, CDCl$_3$) 163.27, 163.20, 146.88 146.34, 139.70, 131.31, 128.87, 126.69, 119.57, 66.86. IR (CH$_2$Cl$_2$) 3066, 2783, 1736, 1702, 1698, 1252, 755 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 230.5 (calcld. for C$_{10}$H$_9$NO$_4$Na 230.1).

![Chemical Structure](image)

Oligomer 6a (Cbz-L-Ala)(N=N)$_2$(CO$_2$Allyl).

A. 2-allyloxy carbonyl-6-pyridine-carboxylic acid chloride. 2- Allyloxy carbonyl-6-pyridine-carboxylic acid (496.9 mg, 2.41 mmol, 1.0 equiv) was treated with 4 Å molecular sieves (40 mg) in 24.5 mL dry CH$_2$Cl$_2$ followed by oxalyl chloride (1.06 mL, 1.51 g, 12.0 mmol, 5.0 equiv) and DMF (10 mL). After 1 h the solvent was removed in vacuo then dried (0.02 mm Hg) for 1 h. The acid chloride was used without further purification in part B.

B. Amine 1b (1.01 g, 2.01 mmol, 1.0 equiv) was dissolved in 12 mL of pyridine at 0 °C and 4 Å activated molecular sieves (100 mg) were added to the solution. The acid chloride from part A (496 mg, 2.40 mmol, 1.2 equiv) was dissolved in 12 mL of CH$_2$Cl$_2$ and slowly added the mixture of amine 1b. After 1 h, the solution became cloudy and
light yellow. The sieves were then removed via filtration and the filter cake was washed with warm THF (50 mL). The solution was concentrated and redissolved in CH$_2$Cl$_2$ (2 mL) then precipitated into cold hexanes (400 mL). Filtration afforded 6a as a yellow solid 666.8 mg (47 % yield). Mp 207-212 °C (hexanes). $^1$H NMR (250 MHz, DMSO) $\delta$ 11.91 (s, 1H), 10.39 (s, 1H), 8.80 (d, $J$ = 7.75Hz, 1H), 8.62 (bs, 1H), 8.51 (d, $J$ = 8.5Hz, 1H), 8.49 (d, $J$ = 8.5Hz, 1H), 8.31 (d, $J$ = 7.75Hz, 2H), 8.20 (d, $J$ = 8.5Hz, 1H), 7.91 (dd, $J$ = 1.5, 7.6Hz, 1H), 7.82 (m, 2H), 7.68 (t, $J$ = 8.5Hz, 1H), 7.56 (t, $J$ = 7.25Hz, 2H), 7.28 (m, 2H), 7.17 (bs, 5H), 5.88 (m, 1H), 5.41 (dd, $J$ = 1.5, 17.25Hz, 2H), 5.35 (dd, $J$ = 1.25, 10.25Hz, 1H) 5.00 (d, $J$ = 17.5Hz, 1H), 4.96 (d, $J$ = 10.5Hz, 1H), 4.73 (d, $J$ = 5.5Hz, 2H), 4.45 (m, 1H), 1.35 (d, $J$ = 7Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.2, 161.5, 153.5, 153.3, 151.0, 147.0, 139.5, 139.0, 138.9, 137.0, 133.3, 133.2, 131.5, 130.3, 128.4, 128.1, 128.0, 127.6, 126.8, 125.6, 124.1, 123.8, 122.9, 120.5, 119.0, 117.0, 67.2, 66.4. IR (CH$_2$Cl$_2$) 3297, 2916, 2356, 1749, 1683, 1592, 1519 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 733.5 (calcd. for C$_{39}$H$_{34}$N$_8$O$_6$Na 733.2).

**Oligomer 6b (Cbz-L-Ala)(N=N)$_2$(CO$_2$H).** Pd(OAc)$_2$ (10.5 mg, 0.047 mmol, 0.05 equiv) was treated with PPh$_3$ (49.8 mg, 0.188 mmol 0.20 equiv) in 10 mL dry THF. A mixture of (C$_4$H$_9$)$_3$N (1.05 mL, 810.2 mg, 3.76 mmol, 4.0 equiv) and formic acid (99%)
(140 μL, 172.9 mg, 3.76 mmol, 4.0 equiv) in 6 mL of THF was added to Pd(OAc)_2/PPh_3 solution. After 15 min., the yellow catalyst solution was added to a suspension of allyl ester 6a (666.8 mg, 0.94 mmol, 1.0 equiv) in 10 mL of THF. After 1 h, the yellow suspension became dark red. The reaction mixture was concentrated to a red/black oil. Equal volumes (250 mL) of 1M H_2SO_4 and chloroform were added and the layers were separated. The organic layer was then washed with 10 % CuSO_4 (100 mL), 1.5 M potassium bicarbonate, and water (100 mL) then dried (MgSO_4) and concentrated to an orange solid. The residue was purified by column chromatography in 1:1 CH_2Cl_2:hexanes affording 484 mg (78% yield) of a red solid. Mp 173-175 °C (CH_2Cl_2:hexanes). ^1H NMR (400 MHz, CDCl_3) δ 11.95 (s, 1H), 10.40 (s, 1H), 8.93 (d, J= 8.25 Hz, 1H), 8.71 (d, J= 8.25 Hz, 2H), 8.55 (d, J= 8.25 Hz, 1H), 8.39 (d, J= 8.25 Hz, 1H), 8.13 (t, J= 8.25 Hz, 2H), 8.0 (bs, 1H), 7.94 (t, J= 8 Hz, 2H), 7.55 (m, 3H), 7.22 (bs, 7H), 5.50 (bs, 1H), 5.34 (d, J= 8 Hz, 1H), 5.04 (d, J= 8 Hz, 1H), 4.50 (bs, 1H), 4.5 (bs, 1H), 1.52 (d, J= 7 Hz, 3H). ^13C NMR (100 MHz, CDCl_3) δ 161.1, 156.3, 153.2, 153.1, 149.9, 146.5, 140.2, 139.1, 137.2, 133.6, 133.3, 132.8, 132.2, 132.1, 132.0, 131.8, 130.2, 128.5, 1258.4, 128.2, 128.0, 127.4, 125.9, 124.1, 120.3, 119.6, 116.4, 67.4, 29.7, 19.2. IR (CH_2Cl_2) 3500, 2237, 1700, 1621, 1525 cm⁻¹. HRMS (MALDI) m/z [K]^+ 709.3 (calcd. for C_{36}H_{30}N_8O_6K 709.1).
**Oligomer 8 (Fmoc)(N=N)₂NH₂.** Compound 5 (50 mg, 0.158 mmol, 1 equiv), sodium carbonate (32.8 mg, 0.395 mmol, 2.5 equiv) and DMAP (10 mg) was dispersed in 0.7 mL of CH₂Cl₂ and 0.4 mL of water and cooled to 0 °C. 9-Fluorenylmethyl chloroformate (40.8 mg, 0.158 mmol, 1 equiv), dissolved in a minimal amount of CH₂Cl₂ (0.2 mL), was added dropwise to the stirred solution of diamine 5. After heating at reflux for 6 h, 0.5 M sodium bicarbonate (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried (MgSO₄), and concentrated. The resulting residue was purified by column chromatography 5:1 Hex:EtOAc affording 8 as a light yellow solid. 53.7 mg (63.1% yield). Mp 145-147 °C (hexanes:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 10.0 (s, 1H), 8.39 (s, 2H), 8.02 (d, J= 8Hz, 1H), 7.96 (d, J= 8Hz, 2H), 7.87 (d, J= 1H), 7.80 (d, J= 8Hz, 2H), 7.71 (m, 3H), 7.51 (t, J= 8Hz, 1H), 7.42 (t, J= 8Hz, 2H), 7.33 (t, J= 8Hz, 2H), 7.20 (m, 2H), 6.80 (m, 2H), 5.96 (bs, 2H), 4.56 (d, J= 8, 16Hz, 2H), 4.38 (t, J= 8, 16Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 153.2, 143.8, 141.4, 138.7, 133.1, 132.8, 129.8, 128.1, 127.8, 127.2, 125.1, 124.5, 122.8, 120.1, 119.1, 117.5, 117.1, 116.1, 67.3, 47.1. IR (CH₂Cl₂) 3390, 3063, 2360, 1732, 1590, 1516, 1310, 1210 cm⁻¹. HRMS (MALDI) m/z [Na]⁺ 561.1 (calcd. for C₃₃H₂₈N₆O₂Na 561.2).
Oligomer 9 ((Cbz-L-Ala)(N=N)₄(Fmoc)). Oligomer 8 (443.2 mg 0.823 mmol 1.2 equiv) was dissolved in 3 mL of CH₂Cl₂ and transferred via cannula over 5 min. to a mixture of acid 6b (459.6 mg, 0.722 mmol, 1.0 equiv), HATU (250 mg, 0.9 equiv, 0.650 mmol) and DIEA (0.150 mL, 115 mg, 0.874 mmol, 1.21 equiv) in 3 mL DMF. The reaction immediately became dark red and was allowed to stir for an additional 8 h. At that time, the mixture was diluted with 200 mL of chloroform and washed with equal volumes (200 mL) of 1M H₂SO₄, 0.5 M sodium bicarbonate, 10 % CuSO₄, and water. The organic layer was dried (MgSO₄) and evaporated to a red foam. The foam was purified by column chromatography in 1:1 CH₂Cl₂:hexanes to afford 621 mg of a red solid (72 % yield). Mp 110-112 °C (CH₂Cl₂:hexanes). ¹H NMR (400 MHz, CDCl₃) δ 11.54 (s, 1H), 11.53 (s, 1H), 10.40 (s, 1H), 9.75, (s, 1H), 8.69 (d, J= 8.4Hz, 1H), 8.45 (m, 5H), 8.00 (m, 3H), 7.70 (d, J= 8Hz, 2H), 7.65 (t, J= 8.4Hz 2H), 7.60 (d, J= 8Hz, 2H), 7.55 (m, 5H), 7.35 (t, J= 8.4Hz, 2H), 7.21 (m, 16H), 6.85 (m, 3H), 5.70 (bs, 1H), 5.12 (d, J= 12.4Hz, 1H), 4.92 (d, J= 11.6Hz, 1H), 4.46 (d, J= 7.2Hz, 2H), 4.37 (m, 1H), 4.21 (m, 1H), 1.28 (d, J= 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 153.9, 153.3, 153.1, 143.7, 143.1, 141.3, 141.4, 138.6, 136.9, 135.6, 133.1, 132.8, 129.8, 128.2, 127.8, 127.2, 127.1, 125.1, 124.5, 123.9, 122.7, 120.8, 119.0, 117.4, 117.0, 116.1, 67.3, 47.0, 30.9, 29.7. IR (CH₂Cl₂) 3353, 3187, 2908, 2251, 1803, 1733, 1607, 1587, 1521 cm⁻¹. HRMS (MALDI) m/z [Na]⁺ 1213.6 (calcd. for C₆₉H₅₄N₁₄O₇Na 1213.4).
Oligomer 2g (Cbz-L-Ala)₂(N=N)₄(NH₂). Oligomer 9 (621 mg, 0.52 mmol, 1.0 equiv) was treated with 4 Å molecular sieves (40 mg) in 2.6 mL of distilled DMF at 0 °C. Piperidine (520 μL, 440 mg, 5.217 mmol, 10.0 equiv) was then added to the solution. After 3 h, the solution was diluted with 150 mL chloroform and washed sequentially with 100 mL volumes of water, 1M H₂SO₄, 0.5 M aq. sodium bicarbonate, 10 % aq. CuSO₄, and water. The organic extracts were dried (MgSO₄) and evaporated to a red solid. This residue was purified via column chromatography in 2:1 hexanes:EtOAc to yield 410.8 mg (81.3 % yield) of a red solid. Mp 150-156 °C (CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 11.80 (s, 1H), 11.70 (s, 1H), 10.10 (s, 1H), 8.70 (d, J= 8.4Hz, 1H), 8.55 (d, J= 8.4Hz, 1H), 8.50 (d, J = 8.4Hz, 1H), 8.49 (m, 2H), 8.20 (t, J= 8Hz, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.70 (d, J= 8Hz, 1H), 7.55 (m, 3H), 7.45 (d, J= 8.4Hz, 1H), 7.26 (m, 14H), 7.18 (t, J= 8.4Hz, 1H), 6.91 (m, 3H), 6.80 (m, 2H), 5.93 (s, 2H), 5.60 (bs, 2H), 5.11 (d, J= 12Hz, 1H), 4.94 (d, J= 11.6Hz, 1H), 4.45 (bs, 1H), 1.30 (d, J= 6.8Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 161.2, 153.1, 153.0, 152.4, 149.9, 149.8, 143.0, 139.6, 139.3, 139.2, 139.1, 136.8, 136.3, 136.2, 136.0, 135.9, 133.3, 133.1, 132.9, 132.7, 129.3, 129.1, 128.8, 128.6, 128.3, 128.1, 125.8, 125.7, 124.4, 123.9, 123.6, 123.5, 123.3, 123.3, 121.0, 120.4, 120.2, 120.0, 118.1, 117.9, 117.4, 117.1, 115.4, 67.0, 51.7, 29.8. IR (CH₂Cl₂) 2980, 1705,
1620, 1521, 1211 cm$^{-1}$. HRMS (MALDI) $m/z$ [Na]$^+$ 991.5 (calcd. for C$_{54}$H$_{44}$N$_{14}$O$_5$Na 991.3).

Oligomer 3a (Cbz-L-Ala)$_2$(N=N)$_8$. Compound 2g (103 mg, 0.1032 mmol, 2.1 equiv), DMAP (15 mg) and 4 Å molecular sieves (40 mg) was dissolved in a mixture of 100 μL of pyridine and 500 μL of CH$_2$Cl$_2$ and cooled to 0 °C. Pyridine-2,6-dicarbonyl chloride (10 mg, 0.0491 mmol, 1.0 equiv) in 500 μL was added dropwise over 15 min. The sieves were then removed via filtration and the solvents were evaporated at reduced pressure (16 mm Hg). The resulting orange residue was dissolved in 100 mL CH$_2$Cl$_2$ and washed sequentially with 100 mL volumes of water, 1M H$_2$SO$_4$, 0.5 M aq. sodium bicarbonate, 10 % aq. CuSO$_4$, and followed by water. The organic layers were concentrated and the resultant residue was further purified by column chromatography in 2:1 hexanes:EtOAc to afford 11.4 mg (11.2 %) yield of the red powder. Mp 200 °C dec (hexanes:EtOAc).$^1$H NMR (400 MHz, DMSO, 70 °C) $\delta$ 11.10 (s, 2H), 10.87 (s, 2H), 10.63 (s, 2H), 9.90 (s, 2H), 8.39 (d, $J$ = 8Hz, 2H), 8.18 (d, $J$ = 8Hz, 2H), 7.95 (t, $J$ = 8Hz, 2H), 7.85 (t, $J$ = 8Hz, 1H), 7.75 (m, 6H), 7.67 (d, $J$ = 8Hz, 2H), 7.49 (m, 6H), 7.34 (m, 8H), 7.29 (bs, 2H), 7.08 (m, 36H), 6.85 (t, $J$ = 8Hz, 2H), 4.83 (d, $J$ = 16Hz, 2H), 4.73 (d, $J$ = 16Hz, 2H), 4.0 (bs, 2H), 1.21 (d, $J$ = 6.8Hz, 6H).$^{13}$C NMR (100 MHz, DMSO, 70 °C) $\delta$ 170.5, 158.8, 157.7, 155.5, 152.0, 151.5, 151.0, 147.7, 147.6, 147.0, 139.5, 139.2, 139.0, 137.9, 137.8, 137.6,
(3b) (NH2-L-Ala)2(N=N)8. Oligomer 3a (22.2 mg, 0.011 mmol, 1.0 equiv) was treated
with thioanisole (63 μL, 66.6 mg, 0.54 mmol, 50 equiv) and TFA (220 μL, 330 mg, 2.97
mmol, 270 equiv) at 0 °C resulting in a black solution. After 3 h, the mixture was poured
into 10 mL of cold EtOAc and 10 mL of 1.5 M potassium bicarbonate. The organic layer
was separated, dried (MgSO4), and evaporated to a black oil. The oil was further purified
by column chromatography using CH2Cl2 → 99:1 CH2Cl2:MeOH to afford 19.4 mg of
the oligomer 3b (red powder, 100 %) Mp 175 °C dec (CH2Cl2). 1H NMR (400 MHz,
DMSO, 70 °C) δ 11.01 (s, 2H), 10.78 (s, 2H), 10.61 (s, 2H), 8.51 (d, J= 8Hz, 2H), 8.20
(m, 2H), 7.75 (t, J= 8Hz 2H), 7.70 (m, 14H), 7.50 (m, 10H) 7.36 (m, 12H), 7.03 (m,
21H), 5.12 (m, 2H), 3.26 (m, 2H), 1.17 (d, J= 6.8Hz, 6H). 13C NMR (100 MHz, DMSO,
70 °C) δ 151.9, 147.0, 139.9, 139.1, 139.0, 138.4, 137.9, 137.7, 137.4, 136.0, 135.5,
135.3, 135.1, 134.9, 132.9, 131.8, 131.5, 130.0, 129.1, 128.4, 127.8, 127.0, 126.5, 125.5,
125.0, 124.9, 124.2, 123.0, 122.7, 122.1, 122.0, 121.5, 121.3, 120.0, 119.2, 118.0, 117.5,
117.0, 116.1, 115.0, 101.8, 31.9. IR (CH₂Cl₂) 3800, 3332, 2923, 2358, 1700, 1694, 1597, 1542 cm⁻¹. HRMS (MALDI) m/z [K]⁺ 1839.7 (calcd. for C₉₀H₇₇N₂₉O₈K 1839.5).
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423.


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CHAPTER 3
DYNAMIC, AXIALLY CHIRAL LIGANDS

3.1 Introduction

The creation of a chiral-racemic ligand that can be controlled through coordinatively coupled equilibria to yield a single handed sense is the goal of many chemists. Enzymes function by the transfer of chiral information from their folded secondary structure to active sites— the creation of a synthetic catalyst derived from small molecules that operates under the same mechanism is an as yet unachieved goal. These natural systems are highly specific and as a result, have limited use. Synthetic systems that mimic the behavior of these enzymes could potentially join the high selectivity of enzymes with the use on a broader range of compounds. The ability to synthesize such a ligand for homogeneous asymmetric catalysis is an important step towards the generation and understanding of biological systems.

3.2 Tropos and Atropos

3.2.1 Bidentate BINAP Ligands

Stereoisomers that exist due to hindered rotation around a single bond are referred to as atropisomers. Steric strain prevents facile rotation around this bond. Atroposomers
are defined as possessing the ability to interconvert between their two helical antipodes with a half-life of more than 1000 s at a particular temperature and a barrier of rotation of no larger than 22.3 kcal/mol.86

Perhaps the most ubiquitous variety of atropos molecules are grounded in Niyori’s BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) scaffold (Figure 3.1).87,88 In his initial report of this ligand, the rhodium coordinated species was shown to have high conversion and selectivity on the reduction of several olefins towards the generation of synthetic amino acids (Figure 3.2). Scores of variations of this molecule from changes in substitution pattern, metal substitution, or functionality have been investigated exhaustively.89-92

![Figure 3.1: Enantiomeric forms of Niyori’s BINAP](image-url)
### 3.2.2 Monodentate BINAP Ligands

The RajanBabu group has made use of this binaphthyl scaffold for the hydrovinylation of various aromatic olefins. Their design consisted of additions to the 3'-position of a 2-diarylphosphino-2'-alkoxy-1,1'-binaphthyl (MOP) monodentate chiral binaphthyl core. They were able to show that the addition of a single methyl group resulted in a dramatic increase on the enantioselectivity of the hydrovinylation reaction (Figure 3.3). Interestingly, when a chiral phospholane is used at the 2-position, there is no effect on the resultant enantioselectivity.

<table>
<thead>
<tr>
<th>R =</th>
<th>Catalyst</th>
<th>Prod. Config.</th>
<th>Yield</th>
<th>% ee</th>
</tr>
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<tr>
<td>E-Ph</td>
<td>(R)</td>
<td>(S)</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>(S)</td>
<td>(R)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Z-Ph</td>
<td>(R)</td>
<td>(S)</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>H</td>
<td>(S)</td>
<td>(R)</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

Figure 3.2: Nioryi’s BINAP catalysis
2,2'-binaphthol (BINOL) scaffold is often used with, but not limited to the synthesis of phosphine ligands. Orpen and Pringle have incorporated a phosphonite into this axially chiral ligand (Figure 3.4). Their easily synthesized rhodium complexes were shown to be comparable or superior to those originating from similar bidentate analogs in the reduction of methyl-2-acetamido acrylate and methyl-2-acetamido cinnamate with ee’s up to 92 %.

Figure 3.3: RajanBabu’s monodentate BINAP for hydrovinylation
Pringle’s work led Feringa to create an axially chiral, monodentate phosphoramidite ligand and compare its activity to the bidentate analog (Figure 3.5). The researchers were able support Pringle’s earlier claims and demonstrate that the conformational rigidity of bidentate ligands is not necessary for successful rhodium catalyzed asymmetric reactions. Feringa’s catalyst was easily synthesized from commercially available starting materials and gave quantitative conversion and excellent ee’s in the reduction of several dehydroamino acid derivatives (Figure 3.6). In a comparison, the bidentate analog only gave 56 % conversion after 24 h with only 72 % ee under the same
reaction conditions. High pressures accelerated the reaction and yielded the same product ee, a fact in stark contrast to the typical results observed for many bidentate ligands.  

In another example of monodentate phosphoramidites incorporated into BINOL ligands, the Chan group has employed (S)-2,2'-O,O-(1,1'-binaphthyl)-dioxo-N,N-

![Figure 3.5: Feringa’s MonoPhos phosphoramidite ligand (left) compared to its bidentate analog (right)]](image)

![Figure 3.6: Feringa’s MonoPhos results. All reactions gave 100 % conversion and R stereochemistry after 20 h.]](image)

<table>
<thead>
<tr>
<th>R, R'</th>
<th>Solvent</th>
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<th>% ee; 25 °C</th>
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<td>99.6</td>
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<tr>
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<td>95</td>
</tr>
<tr>
<td>Ph, Me</td>
<td>CH₂Cl₂</td>
<td>98.4</td>
<td>93.2</td>
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<tr>
<td>Ph, Me</td>
<td>EtOAc</td>
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<td>95.1</td>
</tr>
<tr>
<td>p-OAc-m-OMePh,Me</td>
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<tr>
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</tr>
<tr>
<td>Ph, H</td>
<td>EtOAc</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In another example of monodentate phosphoramidites incorporated into BINOL ligands, the Chan group has employed (S)-2,2'-O,O-(1,1'-binaphthyl)-dioxo-N,N-
diethylphospholidine for the use in the reduction of aryl-enamides and aryl-α-dehydroamino acid derivatives to generate synthetic amino acids (Figure 3.7). The advantage of systems similar to the one Chan describes are not limited to high conversions and ee’s, but also the ease of synthesis.

3.3 Stereocontrol Through Covalent Bonds

Jonathan Clayden’s group was able to synthesize a system that can govern stereocontrol of a Grignard addition at a remote pro-chiral site over a span of twenty bonds (2.5 nm). This behavior is similar to natural systems’ mechanism of transfer of chiral information to an active site. Figure 3.8 illustrates the method by which the control of conformationally flexible bisxanthenes by the introduction of an oxazolidine unit. The ee’s of the produced secondary alcohol after oxazolidine removal was greater than 90 % in all cases. Through scrambling of the resultant stereochemistry of the oligomer’s alcohol substituent, the researchers were then able to reintroduce the
oxazolidine unit to further confirm the amide bond’s role in the transfer of chirality through the length of the molecule.

In another example of remote chiral control, the Parquette group has recently synthesized a biaryl-based dendritic catalyst to explore the methods of long-range translation of chiral information over 14 bonds. The researchers appended an oxazoline dendrimer at the 3,3’ position of the conformationally dynamic 2,2’-
bis(diphenylphosphinoxy)biphenyl scaffold.\textsuperscript{105,106} They were able to observe changes in chirality at the central biphenyl core through covalent bonds as a result of asymmetry at the periphery of the molecule (Figure 3.9).

**Figure 3.9:** Chiral information propagates from the dendron terminal groups to the catalytic center via the biphenyl core, which serves to relay chirality to the catalytic site via its axial chirality.

Originally, the researchers appended the dendron with a chiral glycol unit (compound 3.2, Figure 3.10) but this was shown to be too flexible and yielded poor selectivity in the
catalytic reduction reaction (Figure 3.11). When the source of chirality was changed to the more rigid oxazoline group (compound 3.3) the resulting ee of the test reduction reaction increased dramatically (57 % ee at rt; 91 % ee at –20 °C). This result is similar to the rt BINAP control example (3.1).

Figure 3.10: Results of Parquette’s different catalysts in reduction shown in Figure 3.3

To verify the transfer of chirality was in fact through covalent bonds and not via steric interactions in space, the researchers changed the biphenyl- core to an atropisomeric, rigid binaphthyl- core. Here they employed an R binaphthyl- core that, according to earlier research, when coupled with the oxazoline dendron, should result in a mismatched catalytic result. Indeed, when subjected to catalytic conditions, the product was the R

79
stereoisomer instead of the dendrimer-preferred $S$; this result confirms that the chiral information of the dendron is undeniably relayed through the covalent bonds of the catalyst.

![Figure 3.11: Catalytic reaction](image)

### 3.4 Benzophenone Ligands and Catalysts

Benzophenone is a compound known for its dynamic conversion between two axially chiral enantiomers (Figure 3.12).\textsuperscript{107,108} Control of this conversion is greatly important because it can be used for determination of chiral acids,\textsuperscript{109} alcohols,\textsuperscript{110-113} and natural\textsuperscript{114} or unnatural amino acids.\textsuperscript{115} The ability to manage this exchange leads to the possibility one could control the resultant chirality and transfer it to the active site of a catalyst in an efficient manner.\textsuperscript{116}

![Figure 3.12: Interconversion between benzophenone’s two helical antipodes](image)
Mikami first devised the use of benzophenone as a ligand for asymmetric catalysis in 2006. Asymmetry was granted through coordination with (S,S)-diphenylethyl diamine (DPEN) chiral diamine (Figure 3.13). Comparing the diphosphino-benzophenone (DPBP) to (R)-BINAP with DPEN as the chiral inducer, the DPBP ligand had both larger percent conversion and a higher resultant ee for the reduction of several benzylic amines (Figure 3.14).

Figure 3.13: Mikami’s DPBP ligand and (S,S)-DPEN chiral inducer
The Ding group created a rigid bidentate benzophenone through the coordination of a metal and various chiral diamines. The researchers equated the conformational stability of their ligand to previously reported BINAP and biphenyl analogs; they noted that once coordinated, the benzophenone ligand becomes static and does not convert between its two helical antipodes (Figure 3.15). The catalyst gained its handedness by coordination to optically pure diamines which had also been coordinated to Ru\textsuperscript{II} metal (Figure 3.15). In various alcoholic solvents, the catalyst was able to reduce a wide assortment of aryl carbonyls to their corresponding alcohols with greater than 99 \% conversion and generally greater than 90 \% ee. Interestingly, the researchers

<table>
<thead>
<tr>
<th>R</th>
<th>Diphosphine</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<tr>
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<td>(R)-BINAP</td>
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<td>72</td>
</tr>
<tr>
<td>naphthalene</td>
<td>DPBP</td>
<td>&gt; 99</td>
<td>99</td>
</tr>
<tr>
<td>o-tolyl</td>
<td>(R)-BINAP</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
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<td>DPBP</td>
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<td>99</td>
</tr>
<tr>
<td>m-tolyl</td>
<td>(R)-BINAP</td>
<td>97</td>
<td>68</td>
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<td>91</td>
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<td>DPBP</td>
<td>97</td>
<td>89</td>
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</table>

Figure 3.14: Mikami’s catalytic results
hypothesized that the main feature that caused the catalyst to be conformationally stable is that the bridging carbonyl also coordinates to the metal; they did not address the possibility that the ligand’s carbonyl could reduce under the reaction conditions.

To explore the role the benzophenone carbonyl plays in the catalyst stability, Mikami produced a reduced version of the scaffold for comparison to the oxidized version. It was theorized this reduced species might be present in the hydrogenation reaction. In the absence of the ketone, the percent conversion and resultant ee was significantly lower (Figure 3.16). This result confirms the earlier hypothesis that the benzophenone carbonyl also coordinates the metal. The researchers also determined the benzophenone catalyst generally produced higher ee’s than BINAP on a litany of benzylic ketones.
Mikami has succeeded his benzophenone work by the full reduction of the ligand’s carbonyl to a methylene spacer.\textsuperscript{121,122} This more reactive phosphoramidite catalyst was again more efficient more selective than the BINOL derived phosphoramidite class towards several different metal-mediated alkylation reactions. The results of several of these catalytic reactions are shown in Figure 3.17.
3.5 Benzophenone as a Chiral Sensor

A recent communication employed 2,2′-dihydroxybenzophenone as a chiral sensor to detect the optical purity of synthetic amino acids (Figure 3.18). Azobenzene chromophores were appended to the molecule in the 5,5′ positions for tracking chiral induction spectroscopically (Figure 3.19). Various amino acids were then introduced to the scaffold via imine formation at the bridging carbonyl. The induced chirality is then expressed through the length of the compound and can be tracked by CD spectroscopy. Use of opposite enantiomers of the inducing amino acid yielded an overall sign change in the CD spectra (Figure 3.20).
The researchers revealed the hydrogen bonding between the imine and the 2,2'-dihydroxy subunits are integral to the stability of the complex. If the imine is dissolved in a protic solvent, the hydrogen bonding network is disrupted and chirality is not transferred. Additionally, if the amino acids exist in a form other than a carboxylate salt (due to pH changes or blocking of the acid functionality), then induced chirality decreases greatly. Another advantage to the 2,2'-dihydroxy substituents is imine
formation occurs within minutes at room temperature whereas without these stabilizing interactions, the imine requires several weeks to form.\textsuperscript{123}

\textbf{Figure 3.19:} Conformational change induced by introduction of amino acid

\textbf{Figure 3.20:} Induced circular dichroism of azo-benzophenone compound
The next chapter will join the concepts of introducing chirality into a benzophenone architecture and then employing the subsequent ligand for asymmetric catalysis. We are hypothesizing that chirality can be amplified through a dynamic scaffold and then transferred to a catalytically active site.

3.6 Conclusions

There are numerous unique strategies for chiral induction in synthetic systems. The fact that, “achieving 95 % ee only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane,” the design of usable synthetic catalysts is quite challenging. Applying chirality to synthetic, dynamic systems to approximate the methods by which biological processes operate is important towards understanding how these methods act; this knowledge can also lead to the necessary insight for the rational design of useful synthetic catalyst systems.
3.7 References


CHAPTER 4

PROGRESS TOWARDS THE DESIGN AND SYNTHESIS OF A DYNAMIC, AXIALLY CHIRAL BENZOPHENONE-BASED PHOSPHOROUS CATALYST

4.1 Introduction

Chiral induction is an important field in chemistry that encompasses a wide variety of subjects such as the design of biomimetic systems\textsuperscript{1,2,78,79} to the creation of useful catalysts\textsuperscript{90-92,99,104}. Prior work in the use of benzophenone as a ligand for metal mediated reactions has focused exclusively on the use of chiral diamines to generate a handed, rigid ligand\textsuperscript{116-118,120-122}. Kim, Chin, and Hong have uniquely made use of benzophenone’s ability to exist in two enantiomeric, propeller-like forms to test for the optical purity of synthetic amino acids\textsuperscript{123}. This chapter reports progress towards benzophenone as a chiral, dynamic ligand for asymmetric catalysis. The proposed method of asymmetric induction results from a simple chiral amine introduced into the racemic benzophenone scaffold. This chiral perturbation will propagate through the compound such that it forces benzophenone to adopt a single handed sense. As a result, this handed bias can then be used to influence the chiral environment around a metal atom to generate a chiral catalyst.
4.2 Research Design

Benzophenone exists in two enantiomeric propeller-like forms. If a handedness could be imparted to this racemic structure then it is hypothesized that the chiral information could be amplified through the molecule’s skeleton and then transferred to a catalytically active site. Perhaps one of the reasons that BINAP is an efficient and useful catalyst is its ability to retain chiral handedness yet still be conformationally flexible allowing for facile introductions of substrates. According to studies performed by Mikami, the coordinated benzophenone scaffold also possesses this flexibility. However, prior studies have shown that the coordinated benzophenone ligands are not conformationally dynamic. Our goal is to create a dynamic catalyst that utilizes benzophenone and study how chiral information is propagated through the ligand and transferred to the active site.

Figure 4.1: 2-2′-dihydroxy benzophenone’s two enantiomeric forms
There are several advantages of this type of catalyst. One benefit is the short and relatively simplistic approach to the target compound—a great improvement to some elegantly designed, yet complex systems.\textsuperscript{104} Another novel benefit to the proposed system would be the modular nature of chiral induction. Different enantiomers of a chosen chiral amine would produce opposite diastereomers of catalyst. In this way, a researcher can choose which catalyst would be necessary to undergo a stereospecific reaction to yield the desired product and \textit{vice-versa}. In theory, if a particular imine catalyst yielded the incorrect product stereoisomer, obtaining the correct product would be no more difficult than using the enantiomer of the previously utilized amino.

Originally we envisioned substituents on the 4,4′ position possessing the same connectivity as reported in the literature (Figure 4.2).\textsuperscript{123} We also hypothesized that changing the connectivity to the 6,6′ position would result in more steric interaction between the two phenyl groups that could be transferred to the catalytic site. Aryl phosphines were envisioned for use because of their stability under typical laboratory conditions resulting in easy bench top manipulations. Later the functionality can be manipulated to other phosphorus containing groups such as the more reactive phosphoramidites to be exploited in different catalytic reactions.\textsuperscript{88,125-134} This modularity is integral for selecting the best catalyst and metal combination for maximum effectiveness.
The proposed method of chiral induction for the proposed benzophenone system originally was through the introduction of a chiral benzyl- or akyl amine such as D-\textit{alpha}-methylbenzyl amine or D-\textit{alpha}-methylecyclohexyl amine to the carbonyl of the benzophenone. The resultant imine would be stabilized by favorable 1,3-hydrogen bonding interactions (Figure 4.3).\textsuperscript{123} This modular chiral source would allow for a cost-effective supply of handedness which could be fine-tuned to a particular reaction (\textit{id est} more or less chiral bulk, solubility, or different R- group choices). This strategy is similar to previously used sources of chirality such as atropisomers of binaphthyl compounds that are not dynamic or amines that must be coordinated to a metal such as rhodium.
4.3 Results and Discussion

Unfortunately, both amino acids and aryl R- groups have posed a solubility problem. Additionally, the acid moiety could potentially interfere with the formation and stability of the phosphoramidite catalyst (Figure 4.4). It was for this reason that D-alpha-methylbenzyl amine was utilized in lieu of an amino acid as a chiral perturbation. However, this imine also proved to be insoluble in organic solvents. Fortunately, when the D-alpha-methylbenzyl amine was replaced with D-alpha-methylocylohexyl amine, the resulting imine increased in solubility.
A drawback of the proposed catalyst design is that it cannot be used for reduction reactions because it would result in the transformation of the imine to a secondary amine thereby negating the hydrogen bonding of the catalyst. However, it should be noted that this supposed limitation has not stopped prior researchers from using reaction conditions that are not amenable to their catalyst system.\textsuperscript{118}

One of our goals with this modular scaffold was to create several catalysts of varying composition (\textit{id est.} different sources of chirality; phosphoramidites vs. phosphines; different substitution patterns of the phosphorus; metal coordination by oxazoline end groups; \textit{et cetera}.) to study the differences in chiral induction and catalyst efficacy. While rational catalyst design has been referred to as a “pipe dream”\textsuperscript{135} as of late, perhaps
some insight may be gained into how to better construct a catalyst for a specific asymmetric application.

### 4.3.1 Synthesis

The original design of the molecule consisted of the installation of a pair of nitro-groups in the 5,5′ position of 2,2′-dihydroxybenzophenone (Scheme 4.1). The bis-nitro compound could then either be reduced to provide an amine that can be appended with the Trost-type ligand, or converted to a different functionality such as a halide. The nitration proceeded smoothly with an average of 40 % yield of the desired compound and a consistent yield of 50 % of the 3,5′ regio-isomer.\textsuperscript{136,137} The reduction of the nitro groups under either H\textsubscript{2} gas or with acidic tin then encountered difficulties, as the diamine was difficult to isolate. This complication was likely due to intermolecular imine oligomerization. Regardless, attempts to convert this amine to a halide or produce an amide bond via countless methods proved fruitless. Only sub-marginal yields of the bromine variant were obtained using copper chemistry and purification was near impossible on such a small scale.\textsuperscript{138}

![Scheme 4.1: Nitration and reduction of 2,2′-dihydroxy benzophenone](image-url)
In light of the difficulties observed with the initial synthetic strategy, efforts were then shifted towards a Friedel-Crafts approach (Scheme 4.2).\textsuperscript{139} Initially the free hydroxy’s-were protected with as acetate groups. Under reaction conditions, the acetates were cleaved leading to acylated side products. This functionality was varied to methoxy-, allyl-, alloc-, and piv- groups and then subsequently revealed to the hydroxy- in the nucleophilic unit. All of the hydroxy- protecting variants were cleaved and did not result in any product.

![Scheme 4.2: Friedel-Crafts pathway](image)

Unfortunately, attempts utilizing different protecting groups, solvents, temperatures, or Lewis acid catalysts also provided no yield of the intended compounds. The only major fractions isolated were starting materials, deprotected starting materials, or the symmetrical anhydride from incomplete acid chloride formation.
The next strategy employed an organo-lithium approach with a different connectivity (Scheme 4.3). This connectivity allows for excellent selectivity for deprotonation with organo-lithium reagents for the potential of more steric crowding around the proposed catalytic site. The synthesis began with resorcinol first mono-protected as a methoxy-resorcinol\textsuperscript{140} which was then converted to 3-methoxy-methyl anisole.\textsuperscript{141} This bis-protected compound was then \textit{ortho}-lithiated and quenched with DMF to yield a functionalized benzaldehyde.\textsuperscript{142} The resulting aldehyde was then used to quench another equivalent \textit{ortho}-lithiated 3-methoxy-methyl anisole to grant a symmetrical dibenzyl alcohol (Scheme 4.4). The oxidation to the corresponding benzophenone was performed with the Dess-Martin periodinane (DMP) in good yield.\textsuperscript{143} Earlier attempts at using various chromium or modified Swern conditions were been less than favorable (Table 4.1). Chromium reagents had a tendency to decompose the molecule and cleave the protecting groups whereas Swern and Swern-like conditions replaced the bridging hydroxide with a halide.
Great difficulty was also met in the removal of the methoxy-methyl (MOM) protecting groups (Table 4.2).\textsuperscript{152} Under typical mineral acid conditions, the reaction proceeds quickly, but yields large amounts of baseline compounds. Originally these were believed to be quinine-like isomers of the product, but upon adjusting the pH of the isolated material, no product was observed. Most likely, these are resorcerene type polymers. After screening several methods for MOM-deprotection, success was achieved via an \textit{in-situ} generation of MgBr\textsubscript{2} and treatment with ethane thiol (Table 4.2, Scheme 4.4).\textsuperscript{153-155} The reaction proceeded quickly with a near-quantitative yield.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>% Yield</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC\textsuperscript{144}</td>
<td>0</td>
<td>Baseline</td>
</tr>
<tr>
<td>Jones\textsuperscript{145,146}</td>
<td>5</td>
<td>Over-oxidized</td>
</tr>
<tr>
<td>Swern\textsuperscript{147,148}</td>
<td>&lt; 10</td>
<td>Chlorinated</td>
</tr>
<tr>
<td>Modified Swern\textsuperscript{149}</td>
<td>20</td>
<td>Chlorinated</td>
</tr>
<tr>
<td>NBS conditions\textsuperscript{150}</td>
<td>50</td>
<td>Brominated</td>
</tr>
<tr>
<td>Dess-Martin\textsuperscript{143,151}</td>
<td>Quantitative</td>
<td>Desired</td>
</tr>
</tbody>
</table>

\textbf{Table 4.1: Oxidation Conditions}

\textbf{Scheme 4.4:} Coupling and subsequent oxidation and deprotection of pre-catalyst
After removal of the MOM- groups, the now revealed hydroxy substituents were converted to triflates\textsuperscript{159} to be later used in metal mediated conversion to phosphines (Scheme 4.5). The methoxy functionalities were then cleaved with BBr\textsubscript{3} to reveal the free benzyl hydroxy groups.\textsuperscript{160}

![Scheme 4.5: Substitution and deprotection of benzophenone pre-catalyst](image)

Conversion of the triflate groups to phosphines or phosphoramidites\textsuperscript{130} at this point in the synthesis proved to be unfeasible. Several methods were screened including different combinations of transition metals, ligands, nitrogen bases, solvents, temperatures, and reaction times. Metals NiCl\textsubscript{2}(dppe),\textsuperscript{88,118,161-163} Pd(PPh\textsubscript{3})\textsubscript{4},\textsuperscript{133} and Pd(OAc)\textsubscript{2}\textsuperscript{134}
resulted only in starting materials although occasionally nickel reduced the triflate to an aryl product; a result that illustrates the first few steps of the catalytic cycle are feasible, but the insertion of the phosphine was problematic most likely due to steric.

Additionally, attempts to shorten the synthesis by several steps through the utilization of a dimerization approach were attempted.\textsuperscript{164} Unfortunately, efforts at performing a single coupling of a 3-methoxy-methyl anisole-cuprate species with phosgene or triphosgene to yield the desired benzophenone only yielded recovered starting material (Scheme 4.6). This dimerization was attempted with several different metals and in the absence of metals. The ortho-lithiation was also attempted with a symmetrical dimethoxymethyl resorcinol; however, the MOM- groups could not be selectively deprotected for this strategy to be viable.

Scheme 4.6: Dimerization strategy
4.3.2 Spectral Data

As mentioned earlier, a potentially problematic issue would be the free hydroxyl group on the phenyl ring interfering with the phosphoramidite coordinating with the metal. An rational solution to this problem would be to protect the free hydroxy- as a methoxy- group. However, disrupting the favorable hydrogen bonding to the imine might result in the catalyst losing some induced chirality.

To evaluate this potential difficulty, CD traces of several model systems were examined (Figure 4.5). Control 1 possesses full hydrogen bonding capability whereas 2 has the hydrogen bonding component removed. Control 3 (actually an intermediate towards the target molecule) retains the planned hydrogen bonding and features steric crowding with the addition of substituents at the 6 and 6’ positions. As seen in the spectra in Figure 4.6, the CD of control 1 with the free hydroxy- group in the 2,2’ position gives an intense signal. The non-hydrogen bonding, methoxy- protected 2 reveals a
slightly decreased intensity and a change of sign. This result suggests that the lack of hydrogen bonding in the methoxy-analog might be more dynamic due to the loss of stability.

Figure 4.6: Evaluation of hydrogen bonding’s effect
CD’s of control compounds 1 and 3 in Figure 4.7 illustrate the steric interaction at the 6,6’ site of 3 does not result in a significant loss of signal intensity which can be interpreted as a retention of chirality with an increase in steric bulk.

Figure 4.7: Effect of steric crowding at the 6,6’ positions
4.4 Conclusions

The initial steps towards a dynamic, modular, axially chiral catalyst have been reported. Unfortunately, the research has experienced difficulties with the final synthetic steps. Current work in our research group is underway to remedy the synthetic issues by alteration of the catalyst design for a more facile path towards a target molecule. We have seen that intramolecular forces and slight chiral perturbations are capable of imparting bias to the benzophenone skeleton in a single-handed sense.

4.5 Experimental Section

General Methods.

Infrared spectra were recorded on a Perkin-Elmer Model 1600 instrument. $^1$H NMR was recorded at 400 MHz or 500 MHz and $^{13}$C NMR spectra on a DPX-400 or DRX-500 instrument as indicated. Circular dichroism (CD) measurements were carried out on an Aviv 202 CD spectrometer, using optical grade solvents and quartz glass cuvettes with a 10 mm path length. Electrospray mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. MALDI-TOF spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All starting materials were used as supplied from commercial suppliers unless otherwise noted. All reactions were carried out under a $N_2$ atmosphere unless otherwise noted. Dimethylformamide (DMF) was dried by distillation from MgSO$_4$; Tetrahydrofuran (THF) and diethyl ether ($$Et_2$$O) were distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium
hydride. All melting points were recorded in glass capillaries and are uncorrected. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents.

**Abbreviations:** DMF = \(N,N\)-dimethylformamide; TFA = trifluoroacetic acid; TMEDA = tetramethylethlenediamine HNO\(_3\) = nitric acid; \(i\)-PrOH = isopropyl alcohol; \(n\)-BuLi = \(n\)-butyl lithium; \(t\)-BuLi = \(t\)-butyl lithium; TMS-Cl = trimethyl silylchloride; TLC = thin layer chromatography; Me\(_2\)SO\(_4\) = dimethyl sulfate. DIEA = \(N\)-ethyl-\(N\)-(1-methylethyl)-2-propanamine; MOM = methoxy-methyl.

\[\text{HO} \quad \text{Br}\]

\[\text{HO} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H}\]

11.14.X\(^{136,137}\)

The 4,4′-dihydroxy benzophenone (1.0 eq, 2.33 mmol, 500 mg) was dissolved in 10 mL acetonitrile and 6.1 mL of 30 % HNO\(_3\) was added drop wise over twenty min. After two hours, the reaction was concentrated *in vacuo* to a light solid. This solid was dissolved in 20 mL ethyl acetate and washed with brine thrice. The organic extract was dried,
1.45 g (1.0 eq, 5.97 mmol) of the starting aldehyde was dissolved in 60 mL acetone and treated to 3.55 mL of a pre-made Jone’s oxidation solution (1.1 eq, 6.56 mmol) at 0 °C. After 1h, 15 mL of i-PrOH was added slowly to the dark solution. The resultant blue-green suspension was filtered through celite and concentrated in vacuo to a white solid. The solid was taken up in dichloromethane and washed with brine, dried, and concentrated to a grant 1.55 g as a white solid (quant. yield). Mp 215 °C (CH₂Cl₂). ¹H-
NMR (500 MHz, CDCl₃, 22 °C) δ 8.25 (doublet, \( J = 2.5 \) Hz, 1H), 7.55 (doublet of doublets, \( J = 2.5, 8.5 \) Hz, 1H), 7.05 (doublet, \( J = 8.5 \) Hz, 1H), 2.36 (singlet, 3H). \(^{13}\)C-NMR δ 169.3, 168.0, 150.3, 137.7, 135.2, 125.8, 123.8, 119.2, 20.9. IR (CHCl₃) 2800, 1790, 1686, 1201 cm\(^{-1}\). HRMS (ESI-MS) \( m/z \) [Na] + 280.9 (calcd. for C₉H₇BrNaO₄ 280.94).

3-methoxyphenol; 150-19-6; 13.7.X\(^{140,165}\)

Resorcinol (12.06 g, 1.0 eq, 109.5 mmol), dried potassium carbonate (2.9 eq, 31.8 mmol, 44 g) and 60 mL of acetonitrile and 20 mL of DMF were placed in a 500 mL flask with condenser under N₂. Me₂SO₄ was added slowly over five minutes. After a reaction period of fifteen minutes, the reaction turned a dark color. After 1.5 hours, the now lighter colored reaction was judged to be complete by TLC and was concentrated on a rotovap to a white residue. This was dissolved in ethyl acetate and washed with water. The gold organic layer was separated from the black aqueous layer. The organic layer was washed with brine, dried and concentrated to a red oil. Chromatographed in 6:1 hexane:ethyl acetate to yield 7.01 g of a gold oil (51.6 % yield). \(^1\)H-NMR (400 MHz, CDCl₃, 22 °C) δ 7.11 (triplet, \( J = 8 \) Hz, 1H), 6.45 (multiplet, 3H), 3.80 (s, 3H). \(^{13}\)C-NMR
4.6 g of sodium hydride (3.0 eq, 193.7 mmol) was suspended in 130 mL of distilled THF and cooled to 0 °C. The 3-hydroxy anisole (1.0 eq, 8.02 g) was then added drop wise over fifteen minutes. The now gray suspension was allowed to warm to rt. 10.3 mL methoxy-methyl chloride (2.1 eq, 135.6 mmol, 10.9 g) was added after one hour. After 30 minutes, the reaction was again cooled to 0 °C and water was added slowly to yield a yellow suspension. This reaction was concentrated on a rotovap to a yellow oil with a white solid. The flask’s contents were then dissolved in 200 mL each of water and ethyl acetate. The organic layer was removed and the aqueous layer was extracted thrice more with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated to a yellow oil. This crude oil was purified by column chromatography (6:1 hexane:ethyl acetate) as a clear oil. 4.62g (42.5 % yield). $^1$H-NMR (400 MHz, CDCl$_3$, 22 °C) δ 7.20 (triplet, $J$= 8Hz, 1H), 6.67 (doublet of doublet of doublets, $J$= 2, 4, 8 Hz, 1H), 6.63 (triplet, $J$= 4Hz, 1H), 6.58 (doublet of doublet of doublets, $J$= 2, 4, 8 Hz, 1H),
5.18 (singlet, 2H), 3.81 (singlet, 3H), 3.50 (singlet, 3H). $^{13}$C-NMR $\delta$ 160.8, 158.5, 129.9, 108.4, 107.5, 102.7, 94.5, 56.0, 55.3. IR (CH$_2$Cl$_2$) 1300, 1195 cm$^{-1}$. HRMS (ESI-MS) $m/z$ [Na]$^+$ 191.1 (calcd. for C$_9$H$_{12}$NaO$_3$ 191.07).

2-Methoxy-6-(methoxymethoxy)benzaldehyde; 73220-19-6; 13.9.X

3.53 g of 3-methoxy-methyl anisole (1.0 eq, 20.99 mmol) with 3.5 mL TMEDA (1.1 eq, 23.09 mmol, 2.68 g) were cooled to $-78$ °C in 50 mL Et$_2$O. $t$-BuLi (15.4 mL, 1.1 eq, 23.09 mmol, 1.5 M) was added over five minutes. The reaction became yellow and cloudy. After 1h, 3 mL of distilled DMF (2.0 eq, 73.1 mmol, 3.06 g) was added. The reaction became a lighter color. This addition was followed by 3.5 mL (1.3 eq, 27.29 mmol, 2.96 g) of TMS-Cl an hour later. Water was then added and the gooey-yellow solution was allowed to warm to rt. The reaction was concentrated $\textit{in vacuo}$, dissolved in 100 mL ethyl acetate and the organic layer was removed. The organic extract was then washed with 10 % copper (II) sulfate followed by brine, dried, and concentrated to a yellow oil. This was chromatographed through a plug of silica in 5:1 hexanes:EtOAc to yield 4.10 grams of a yellow oil (quantitative yield). Mp 141-143 °C (hexanes:EtOAc).

$^1$H-NMR (400 MHz, CDCl$_3$, 22 °C) $\delta$ 11.95 (singlet, 1H), 7.35 (triplet, $J=8$ Hz, 1H), 6.47
(doublet, \( J = 8 \text{Hz}, 1 \text{H} \)), 6.33 (doublet, \( J = 8 \text{Hz}, 1 \text{H} \)), 5.40 (singlet, 2H), 3.83 (singlet, 3H), 3.50 (singlet, 3H). \(^{13}\)C-NMR \( \delta \) 194.3, 163.6, 162.5, 138.4, 110.8, 109.7, 101.0, 94.9, 56.7, 55.8. IR (CH\(_2\)Cl\(_2\)) 2095, 1620, 1398, 1200 cm\(^{-1}\). HRMS (ESI-MS) \( m/z \) [Na] + 219.1 (calcd. for C\(_{10}\)H\(_{12}\)NaO\(_4\) 219.06).

\[
\text{\includegraphics[width=0.5\textwidth]{structure.png}}
\]

14.1.X

398.6 mg (1.0 eq, 2.37 mmol) of the 3-methoxyl-methyl anisole and 250 \( \mu \)L (1.1 eq, 2.61 mmol, 190.6 mg) of TMEDA were cooled to –78 °C in 5.0 mL Et\(_2\)O. 1.5 mL of t-BuLi (1.05 eq, 2.49 mmol, 1.6 M) was added slowly over 25 min. The aldehyde (488 mg, 1.05 eq) in 2.0 mL Et\(_2\)O was then added to the pale yellow suspension after 1 h. The reaction was then warmed to room temperature. Water was added to the reaction and then the organic layer was removed. The aqueous layer was acidified and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated to a light oil. This was chromatographed in 4:1 hexanes:EtOAc to yield 261.0 mg (30 % yield). Mp 220 °C dec (hexanes:EtOAc). \(^1\)H-NMR (400 MHz, CDCl\(_3\), 22 °C) \( \delta \) 7.09 (triplet, \( J = 8 \text{Hz}, 2 \text{H} \)), 6.70 (doublet of doublets \( J = 2, 8 \text{Hz}, 2 \text{H} \)), 6.57 (doublet of doublets,
$J$=2, 8 Hz, 2H), 5.66 (doublet, $J$= 8 Hz, 1H), 5.06 (singlet, 4H), 3.79 (singlet, 6H), 3.26 (singlet, 6H). $^{13}$C-NMR $\delta$ 158.6, 155.6, 127.8, 121.3, 107.5, 105.4, 94.4, 64.8, 56.0, 55.8. IR (CH$_2$Cl$_2$) 3501, 2954, 2900, 1593, 1469, 1295 cm$^{-1}$. HRMS (ESI-MS) m/z [Na]$^+$ 387.1 (calcd. for C$_{19}$H$_{24}$NaO$_7$ 387.11).

**14.2.X$^{143,151}$**

The benzyl alcohol (1.05 g, 2.75 mmol, 1.0 eq) was dissolved with NaHCO$_3$ (2.31 g, 27.5 mmol, 10 eq) in 5 mL of distilled chloroform at room temperature under nitrogen. The Dess-Martin periodinane was added in 5 mL CHCl$_3$ that had been previously doped with water. After 1.5 h, 2 mL of 1M NaOH was added to the white suspension and stirred for 15 minutes. The organic layer was then removed and the aqueous layer was washed thrice more with chloroform. The combined organic layers were washed with brine, dried, and concentrated to an orange-white residue. This was pre-absorbed to silica and chromatographed in 4:1 $\rightarrow$ 2:1 hexanes:ethyl acetate. The compound was concentrated to a yellow oil that became an oily solid upon prolonged treatment to vacuum. The reaction yielded 859.6 mg (86 % yield). Mp 107-110 °C (hexanes:EtOAc). $^1$H-NMR
(400 MHz, CDCl₃, 22 °C) δ 7.08 (triplet, J= 8 Hz, 2H), 6.71 (doublet, J= 8Hz, 2H), 6.56 (doublet, J= 8 Hz, 2H), 5.08 (singlet, 4H), 3.78 (singlet, 6H), 3.28 (singlet, 6H). ¹³C-NMR δ 194.5, 158.7, 156.1, 127.3, 120.3, 107.4, 105.4, 94.5, 55.9, 55.8. IR (CH₂Cl₂) 2900, 1587, 1470, 1151 cm⁻¹. HRMS (ESI-MS) m/z [Na] + 385.1 (calcd. for C₁₉H₂₂NaO₇ 385.13).

14.3.X
The protected benzophenone (115.8 mg, 1.0 eq, 0.320 mmol) was dissolved in 1.0 mL of acetonitrile and then subjected to 530 μL 6M HCl (10.0 eq, 3.20 mmol) at rt. After 3 h, the yellow solution was washed with 50 mL of DCM. The organic extract was washed with brine, dried, and concentrated to a yellow residue. The residue was passed through a plug of silica with 5:1 hexanes:ethyl acetate as the eluent to yield a yellow/white solid, 30 mg, 32 % yield. Mp 140-143 °C (hexanes:EtOAc). ¹H-NMR (400 MHz, CDCl₃, 22 °C) δ 10.09 (s, 2H), 7.31 (triplet of doublets, J = 4, 8Hz, 2H), 6.63 (doublet of doublets, J = 4, 8Hz, 2H), 6.35 (doublet of doublets, J = 4, 8Hz, 2H), 3.57 (singlet, 6H). ¹³C-NMR δ
194.3, 163.7, 162.5, 138.4, 110.9, 109.9, 101.0, 55.8. IR (CH$_2$Cl$_2$) 3500, 1585, 1469, 1154 cm$^{-1}$. HRMS (ESI-MS) $m/z$ [Na] $+$ 297.1 (calcd. for C$_{17}$H$_{14}$NaO$_5$ 297.07).

16.3.X$^{159}$

The starting benzophenone (500 mg, 1.0 eq, 1.82 mmol) (14.3.X) was dissolved in 3.3 mL each of pyridine and CHCl$_3$ under nitrogen. Triflic anhydride (1.5 mL, 2.36 g, 5.0 eq, 8.39 mmol) was added slowly over ten minutes. During the addition the reaction changed color from yellow to orange and then eventually black. After five hours, the reaction was concentrated on a rotovap to a black solid. The residue was dissolved in CHCl$_3$ then washed sequentially with equal volumes of 1M H$_2$SO$_4$, 10 % CuSO$_4$, and brine. The organic layer was dried over Na$_2$SO$_4$ and filtered through a plug of SiO$_2$ to yield 867.7 mg as a white solid (86.3 % yield). Mp 152-155 °C (CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$, 22 °C) $\delta$ 7.47 (triplet, $J$= 8Hz, 2H), 7.00 (doublet, $J$= 8Hz, 2H), 6.92 (d, $J$= 8Hz, 2H), 3.66 (singlet, 6H). $^{13}$C-NMR $\delta$ 186.6, 159.0, 147.1, 132.3, 120.0, 116.9, 113.9, 111.5, 56.3. IR (CHCl$_3$) 2910, 1721, 1626, 1585, 1471, 1149 cm$^{-1}$. HRMS (ESI-MS) $m/z$ [Na] $+$ 561.0 (calcd. for C$_{17}$H$_{12}$F$_6$NaO$_9$S$_2$ 560.97).
200 mg of the starting protected benzophenone (1.0 eq, 0.371 mmol) was dissolved in 3.7 mL of CHCl₃ under N₂ at 40 °C. BBr₃ (175 μL, 464.2 mg, 5.0 eq) was added as one amount. Reaction was refluxed for 8 h and then poured into 100 mL water. The organic layer was removed and washed with brine, dried over Na₂SO₄, and filtered through a plug of SiO₂. The brown solid and then chromatographed with DCM as the eluent to give 48.5 mg (26 % yield) as a white solid. Mp 160-162 °C (CH₂Cl₂). ¹H-NMR (400 MHz, CDCl₃, 22 °C) δ 9.83 (s, 2H), 7.58 (triplet, J = 8Hz, 2H), 7.18 (doublet of doublets, J = 4, 8Hz, 2H), 6.86 (d, J = 8Hz, 2H). ¹³C-NMR δ 194.8, 161.6, 147.1, 136.1, 123.8, 119.2, 116.8, 113.2. IR (CHCl₃) 3510, 1720, 1620, 1582, 1470, 1152 cm⁻¹. HRMS (ESI-MS) m/z [Na] + 532.9 (calcd. for C₁₅H₈F₆NaO₉S₂ 532.9).
4.6 References


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CHAPTER 5

STRUCTURE AND SELF-ASSEMBLY OF PERYLENE AMPHIPHILES INTO VARIOUS 1D N-TYPE NANOSTRUCTURES

5.1 Introduction

The ordered self-assembly of poly-aromatic molecules are an emerging field in materials science. These assemblies are commonly employed in the creation of synthetic photovoltaic cells for the conversion of light to electrical energy.\textsuperscript{169,170} The majority of assemblies of this kind are comprised of electron rich n-type semiconductors; however it is necessary to generate electron poor p-type assemblies comprised of \(\pi\)-assemblies to act as complementary partners in the development of charge separated pairs.\textsuperscript{171-174} This process takes place by the excitation of an electron to a higher energy orbital of a donor molecule which then transfers to an acceptor molecule.\textsuperscript{175-178} Additionally, it is highly desirable to control the well-defined arrangement of the assemblies by the addition of different solubilizing groups.\textsuperscript{179} The manner by which these molecules are arranged determines many of the assembly’s properties.\textsuperscript{180,181} Better design in the field of charge separated molecules will lead to higher efficiency and better power conversion in these
These synthetic assemblies can then be applied towards the creation of high efficiency, low-cost photovoltaic cells. These three dimensional networks have been used for functional nanomaterials such as transport channels, nanotube materials, gels, optoelectronic devices, and sensing.

The introduction of chirality into supramolecular scaffolds is essential in drawing comparisons to natural systems. Sugars, nucleic acids, and amino acids are common asymmetric directors in biological structures. The ability to mimic analogs of the body’s self-assembling processes is important to the understanding of how certain diseases act upon humans. Chirality in supramolecular systems is also a useful technique to monitor the formation of assemblies by spectroscopic methods such as circular dichroism.

Amyloidosis is the transition of the body’s α-helix rich proteins into β-sheet assemblies. A protein’s conversion of its secondary structure into this diseased amyloid form is generally associated with the aging process. In mammalian systems, this change is likely due to oxidation of the body’s proteins by free radicals. These depositions of proteins with an irregular secondary structure, are presumed to cause many diseases including Parkinson’s, Type II diabetes, and Alzheimer’s. The cross-linked β-sheet assemblies are far less soluble than their natural α-helix analogs. Understanding the controlling factors of this transition through synthetic means by varying hydrophobic regions and altering protein sequences to changing secondary structure is essential in elucidating the causes, treatments and preventions of amyloidosis.
Perylene is a long-known polycyclic, polyaromatic molecule historically utilized as a dye and pigment. It has only been recently used in n-type (electron poor) semiconductor and self-assembly research. We focused our research on perylene diimides (also referred to as perylene bisimides) because of its potential as an electron acceptor for solar energy conversion, in molecular electronics, in light harvesting, as semi-conductors, in self-repairing self-assembly, in molecular recognition, and biomimetic electron-transfer units.

5.2 Achiral Self-Assembly of Perylenes

Frank Würthner has contributed numerous publications in the field of self-assembly of perylene. In an achiral example, a symmetrical perylene with long aliphatic chains was synthesized (Figure 5.1). The fibers of the assembly formed a gel at < 2 wt % in non-polar aliphatic or aromatic solvents (Figure 5.2, inset). The change from monomer to gel was observed via UV spectra while decreasing the temperature of the sample (Figure 5.2). More polar solvents interfered with the intermolecular hydrogen bonding between the monomer subunits and prevented gelation. Interestingly, the compound effectively gelated in thiophene—a p-type semiconductor that is electron rich. The combination of an electron rich compound with one that is electron poor can result in a formation of a gel that is capable electron transport. The subsequent mixture of enantiomeric assemblies that formed can be viewed by atomic force microscopy (AFM) (Figure 5.3).
A common example of perylene assemblies are discotic helical columns. Often these are facilitated by solvent-assisted nucleation/solvophobic effects. As illustrated above, Würthner and his researchers constructed a chiral perylene dye that assembles into semi-conducting rods (Figure 5.4). These chiral assemblies are concentration and temperature dependant. At low concentration or high temperature the monomers
assemble into $M$-dimers. With time, the dimers equilibrated into polymers with a $P$-helical sense.

![Figure 5.4: Würthner’s discotic perylenes](image)

### 5.3 Bay Substitution of Perylene Diimides

Another common morphology for perylenes are nanofibers. The fibriller structures are often comprised of monomers aggregating into $\beta$-sheets. These assemblies possess a helical pitch, length, width, and height that can be quantified through a combination of imaging techniques such as tunneling electron microscopy (TEM) and AFM. Recently

![Figure 5.5: Bay substituted PDI/OPV assembly](image)
the Würthner group has produced well-defined chiral fibers by the incorporation of donor and acceptor moieties linked by several favorable intermolecular hydrogen bonding interactions to chiral melamines (Figure 5.5).\textsuperscript{187} The monomer triads then assembled into supramolecular fibers. This assembly of donor and acceptor arrays led to unspecified charge separation that could be applied in photovoltaic and nanoscale devices.\textsuperscript{204}

![Figure 5.6: AFM image of Figure 5.5](image)

Chirality has also been introduced to perylenes via substitution of the bay-region of the diimide.\textsuperscript{209,210} Substitution of the bay region creates steric strain that forces the perylene to twist into two enantiomeric forms.\textsuperscript{192} The perylene bay region is the internal aromatic area of the perylene molecule that point towards each other and results in steric crowding (–O–Ar in Figure 5.7).\textsuperscript{211} This twisting of the perylene causes an increase in solubility due to a decrease in self-assembly.\textsuperscript{212,213} This phenomenon results from twisting of the PDI which results in a reduced tendency for aggregation as a consequence of a decrease in $\pi-\pi$ stacking ability. The varying of the size and functionality of the bay
substitution groups has dramatic results on the stability of the assemblies by increasing solubility and decreasing the forces necessary for intermolecular association.\textsuperscript{214} This tuning technique has been exploited in the synthesis and study of supramolecular building blocks that for supramolecular architectures. Bay substitution has been employed by Würthner in four pyridine-appended perylenes to coordinate metals in square nanostructures\textsuperscript{215-217} (Figure 5.7) and Wasielewski in his synthesis of porphyrin-centered tetrameric perylenes assemblies\textsuperscript{199} (Figure 5.8).

\textbf{Figure 5.7}: Würthner’s tetrameric, bay substituted perylene
Wasielewski’s system (Figure 5.8) features four perylenes linked to a porphyrn core. The design allows for light harvesting and charge transfer from the electron-poor perylenes towards the zinc coordinated porphyrn core. The compound displays spectroscopy evidence for aggregation at extremely high temperatures and low concentrations over a vast sampling of solvents. This aggregation allows for excellent light harvesting properties; when the PDI chromophores are selectively excited with a laser, there is ultrafast energy transfer to the central zinc porphyrin in 1.3 ps. This event is followed by exciton hopping between zinc units at 160 fs that approaches the vibrational time scale.

Figure 5.8: Wasielewski’s porphyrn/perylene tetramer
Würthner has appended biphenol to perylene to create two “inherently” chiral enantiomeric folded structures that were separable via chiral HPLC (Figure 5.9). Bis-biphenol substitution at the bay position adds rigidity and hinders twisting between the two handed PDI’s through steric interactions. The two enantiomers racemize at an elevated temperature but were sufficiently stable at room temperature. The researchers hypothesize the remaining aryl chlorines could be further functionalized for use in chiral recognition or catalysis. The properties of the twisted perylenes with regard to charge separation were not addressed by the publication.

Würthner also was able to synthesize a synthetic cyanine dye analog (Figure 5.10). The bay-substituted PDI featured strong bathochromically shifted absorptions; narrow fluorescence bandwidths; and a high fluorescence yield—properties similar to the naturally occurring cyanine aggregates. This assembly is characterized by a rare $J$-aggregate with a fluorescence quantum yield near unity—ordinarily, perylene diimides
form stacked $H$-type aggregates. The unique optical properties and intermolecular interactions are a direct consequence of bay-substitution of the perylene such as the transition to the less common $J\text{-}$ aggregate. With these unique traits, the authors state the assemblies have potential in photonics, photovoltaics, and fluorescence sensing.

Recently, Ullmann couplings have been employed to link several PDI’s together to create a twisted chiral scaffold. The researchers reported an efficient synthesis and
were able to isolate both $M$ and $P$ enantiomers of the perylene diimides. The absolute configurations were elucidated through comparison of the experimental CD’s with ones obtained by several different computational methods (Figures 5.11 and 5.12). The different chiral forms have no effect on the properties of the assemblies. Due to the electron accepting ability of the PDI’s (as judged by electrovoltaic experiments) and fluorescence quenching, the compounds are very suitable for use in opto-electronic devices. The phenomenon of quenching is Förster resonance energy transfer (FRET). This behavior is important to this class of devices because it is associated with complex formation and energy transfer.

Figure 5.11: Left: B3LYP/3-21G* computed structures for the two enantiomeric dimers. Top right: Experimental CD’s. Bottom right: Calculated CD’s.
5.4 Novel Perylene Morphologies

Perylenes are commonly incorporated into thin films. These materials are often amphiphilic assemblies that are deposited on a surface or suspended as a Langmuir-Blodgett film. Xie has reported an assembled perylene system with a charged dimethyl amine on one end of the imide and a long alkyl chain on the opposing face (Figure 5.13). The amphiphiles were deposited as a thin film that then assembled into fibers. This monomer interacts with a charged polyacetate oligomer to produce a p-/n- type semi-conducting dyad.
Double-decker perylene cages are a unique architecture that have been synthesized via metal-porphyrin coordination (Figure 5.15). The sandwich-like assembly consisted of a covalently coordinated stacks between three zinc porphyrins and three pyridine-substituted perylenes. The workers were able to characterize the formation of an assembly by observing fluorescence quenching of the complex. Quenching is due to electron transfer by chromophores that are closely associated in space. Additionally, simple $^1$H-NMR experiments were used to conclude that the assemblies formed a 1:3
stoichiometry. The assemblies are capable of efficient photoinduced electron transfer and best preformed in non-polar solvents such as toluene and dichloromethane.
Figure 5.15: Zinc porphyrin/PDI cages
Similar to the previous example of metal coordination, organic molecules have been used to aid in forming supramolecular complexes and assemblies. Melamine and similar functionality combinations have been used to coordinate perylene monomers in order to form a large assembly. A recent example of this strategy joined a pair of melamines to a perylene diimide monomer with a carbon chain linker to create a supramolecular polymer (Figure 5.16). These PDI’s were found to assemble but after the addition of a cyanurate molecule (dCA), a different type of assembly resulted by the generation of three complementary hydrogen bonds (Figure 5.17). Additionally, the assemblies were tuned by the substitution of the ethylene linker to a trimethyl amine linker between the perylene and the melamine. These changes were observed AFM and dynamic light scattering (Figure 5.18). The assemblies may have potential as optically and electronically active nanomaterials. The researchers found that there is an increase in the solubility of the assemblies compared with a supramolecular polymer comprised of the same components. From the researchers’ conclusions the assemblies are reportedly useful in “fabrication of organic bulk materials.”
The Sun group has incorporated a perylene into several novel photochromic nanostructures.225 The researchers related that a diarylethene functionalized perylene diimide dyad assembled into aggregates via an innovative re-precipitation method. This technique works through dissolving the molecules in a solvent in which it is soluble in and then dropping it into a solvent in which it is insoluble. The solid is collected and the process is repeated. The researchers also hypothesized the mechanism by which the assembly changes from small structures into nanotubes are comparable to the mechanism by which natural systems operate. Initially the molecules organized into tape-like assemblies and then with time for equilibration they became vesicles and eventually grew into a structure similar in appearance to a pearl-necklace (Figures 5.19 and 5.20). This unique architecture then later transitioned into fibers that eventually grew into nanotubes.
(Figures 5.19 and 5.20). Through the use of ultra-violet irradiation the fluorescence of the assemblies can be regulated. The researchers propose that this property has potential use in photochromic switches.

**Figure 5.19:** Sun group’s change in assemblies of NDI’s with time

**Figure 5.20:** Cartoon rendition illustrating change in assemblies of NDI’s with time
Polyaromatic analogs of perylene such as the smaller naphthalene have also generated nanotubes. The Sanders group has successfully employed naphthalene diimides to create chiral assemblies stabilized via hydrogen bonds. Sanders varied the naphthalene monomers with several different imide units and side chains that were comprised of various amino acids (Figure 5.21). Through the use of different protecting groups on the amino acids the stabilization of the nanotubes could be changed or “tuned”. Additionally, the identity of the amino acid also determined the chiral handedness of the assembly.

**Figure 5.21:** Sanders’ various imides
5.5 Self-Assembly of Various L-Lysine NDI Amphiphiles

Parquette has shown that an amphiphilic, di-peptide appended naphthalene diimide is capable of generating β–sheet assemblies.\textsuperscript{227} This use of the self-assembling naphthalene monomer for electron transport is unique due to NDI’s electron poor (n-type) nature.\textsuperscript{228} The assembly is designed to have intermolecular hydrogen bonds and π-π associations across lysine and naphthalene monomer units (Figure 5.23). An aqueous environment further facilitates these electrostatic interactions. Additionally, by placing the polar lysine adjacent to the hydrophobic naphthalene, it was theorized the result would be similar to the design of β–sheet forming peptides. By varying the relative positions of the NDI on the di-peptide, the resultant amyloid nanostructures were changed from nanoribbons (di-peptide B) to dually stranded nanofibers (di-peptide A).

\textbf{Figure 5.22:} Schematic of Sanders’ nanotubes
In a subsequent publication, Parquette has shown that protecting the terminal amine of the previously described lysine-NDI using FMOC- generates β-sheet hydrogel assemblies at low concentrations. The assembly is stabilized by hydrogen bonding and π-π stacking designed thoughtfully into the monomer units. The researchers observed a delicate balance between solubility and electrostatic repulsion (Figure 5.24): too much repulsion between charged amine groups led to prevention of assemblies. However due to the hydrophobicity of the NDI, the charged amine group was essential for solubility. It was discovered that additional π-π stacking from interdigitating fluorene protecting groups was essential for gelation. The assemblies were shown to assemble in water and were disrupted in TFE—UV, FT-IR, CD, TEM, AFM, and X-ray diffraction (XRD) were employed to characterize the assemblies.
Continuing the work with 1-D nanostructures, the Parquette group has altered the previous examples’ design by decreasing the di-peptide to a single lysine residue. The lysine acts as a hydrophilic attachment point to the hydrophobic naphthalene diimide and n-butyl amine (Figure 5.26).
This amphiphilic design explored the differences in changing the terminal carbonyl from an acid to an ester to an amide. These minor variations manifested themselves in large changes in regard to the resulting nanostructures: the free acid formed a nanotube, the ester formed a larger, bi-layered nanotube, and lastly the amide formed a coiled-ribbon that grew into a nanotube (Figure 5.27).

Figure 5.26: Intermolecular forces governing assembly of Parquette’s NDI’s

Figure 5.27: Mix of NDI assemblies
5.6 Conclusions

Self-assembly is an important technique towards the understanding of biological systems. Introduction of chirality into these systems is crucial to bio-mimicry. The ability to design, create, study, and apply the synthetic analogs of natural systems is vital in continuing the understanding of the operation of biological processes. Improved assemblies that feature thoughtful design elements such as increased rigidity and stronger associations can facilitate facile electron transfer. Additionally, overlapping of chromophores can allow the transfer from donors to acceptors resulting in more adequate photovoltaic devices. Self-assembly is an important step in the creation of more efficient solar-cells; more efficient electronics such as light emitting diodes and semi-conductors; and other future nano-devices.\textsuperscript{231}
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CHAPTER 6

AQUEOUS SELF-ASSEMBLY OF A L-LYSINE BASED PERYLENE AMPHIPHILE INTO 1-D N-TYPE NANOSTRUCTURES

6.1 Introduction

Self-assembly of 1-D nanostructures has increasingly moved to the forefront of research due to their potential use in light emitting diodes, photovolatics, and transistors.\textsuperscript{232-234} Originating from Parquette’s earlier amphiphilic NDI studies,\textsuperscript{229} we hypothesized that enlarging the hydrophobic, aromatic unit from a naphthalene diimide to a perylene diimide would increase the propensity to form assemblies by enhancing the $\pi$-$\pi$ stacking interactions and the overlapping of chromophores. Additionally, the molecule’s absorption is red-shifted, which is more appropriate for use in photovoltaic devices. The remaining electrostatic interactions provided by lysine would then direct the formation of assemblies similar to those reported in the prior use with NDI. The target molecules were designed to be simple amphiphiles; the $n$-butyl-perylene portion is hydrophobic and the lysine, in various protected forms is can be either hydrophobic or hydrophilic.
6.2 Research Design

The ordering of amphiphilic molecules by their polar and nonpolar functionalities is an important factor governing self-assembly.\textsuperscript{235,236} Amphiphilic forces dictate many of the properties of biological events such as the activity of certain antibiotics\textsuperscript{237} and membrane translocation.\textsuperscript{238} The understanding of these forces is important to their subsequent application in synthetic systems. The goal of this work is to control the organization of supramolecular polymeric fibers through noncovalent interactions—resulting in assemblies reminiscent of those found in biological systems. The target molecules’ designs developed from iterative changes to our earlier work depicted in Figure 6.1.\textsuperscript{227,229,230} Previously, the Parquette group studied a charged \(\varepsilon\)-amine from lysine which was built into a di-peptide and a terminal amide group appended to an amphiphilic naphthalene diimide.\textsuperscript{227} This design was then later shortened from a di-peptide to a mono lysine residue.\textsuperscript{230} The reported system is derived from the latter molecule and will feature cooperative \(\pi-\pi\) stacking,\textsuperscript{239} hydrogen bonding,\textsuperscript{240,241} and solvophobicity\textsuperscript{207,242} to generate various nanostructures.

![Figure 6.1: Previously reported NDI/lysine monomers](image-url)
In our current design (Figure 6.2), we changed the electronically active component from a naphthalene unit, to the larger perylene. This alteration resulted in a more defined chromophore and greatly increased the affinity for π-π stacking by the addition of two more aromatic units.\textsuperscript{243-245} Unfortunately, these additional aryl rings result in decreased solubility.\textsuperscript{193} The PDI monomers and assemblies are characterized by an intense color whereas the naphthalene based compounds are white solids that form clear solutions.

![Four proposed PDI/lysine molecules](image)

\textit{Figure 6.2:} Four proposed PDI/lysine molecules

The two end-groups were selected because of their ability to promote solvation of the molecule by two distinct methods: the alkyl chain for non-polar, organic solvents, and the charged amino acid for polar solvents. We hypothesized this amphiphile would direct the formation of supramolecular assemblies.\textsuperscript{221,246} The interactions between monomer units can be controlled through increasing or decreasing the pH of solution. This titration can be monitored spectroscopically and reveals that at low pH assembly formation is discouraged whereas the assemblies form at high pH (\textit{vide infra}).

Additionally, we are curious as to the importance of electrostatic interactions on the transfer of chirality of the monomer unit to the overall supramolecular assembly. To
explore this feature, we synthesized four differently protected variants—amine protected; acid protected; fully protected; and finally globally deprotected Zwitter ion (Scheme 6.1). These four molecules can assist in understanding the effects of blocking a single electrostatic component selectively (Scheme 6.1).

Finally, the stacking of π-systems can potentially allow for intermolecular charge migration over a long range.\textsuperscript{247,248} In the future, these electron poor aggregates (n-type) will be paired with electron rich (p-type) aggregates such as oligo(p-phenylene vinylene) oligomers or thiophene oligomers to create dyad stacks\textsuperscript{204,249,250} or fibers that can engage in electron transfer.\textsuperscript{251} Potentially, the solid state assemblies could be utilized in nanodevice applications such as nanowires.\textsuperscript{231,252}

### 6.3 Results and Discussion

#### 6.3.1 Synthesis

The synthesis began by adding a mixture of α-protected lysine and \textit{n}-butyl amine to a refluxing suspension of perylene-bis-anhydride in pyridine (Scheme 6.1).\textsuperscript{222,227} After flash chromatography, the reaction afforded the desired unsymmetrically substituted diimide (1) in reasonable yield. The acid and amine functionalities on the lysine can be manipulated via several different protection/deprotection conditions to yield four different compounds (Scheme 6.1).\textsuperscript{253,254}
6.3.2 Spectral Data

Circular dichroic spectra of 1 - 4 illustrate that only the Zwitter ion (2) expresses any chiral information (Figure 6.3 – 6.6). However, that is not to assert that the other three molecules are not forming assemblies;250 in fact all of the PDI’s lack aromatic signals in the $^1$H-NMR which might be due to the loss of conformational freedom in an assembly.255-257 Additionally, all individual NMR signals were very broad even when dilute solutions were used due to the existence of polymeric aggregates.219 This phenomenon was observed in deuterio- water, dimethyl formamide, methanol, acetone, chloroform, acetonitrile, benzene, and dichlormethane from room temperature to 78 °C (in solvents with the appropriately high boiling point). Unfortunately, due to this behavior, NMR was not a viable technique for characterization.

Scheme 6.1: Synthetic scheme of compounds 1 - 4
Figure 6.3: CD’s of PDI amphiphile 1 normalized for concentration

Figure 6.4: CD’s of PDI amphiphile 2 normalized for concentration
The CD spectra relate the intermolecular interactions between the lysine amine and acid are very important for transmitting the chiral information from the monomers to the assembly. Removing any of the electrostatic components of the lysine through either competing solvents or blocking groups appears to strongly discourage the transmission of chiral information. This rationale explains why only compound \(2\) gives the only observable signals in the CD spectra. However, even with no apparent CD transitions, one can still assume that the perylenes are then stacking upon one another without communication of chiral information. Compound \(2\) has a Cotton effect in methanol with a peak at 436 nm and a trough at 504 nm (along the \(N\)-axis) and centered around the 0–2
transition (short axis) at 469 nm (Figure 6.4). The evidence for assembly is additionally confirmed by the lack of aromatic protons in the $^1$H-NMR spectra. The lack of chiral induction is not necessarily a failure because in other systems often high concentrations, heat, or sonication are required for the formation of assemblies whereas we are observing success at room temperature and micromolar concentrations.

There is an expectation that methanol as a solvent would interrupt the important hydrogen bonding interaction and prevent the assemblies from transferring their chirality from lysine to lysine; however, methanol has the largest induced CD signal for an organic solvent. The polar-protic solvent could potentially cause a solvophobic effect with the large aromatic perylenes and the long alkyl chains and assist in the $\pi-\pi$-stacking interaction.

As predicted, there is a CD signal observed in both neutral and low and high pH aqueous solutions. However, the acidic and basic solutions’ CD signal is not nearly as intense as the neutral solution (Figure 6.7). This phenomenon is most likely due to unfavorable electrostatic repulsions due to either charged carboxylate or protonated ammonium salts.
UV spectra of the four molecules in favorable solvents such as methanol or water show a decrease in intensity and hypsochromic shifts of the soret bands in relation to trifluoroethanol. This change coupled with the proposed model of assembly of the PDI units aligned along their $N-N$ axis is evidence of $H$-aggregates (Figure 6.8 – 6.11). TFE appears to disrupt the assemblies by interrupting the intermolecular electrostatic interactions between the monomer units. The changes are the most dramatic for $n$-Bu-PDI-NH$_2$-Lys-OH (2), Figure 6.9. This visual observation can be quantitatively confirmed by fluorescence spectra (*vida infra*).
The conclusions drawn from the previously illustrated CD data (Figure 6.7) were further confirmed by pH variations viewed by UV spectra illustrate that acidic and basic solutions of \textit{n}-Bu-PDI-NH$_2$-Lys-OH (2) have increased intensities with relation to the
neutral solution (Figure 6.12)—revealing electrostatic repulsion between the charged atoms on the lysine moiety in acidic or basic solution are preventing intermolecular assembly. Another positive indicator for π–π stacking is the intensities for the 0–0 and 0–1 vibronic transitions have reversed in relation to their monomeric forms (Figure 6.9 and 6.12). The fluorescence data of compound 2 is co-plotted with its corresponding UV spectrum in Figure 6.13. The most intense trace results from 2 in its monomeric form with TFE as a solvent. Both acidic and basic water are essentially baseline and illustrate no fluorescence due to the absence of supramolecular assemblies. Interestingly, compound 2, which has been shown to assemble as judged by other spectroscopic methods in MeOH, has a very intense fluorescence spectrum. This intense signal in a
solvent that promotes assembly is not unprecedented. Large fluorescence quantum yields are common for perylene assemblies but not indicative of a particular type of aggregation.

6.3.3 Tunneling Electron Microscopy Images

The evidence for supramolecular assemblies was further confirmed by tunneling electron microscopy. The sample preparation is outlined in the experimental section (6.5). In micromolar solutions of methanol or basic water, only the fully deprotected lysine-perylene diimide 2 was found to yield fibers. Compounds 1, 3, and 4 were visualized as unassembled, un-defined residues. Interestingly, at low pH no assemblies
were observed, presumably due to lysine’s electrostatic repulsion between monomers of protonated terminal amines.

Figure 6.14 illustrates fine hair-like fibers of compound 2 in a relatively concentrated (20 mM) solution in methanol. As the concentration of the solution is decreased ten-fold (Figure 6.15), the amount of fibers is decreased and the type of assemblies remains unchanged. The unaffected assemblies are evidence that the forces that dominate assembly formation do not waiver regardless of concentration.
After the acquisition of the first series of TEM images, the solutions were then aged for one week resulting in a transition to broad, noodle-like ribbons (Figure 6.16) from the fine, individual fibers. The more dilute solution, however, (Figure 6.17) did not transition into ribbon-like material—this result illustrates the existence of a critical concentration where an increase the likelihood for individual molecules to interact with one another and assemble occurs. From TEM, the broad ribbons measure ca. 9.5 nm wide and 6 nm high (from AFM Figure 6.22). Figures 6.18 and 6.19 (also at 2 mM) did become more organized after aging. Instead of the transition to broad ribbons, the hair-like assemblies grew into twisted fibers.
Figure 6.16: TEM image (copper coated grid); uranyl acetate as negative stain of 20 mM aged of compound 2 in MeOH

Figure 6.17: TEM image (copper coated grid); uranyl acetate as negative stain of 2 mM aged of compound 2 in MeOH
Figure 6.18: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 2 mM in MeOH, aged one week

Figure 6.19: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 2 mM in MeOH, aged one week
As shown in Figure 6.20, when amphiphile 2 was dissolved in high pH water, the fibers were well dissolved yielding only amorphous blotches. When the solution was aged for one week, the PDI amphiphile did not transition into any appreciable assemblies and began to resemble undefined strands yarn (Figure 6.21). A balance between solubility and solvophobic interactions are necessary for the formation of assemblies. The absence of assemblies at high pH are likely due to an increase in solubility of the monomer units.

*Figure 6.20:* TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, in pH 11 water
6.3.4 Atomic Force Microscopy Images

AFM images further confirm the fibrous nature of the assemblies generated from PDI 2. Additionally, Figure 6.22 further confirms the dimensions derived from Figure 6.17 (Compound 2, 20 mM MeOH) yielding a width of ca. 8.4 nm.
6.4 Conclusions

The synthesis and self-assembly properties of four perylene diimide amphiphiles containing an \( L \)-lysine and \( n \)-butyl amine was reported. The combination of hydrogen bonding and electrostatic and \( \pi-\pi \) stacking interactions created an \( n \)-type organic semiconductor that aggregates in highly ordered fiberous assemblies. Ideally, these assemblies can be used in organic optoelectronic devices.
6.5 Experimental Section

General Methods

All starting materials were used as supplied from commercial suppliers unless otherwise noted. All reactions were carried out under a N\textsubscript{2} atmosphere unless otherwise noted. Dimethylformamide (DMF) was dried by distillation from MgSO\textsubscript{4}; tetrahydrofuran (THF) and diethyl ether (Et\textsubscript{2}O) was distilled from sodium/benzophenone ketyl; dichloromethane, acetonitrile and pyridine were distilled from calcium hydride. All melting points were recorded in glass capillaries and are uncorrected. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents.

Fourier transform-infrared (FTIR) was performed on a Shimadzu IFAffinity-1. Ultraviolet (UV) spectra were collected on a Hewlett-Packard 8452A diode array spectrometer. Circular dichroism (CD) spectra were taken with an AVIV 202 CD spectrometer. Atomic force microscopy (AFM) was conducted in tapping mode. Matrix-assisted laser desorption ionization-time of flight MS (MALDI-TOF MS) spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All fluorescence spectroscopy were performed in a Perkin-Elmer LS-50B using a cuvette with a 1 mm or 10 mm path length at 25 °C. Transmission electron microscopy (TEM) was performed with Technai G2 Spirit instrument operating at 80 kV. All reactions were performed under nitrogen atmosphere. All water used for sample preparations was HPLC grade and passed through a membrane filter (0.02 μm) before use.
**Abbreviations:** DMF = \(N,N\)-dimethylformamide; TFA = trifluoroacetic acid; TMEDA = tetramethylethylenediamine; HNO_3 = nitric acid; \(i\)-PrOH = isopropyl alcohol; \(n\)-BuLi = \(n\)-butyl lithium; \(t\)-BuLi = \(t\)-butyl lithium; TMS-Cl = trimethyl silylchloride; TLC = thin layer chromatography; \(\text{Me}_2\text{SO}_4\) = dimethyl sulfate.

**Circular Dichroism (CD) Spectroscopy Measurement.**

CD spectra were recorded on an AVIV 202 CD spectrometer under ambient atmospheric conditions. Experiments were performed in a quartz cell with a 1 mm or 10 mm path length over the range of 190-800 nm at 10 °C.

**Ultraviolet (UV) Spectroscopy Measurement.**

UV spectra were collected on a Hewlett-Packard 8452A diode array spectrometer under ambient temperature and environment. Experiments were performed in a quartz cell with a 1mm or 10 mm path length over the range of 190-800 nm.

**Atomic Force Microscopy (AFM) Measurement.**

The AFM images were collected on a NanoScope IIIa device at ambient temperature in tapping mode using silicon tips (NSC14/AIBS, MikroMasch). 10 μL of the sample solution was diluted 10 fold and then placed on freshly cleaved mica. After adsorption for 30 minutes under moist conditions, the excess solution was removed by absorption onto filter paper. The resultant substrates were rinsed with solvent (50 μL) twice to remove the loosely bound monomers, and then samples were stored in a desiccator *in vacuo* for 1 h before imaging. The scanning speed was at a line frequency of 1.0 Hz, and the original images were sampled at a resolution of 512 x 512 pixels.

**Electron Microscopy Measurement – Negative Stain (TEM) Measurement.**
10 μL drops of sample solution were applied to a carbon-coated copper grid (Ted Pella, Inc.) for 2 minutes and after removal of the excess solution with filter paper, the grid was floated on 10 μL drops of 2 wt % uranyl acetate solution for negative stain for 2 minutes. The excess solution was removed by filter paper. The dried specimen was observed with Technai G2 Spirit instrument operating at 80 kV. The data were analyzed with Image pro software.

Fluorescence Spectroscopy Measurement.

Sample solutions (1 mM) were prepared by dilution from stock solution (20 mM) and equilibrated for 24 h.

Synthesis Procedures

\[ \text{N} \text{N} \text{O} \text{O} \text{O} \text{NH} \text{HO} \text{O} \text{O} \text{O} \text{O} \]

\( n\)-Bu-PDI-Boc-Lys-OH, Compound 1

The 3,4,9,10-perylenetetracarboxylic dianhydride (500 mg, 1.27 mmol, 1.0 equiv) was suspended in 450 mL of pyridine under N\(_2\). 137 μL of \( n \)-butyl amine (101.2 mg, 1.38
mmol, 1.09 equiv) and 7 mL of a solution of 354.7 mg α-Boc-Lys-OH (1.44 mmol, 1.13 equiv) in 20 mL of pyridine was added to the dianhydride at room temperature. The reaction was then slowly brought to reflux. After two hours, another 7 mL of the lysine suspension was added followed by the final amount two additional h later. The reaction was allowed to continue for 16 h at reflux. After cooling to room temperature, the reaction was concentrated to a red solid. This residue was absorbed to SiO$_2$ and was chromatographed with CHCl$_3$ → 100:1 CHCl$_3$:MeOH to yield 274.5 mg (32.3 %) as a purple solid. Mp > 270 °C (MeOH). IR (KBr) 1698, 1651, 1534, 1250, 1166 cm$^{-1}$. HRMS(MALDI) $m/z$ 675.444 (calcd for C$_{39}$H$_{37}$N$_3$O$_8$, 675.446).

The perylene diimide (1) (171.5 mg, 0.254 mmol, 1.0 equiv) was suspended in 2.5 mL DCM under N$_2$ followed by the addition of 2.5 mL of TFA. This mixture was allowed to stir for 2 h at which time it was concentrated on a rotary evaporator to a red residue. This crude material was washed with cold water and cold DCM to yield 140 mg (quant. yield) of a purple solid. Mp 152 °C dec (MeOH). IR (KBr) 2953, 1698, 1645, 1595, 1342 cm$^{-1}$. HRMS(MALDI) $m/z$ 575.142 (calcd for C$_{34}$H$_{29}$N$_3$O$_6$, 575.148).

$n$-Bu-PDI-NH$_2$-Lys-OH, Compound 2$^{254}$

The perylene diimide (1) (171.5 mg, 0.254 mmol, 1.0 equiv) was suspended in 2.5 mL DCM under N$_2$ followed by the addition of 2.5 mL of TFA. This mixture was allowed to stir for 2 h at which time it was concentrated on a rotary evaporator to a red residue. This crude material was washed with cold water and cold DCM to yield 140 mg (quant. yield) of a purple solid. Mp 152 °C dec (MeOH). IR (KBr) 2953, 1698, 1645, 1595, 1342 cm$^{-1}$. HRMS(MALDI) $m/z$ 575.142 (calcd for C$_{34}$H$_{29}$N$_3$O$_6$, 575.148).
**n-Bu-PDI-Boc-Lys-OMe, Compound 3**

The Boc-protected/n-butyl amine (1) (200.0 mg, 0.296 mmol, 1.0 equiv) and 409 mg of potassium carbonate (2.96 mmol, 10.0 equiv) were suspended in 3.0 mL of DMF and heated to 100 °C under N\(_2\). 55 μL of methyl iodide (12.6 mg, 0.888 mmol, 3.0 equiv) was then added to the hot reaction. After 15 h, the reaction was concentrated *in vacuo* to a purple solid. The crude residue was washed with cold DCM and then chromatographed with CHCl\(_3\) → 100:1 CHCl\(_3\):MeOH to give 102.0 mg (50 % yield) of a purple solid. Mp 177 °C dec (MeOH). IR (KBr) 2880, 1697, 1653, 1340 cm\(^{-1}\). HRMS(MALDI) \(m/z\) 689.324 (calcd for C\(_{40}\)H\(_{39}\)N\(_3\)O\(_8\), 689.324).
The globally protected diimide (3) (13.1 mg, 0.019 mmol, 1.0 equiv) was suspended in 200 μL of CHCl₃ under N₂. 100 μL of TFA was added and the solubility immediately increased. After 4 h, the reaction was concentrated to a red solid and washed with a sequence of 5 mL each of water, saturated sodium bicarbonate, and methanol. 10.5 mg (quant yield) of the red solid was collected. Mp 211 °C dec (MeOH). IR (KBr) 2963, 2935, 2873, 1695, 1642, 1599, 1342, 1274, 1166 cm⁻¹. HRMS (MALDI) m/z 589.250 (calcd for C₄₀H₃₉N₃O₈, 589.252).
6.6 References


(269) Zhang, X.; Wu, Y.; Li, J.; Li, F.; Li, M. *Dyes and Pigments* **2008**, *76*. 

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CHAPTER 7

AQUEOUS SELF-ASSEMBLY OF A L-LYSINE BASED PERYLENE BOLA-AMPHIPHILE INTO 1-D N-TYPE NANOSTRUCTURES

7.1 Introduction

In our previous studies, we observed that a correctly functionalized perylene diimide amphiphile could form n-type assemblies through favorable hydrogen bonding and π-π stacking interactions. Further investigation was undertaken to explore how changing the hydrophobic alkyl chain of the previously described PDI to another hydrophilic L-lysine unit would affect the assemblies. This class of amphiphile is called a bola-amphiphile.\textsuperscript{270} The core of the molecule is hydrophobic connected to two hydrophilic headgroups. The synthesis and study of the properties of this particular class of amphiphile will be described in this chapter.

The design of this molecule presumes strong π-π associations between the electron poor aromatic perylenes and the electrostatic interactions of the free amino acids. These communications increase the aqueous solubility of the assemblies in comparison to the
previously described amphiphiles.\textsuperscript{271} In this work, we have seen that a PDI lysine functionalized bola-amphiphile undergoes self-assembly in basic aqueous solutions.

### 7.2 Bola-amphiphilic Perylenes

In a recent example of perylene as a scaffold for bola-amphiphilic assemblies, Würthner and co-workers functionalized both imide sites with protonated spermine and different length alkylcarbonyl linkers (Figure 7.1).\textsuperscript{271} These PDI’s possess excellent water solubility due to the multiple protonated amines; interestingly, the electrostatic repulsions due to charge build-up (six possible protonation sites) did not have any adverse effect on self-assembly. $H$-type rod-like aggregates were observed by AFM and TEM at relatively high concentrations (1 mM).

![Figure 7.1: Würthner’s spermine functionalized amphiphilic PDI](image)

In an alteration of earlier work, Parquette changed his traditionally amphiphilic naphthalene diimide to a bola-amphiphile (Figure 7.2). Their previous NDI amphiphiles
generated ribbons, fibers, and nanotubes.\textsuperscript{227,229} This research marks one of the few 1-D nanotubes created by a bola-amphiphile.

One of unique features of this work is the use of a naphthalene diimide as the hydrophilic portion as opposed to the more common alkyl chains. As illustrated in Figure 7.2, the bola-amphiphile is in the sum of two closely associated amphiphilic molecules. This alteration is novel because the naphthalene portion is often employed as an electron acceptor in semiconductors; the researchers found “efficient exciton migration” throughout the assembly. Additionally, the use of naphthalene relies not only on solvophobicity and electrostatic interactions but also on $\pi-\pi$ stacking to help drive the assembly’s formation. The researchers observed the bola-amphiphiles formed long nanotubes and nanorings (Figure 7.3).
7.3 Research Design

The design of the proposed perylene system involves a simple change from the hydrophobic n-butyl chain, to the hydrophilic lysine. In addition to this alteration, the hydrophobic perylene is retained and that a different type of amphiphile results. We hypothesize these changes will also result in another type of supramolecular assembly from those previously described. The previously utilized forces driving the assemblies: hydrogen bonding, solvophobicity, and the \( \pi-\pi \) associations have been preserved. Unfortunately, the changes did little to increase solubility; removing the butyl chain greatly decreased solubility in organic solvents and only marginally increased solubility in high pH aqueous solutions. The balance between solubility and the

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Figure 7.3: Schematic of Parquette’s NDI bola-amphiphile
propensity to form an assembly is precarious; the monomer units should be sufficiently soluble to be practical but still retain sufficient solvophobicity to encourage aggregation. The intensity of the CD signal, however, increased by a factor of ca. 10 fold over the standard amphiphilic system (*vida infra*).

As with the previous system, no assemblies were observed in low pH water. However, when the pH was increased to 11, this change in solubility resulted in a dramatic increase in molar ellipticity, blue-shifted UV spectra, and ordered aggregates as viewed by TEM. Another retained feature of our PDI assembly’s design is the electron poor aromatic unit that can participate in charge migration over a long range\textsuperscript{247,248} for use in devices such as nanowires.\textsuperscript{231,252}

### 7.4 Results and Discussions

The synthesis began by adding an excess of α-Boc-Lys-OH to a refluxing suspension of 3,4,9,10-perylenetetracarboxylic dianhydride in pyridine (Scheme 7.1).\textsuperscript{222} After flash chromatography, the reaction afforded the symmetric PDI in a reasonable yield. Through several reactions the protecting groups are manipulated to result in four different perylenes for study (Scheme 7.1).\textsuperscript{253,254}
In stark contrast to earlier research with traditionally amphiphilic PDI’s, now three bola-amphiphilic perylenes form assemblies. The lone exception is compound 4 (NH$_2$-Lys-OMe-PDI-NH$_2$-Lys-OMe) where the acid functionality is blocked as a methyl ester and the amine is fully revealed. Previously, only the globally deprotected perylene was capable of forming assemblies (Chapter 6). No assemblies were observed in low pH solutions, likely a result of electrostatic repulsion by protonated lysine. Interestingly, all four samples gave dramatically different CD spectral curves. Additionally, the compounds were never appreciably soluble in any solvent and were only incidentally soluble in traditional organic solvents. Therefore, as with the previously described amphiphiles, NMR studies were not feasible with the described bola-amphiphiles.$^{219,255}$ The total of this information concerning solubility and end-group interactions underscore the importance of hydrogen bonding on the influence of the formation of supramolecular assemblies and the transfer of chiral information.

Scheme 7.1: Synthesis of Compounds 1 - 4
7.4.1 Spectral Data

7.4.1.1 CD Spectra

The arrangement of the assemblies in solution phase is best monitored by CD spectroscopy. As seen in Figure 4, the bola-amphiphilic PDI (2) has ca. 10 times the intensity of its standard amphiphilic analog. Three of the bola-amphiphiles (1-3) form chiral assemblies whereas compound 4 (NH₂-Lys-OMe-PDI-NH₂-Lys-OMe) has no observable CD transitions likely due to the lack of any favorable hydrogen bonds.

![CD Spectra Graph]

**Figure 7.4:** CD overlay of amphiphile 2 (Chapter 6), (red) with bola-amphiphile 2 (blue)
between the terminal amines. The CD spectra (Figure 7.5 – 7.8) communicate a generally negative overall trace—typically indicative of a right-handed formation.

**Figure 7.5:** CD spectra of Compound 1 in various solvents

**Figure 7.6:** CD spectra of Compound 2 in various solvents

**Figure 7.7:** CD spectra of Compound 3 in various solvents

**Figure 7.8:** CD spectra of Compound 4 in various solvents
Interestingly, it appears as if compound 2 reverses its handedness in high pH solution (Figure 7.6 v. Figure 7.9). Figure 7.6 illustrates that in methanol, there is a large positive signal at 600 nm and a large negative peak at 490 nm. In basic water, the signal is negative above 500 nm and positive at 450 nm (Figure 7.9). Whereas the CD signal in neutral water is fundamentally zero, the intensity of the CD in basic solutions is very large; ca. 10 times greater than in methanol. The reason behind this striking increase in stability is due to intermolecular hydrogen bonding between the carboxylate salt of lysine and an amine from another molecule. These spectra reveal the importance of communication between perylene monomer units. In self-assembly design, any opportunity to allow for the transmission of directing information will create a well-defined secondary structure.

**Figure 7.9:** CD spectra of Compound 2 in aqueous solutions

**Figure 7.10:** UV spectra of Compound 2 in aqueous solutions
7.4.1.2 UV Spectral Data

**Figure 7.11:** UV Spectra of Compound 1 in various solvents

**Figure 7.12:** UV Spectra of Compound 2 in various solvents
The UV spectra for compounds 1, 3, and 4 generally display sharp, well defined peaks except in neutral water due to limited solubility (Figure 7.11 –7.14). The UV spectras’ sharp peaks infer a lack of aggregation; this result seemingly contradicts Figure 7.5 through 7.8’s assertion of chiral transfer in solution as detected by CD. The combined CD and UV data is supported by TEM images for molecules 1, 3, and 4 forming weakly aggregated assemblies (vide infra).

Compound 2 illustrates strong evidence for assembly by its decrease in intensity and strong blue shift suggesting \( H \)-aggregates.\(^{268} \) This shift to shorter wavelengths is amenable to the proposed method of assembly of the PDI monomers along their \( N \text{--} N \) axis.\(^{263} \) The movement to a shorter wavelength is also present in neutral water and TFE, the latter a solvent usually used for disrupting intermolecular assemblies.\(^{227} \) Figure 7.12 also communicates a strong blue shift in basic and acidic water in relation to its monomeric form. Additionally, as can be seen in Figure 7.11, the intensities for the 0–0
and 0–1 vibronic transitions have reversed from their monomeric forms in methanol and for all of compound \(2\); (Figure 7.11 and 7.12) these spectroscopic features are a positive indicator of \(\pi-\pi\) stacking.\(^{218,257,265-267}\)

### 7.4.1.3 Fluorescence Spectral Data

![Fluorescence spectrum diagram](image)

**Figure 7.15:** Fluorescence (solid) and UV (dashed) overlay of compound \(2\) in various solvents. Excitation of TFE and MeOH solutions at 420 nm and pH 11 at 480 nm

The fluorescence spectrum in Figure 7.15 illustrates \(2\) has a strong blue shift of around 60 nm in aqueous basic water in relation to TFE and methanol. The intensity of the UV trace for the high pH water is much greater and shifted to shorter wavelengths in relation to the various protected PDI species \(1, 3,\) and \(4\) (Figure 7.11 – 7.14). The intense fluorescence of compound \(2\) in basic water is yet another indicator for assembly.\(^{192,268}\)
7.4.2 Tunneling Electron Microscopy Images

The evidence for assembly of the PDI’s are additionally characterized through the use of TEM and AFM spectrometry in addition to the previously discussed spectral data.

Figure 7.16: TEM image (copper coated grid); uranyl acetate as negative stain of compound 1, 20 mM in MeOH
Figures 7.16 and 7.17 depict assemblies of compound 1 in methanol. At the higher concentration of 20 mM, what is observed is a dense network of worm-like fibers (Figure 7.16). When the concentration is diluted ten-fold (Figure 7.17), the fibers transition into broader, flat ribbons. Compound 3 forms very similar worm-like assemblies to 1 (Figure 7.18), also in methanol. However, the assemblies were not as common and scarcely populated the TEM grid. Compound 4 showed no observable assemblies by TEM, a confirmation of the previously discussed spectral data. This result is not surprising, as the lack of communication of the monomers with each other through the removal of electrostatic interactions reduces the propensity for supramolecular assemblies.
Of the four compounds, 2 contains the most explicit evidence for assembly by all spectroscopic methods. At relatively high concentration (20 mM) in methanol, Figure 7.19 displays 2 as short, uniformly wide needles. These needles share a width that measures ca. 4 nm wide but an irregular length. After a ten-fold dilution, the needles remain, but there were the occasional twisted fiber measuring 21 nm wide and ca. 120 nm per twist (Figure 7.20).
After another ten-fold dilution, the assemblies formed from PDI 2 remain as small, needle-like assemblies (Figure 7.21). When these solutions are aged for one week, the
assemblies transition from small needles to larger, flat sheets with a higher frequency of twisted ribbons (Figure 7.22).

Figure 7.21: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 200 μM in MeOH
Figure 7.22: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 2 mM aged one week in MeOH

Figure 7.23: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 0.2 mM in pH 11 water
When the solvent used for PDI 2 was changed from MeOH to high pH water, solubility increased, as did the affinity for assembly as judged by the various spectral techniques (Figure 7.9 and 7.10). As seen in Figure 7.23, the same assemblies seen in Figures 7.19 and 7.21 dominate the grid plate. Figure 7.24 illustrates that the occasional twisted bands became thicker and more convoluted and layered. The fibers measured to be 20 nm wide and an average individual length of 120 nm long per twist. These twisted ribbons also possess a right-handed twist sense. After this solution is aged for one week, the broad plates that populated the majority of the TEM plates became larger and the twisted fibers were more entangled (Figure 7.25).

![Image of twisted fibers](image.png)

**Figure 7.24**: TEM image (copper coated grid); uranyl acetate as negative stain of compound 2, 2 mM in pH 11 water
7.4.3 Atomic Force Microscopy Images

AFM images of Compound 2 in basic water conditions confirm the conformation and dimensions observed in Figure 7.24. Figure 7.26 is indicative of the same broad tape-like assemblies of Figure 7.23 with a width of ca. 40-80 nm.
7.5 Conclusions

The synthesis and self-assembly properties of four perylene diimide bola-amphiphiles containing two \( L \)-lysine residues was reported. Through hydrogen bonding and electrostatic and \( \pi-\pi \) stacking interactions, the n-type organic semiconductor can aggregate into highly ordered fiberous assemblies. Ideally, these assemblies can be applied in organic optoelectronic devices.

Figure 7.26: AFM image acquired in tapping-mode on freshly cleaved mica. Compound 2, 250.0 \( \mu \text{M} \) in pH 11 water. Image width = 2.00 \( \mu \text{m} \)
7.6 Experimental Section

General Methods

All starting materials were used as supplied from commercial suppliers unless otherwise noted. All reactions were carried out under a N₂ atmosphere. Dimethylformamide (DMF) was dried by distillation from MgSO₄; tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; dichloromethane, acetonitrile and pyridine were distilled from calcium hydride.

All melting points were recorded in glass capillaries and are uncorrected. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents. Fourier transform-infrared (FTIR) was performed on a Shimadzu IRAffinity-1. Ultraviolet (UV) spectra were collected on a Hewlett-Packard 8452A diode array spectrometer. Circular dichroism (CD) spectra were taken with an AVIV 202 CD spectrometer. Atomic force microscopy (AFM) was conducted in tapping mode. Matrix-assisted laser desorption ionization-time of flight MS (MALDI-TOF MS) spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All fluorescence spectroscopy were performed in a Perkin-Elmer LS-50B using a cuvette with a 1 mm or 10 mm path length at 25 °C. Transmission electron microscopy (TEM) was performed with Technai G2 Spirit instrument operating at 80 kV. All water used for sample preparations was HPLC grade and passed through a membrane filter (0.02 μm) before use.
**Abbreviations:** DMF = \(N,N\)-dimethylformamide; TFA = trifluoroacetic acid; TMEDA = tetramethylethylenediamine HNO\(_3\) = nitric acid; \(i\)-PrOH = isopropyl alcohol; \(n\)-BuLi = \(n\)-butyl lithium; \(t\)-BuLi = \(t\)-butyl lithium; TMS-Cl = trimethyl silylchloride; TLC = thin layer chromatography; Me\(_2\)SO\(_4\) = dimethyl sulfate.

**Circular Dichroism (CD) Spectroscopy Measurement.**

CD spectra were recorded on an AVIV 202 CD spectrometer under ambient atmospheric conditions. Experiments were performed in a quartz cell with a 1mm or 10 mm path length over the range of 190-800 nm at 10 °C.

**Ultraviolet (UV) Spectroscopy Measurement.**

UV spectra were collected on a Hewlett-Packard 8452A diode array spectrometer under ambient temperature and environment. Experiments were performed in a quartz cell with a 1 mm or 10 mm path length over the range of 190-800 nm.

**Atomic Force Microscopy (AFM) Measurement.**

The AFM images were collected on a NanoScope IIIa device at ambient temperature in tapping mode using silicon tips (NSC14/AIBS, MikroMasch). 10 \(\mu\)L of the sample solution was diluted 10 fold and then placed on freshly cleaved mica. After adsorption for 30 minutes under moist conditions, the excess solution was removed by absorption onto filter paper. The resultant substrates were rinsed with solvent (50 \(\mu\)L) twice to remove the loosely bound monomers, and then samples were stored in a desiccator *in vacuo* for 1 h before imaging. The scanning speed was at a line frequency of 1.0 Hz, and the original images were sampled at a resolution of 512 x 512 pixels.

**Electron Microscopy Measurement – Negative Stain (TEM) Measurement.**
10 μL drops of sample solution were applied to a carbon-coated copper grid (Ted Pella, Inc.) for 2 minutes and after removal of the excess solution with filter paper, the grid was floated on 10 μL drops of 2 wt % uranyl acetate solution for negative stain for 2 minutes. The excess solution was removed by filter paper. The dried specimen was observed with Technai G2 Spirit instrument operating at 80 kV. The data were analyzed with Image pro software.

*Fluorescence Spectroscopy Measurement.*

Sample solutions (1 mM) were prepared by dilution from stock solution (20 mM) and equilibrated for 24 h.

*Synthesis Procedures.*

![Chemical structure of Boc-Lys-OH-PDI-Boc-Lys-OH, Compound 1](image)

**Boc-Lys-OH-PDI-Boc-Lys-OH, Compound 1**

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The 3,4,9,10-perylenetetracarboxylic dianhydride (1.0 g, 2.54 mmol, 1.0 equiv) and 1.2 g of α-Boc-Lys-OH (5.08 mmol, 2.26 equiv) was suspended in 300 mL of pyridine under N₂. This mixture was then refluxed for 12 h. After cooling to room temperature, the reaction was concentrated on a rotational evaporator to a dark red solid. The crude residue was absorbed to SiO₂ and chromatographed with 200:1 CHCl₃:MeOH to afford a 904.5 mg (42 % yield) as a purple solid. Mp > 270 °C (CHCl₃:MeOH). IR (THF) 3250, 2900, 1720, 1650, 1300 cm⁻¹. HRMS(MALDI) m/z 848.430 (calcd for C₄₆H₄₈N₄O₁₂, 848.33).

\[
\text{NH₂-Lys-OH-PDI-NH₂-Lys-OH, Compound 2}^{254}
\]

The symmetrical perylene diimide (1) (50.0 mg, 0.06 mmol, 1.0 equiv) was suspended in 600 μL CHCl₃ under N₂. 600 μL of TFA was added to the reaction and the compound immediately became soluble. The end of the reaction was indicated by the formation of solid in the reaction after 6 h. The reaction was concentrated on a rotary evaporator to a red residue. This crude material was washed with cold DCM. The residue was dissolved in water and refluxed with activated charcoal then filtered to yield 35.2 mg (quant. yield)
of a purple solid. Mp 200 °C dec (H₂O). IR (H₂O) 2920, 1691, 1651, 1593 cm⁻¹. HRMS(MALDI) m/z 648.203 (calcd for C₃₆H₃₂N₄O₈, 648.22).

![Chemical Structure]

**Boc-Lys-OMe-PDI-Boc-Lys-OMe, Compound 3**

The protected perylene dilysine imide (1) (50.0 mg, 0.06 mmol, 1.0 equiv) was suspended in 600 μL dry DMF and 81.5 mg K₂CO₃ (0.589 mmol, 10.0 equiv). 22.0 μL of methyl iodide (51.1 mg, 0.360 mmol, 6.0 equiv) was added and the reaction was allowed to stir for thirty minutes and was then heated to 100 °C and the perylene became soluble. After 6 h, the reaction was cooled to room temperature and the DMF was removed *in vacuo*. The purple solid was washed with CHCl₃ and chromatographed in CHCl₃ → 100:2 CHCl₃:MeOH to yield 22.0 mg (43 % yield) as a purple solid. Mp 227 °C dec (CHCl₃:MeOH). IR (THF) 3330, 2958, 2931, 1747, 1712, 1693, 1645, 1593, 1344 cm⁻¹. HRMS(MALDI) m/z 876.559 (calcd for C₄₈H₄₂N₄O₁₂, 876.36).
The bis-protected perylene dilysine imide (3) (9.8 mg, 0.0112 mmol, 1.0 equiv) was suspended in 150 μL CHCl₃ and treated to 150 μL TFA. After 6 h, the reaction was concentrated to a red solid and absorbed to SiO₂. This was filtered through SiO₂ with 30 % MeOH in CHCl₃. The compound was then eluted with NEt₃ and concentrated to give 4.0 mg (53 % yield) as a red solid. Mp 256 °C dec (CHCl₃:MeOH:NEt₃). IR (KBr) 2924, 1674, 1456, 1199, 1130 cm⁻¹. HRMS(MALDI) m/z 676.150 (calcd for C₃₈H₃₆N₄O₈, 676.25).

NH₂-Lys-OMe-PDI-NH₂-Lys-OMe, Compound 4²⁵⁴
7.7 References


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Appendix A

$^1$H- and $^{13}$C- NMR Spectra
Figure B1. Azobenzene 2a RI-BP86/TZVP optimized geometry (left) and the conformation obtained from Monte-Carlo conformational analysis using the AMBER* force field (right).
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<td>300 -&gt; 309 (14.9%)</td>
<td>305 -&gt; 313 (65.7%)</td>
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<tr>
<td>(% contributions for the major excitations)</td>
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*Table B1.* Excited state parameters calculated for azobenzene 2a, for the states with the largest rotatory strengths. Energies listed are shifted by +0.5 eV from the calculated values.
Figure B2. Raw CD and UV-vis spectra calculated for azobenzene 2a as well as a total spectrum with a 0.3 eV Gaussian broadening. Both are blue-shifted by 0.5 eV from the calculated energies. The excitations with the largest contribution to the CD spectrum are labeled accordingly.
Figure B3. UV overlay of two-turn (2a) and four-turn oligomers (4a).
Figure B4. Excited state difference densities for the absorbances of azobenzene 2a with the largest rotatory strengths. Entries a–k correspond to excitations 39, 40, 45, 46, 47, 49, 50, 51, 92, 97, and 99, respectively.
Geometric parameters for the RI-BP86/TZVP optimized azobenzene 2a

143

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