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14. ABSTRACT Most self-assembled nanostructures are static and are in an equilibrated state. The tools in nature involve molecules that undergo self-assembly to provide an organized supramolecular structure that is used in the catalytic, communication, and information storage processes. Allosteric proteins are important for the regulatory cellular and biological functions in organisms. Organisms are in dynamic environments and need regulatory proteins to maintain homeostasis. Allosteric proteins adapt in the presence of external stimuli through small perturbations within the structure as a whole, and switches on and off protein functions in a nonlinear fashion. The changes					
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ABSTRACT

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Some natural assemblies found in nature are not in an equilibrated state, or are dynamic. Like a wrench from a toolbox, dynamic assembled structures can be used without a change in structure and will work the same way every time. Dynamic assemblies remain in a non-equilibrated state due to a constant supply of energy being added to the assembly. Abiotic self-assembly that provides a dynamic structure is very rare. Non-equilibrating assemblies are especially attractive for cell regenerative templates. Recently, pathway assembled structures were designed to yield robust materials. These assemblies utilized molecular arrangements to increase the number of intermolecular interactions. Stabilizing assemblies have been done through crosslinking or polymerizing, and locking the structure into a kinetic state. Recently, our group had reported the self-assembly of small amphiphilic molecules that gave nanotubes. The amphiphile had a lysine polar head with a naphthalene-n-alkyl nonpolar tail. These assemblies, like many amphiphilic assemblies, were sensitive to external input. To lock the assembly, the n-alkyl tail was substituted with a diacetylene polymerizable functionality. We demonstrated that these assemble into nanotubes and can be polymerized to lock the structure that was stable to heat, solvent, and pH conditions. Also, after post-polymer modification, the nanotube morphology was maintained. Gold nanoparticles are attractive in catalytic and medical imaging technologies. Gold salts are most commonly reduced using the Turkevich method, which uses citrate or citric acid as a reducing agent. The lysine-NDI-diacetylene amphiphile, when assembled to nanotubes, was stable enough to withstand an addition of citric acid, sodium citrate, and a decrease in pH. When tetrachloroauric acid was added, the gold(III) was reduced and decorated the nanotubes with gold nanoparticles. Other groups have seen this phenomenon for amine functionalized polymers and carbon nanotubes and are decorated through electrostatic interactions. There are few examples of fiber templates created through a self-assembly process that are capable of surviving the Turkevich methods. We have developed a nanotube assembly that can be decorated with gold nanoparticles with potential catalytic properties

Intramolecular Communication of Peptide-Dendrimer Hybrids and the Self-Assembly of Polymerizable NDI-Diacetylene Amphiphilic Nanotubes

Dissertation

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

By

Nicholas Andrew Bewick

Graduate Program in Chemistry

The Ohio State University

2014

Dissertation Committee:

Professor Jonathon R. Parquette, Advisor

Professor Jovica D. Badjic

Professor Anita E. Mattson

Professor Kisha M. Radliff

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Abstract

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Dedication

I dedicate this document to my parents, Marte and Thomas, my wife Christa, and to my family and friends.

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Vita

2002.....Shrine of the Little Flower Catholic High
School

2007.....B.S. Chemistry, Oakland University

2008 to present Graduate Teaching Associate, Department
of Chemistry, The Ohio State University

Publications

Wyrebek, P., Sniady, A., Bewick, N. A., Li, Y., Mikus, A., Wheeler, K. A., and Dembinski, R. (2009) Microwave-assisted zinc chloride-catalyzed synthesis of substituted pyrroles from homopropargyl azides, *Tetrahedron* 65, 1268-1275.

Shao, H., Bewick, N. A., and Parquette, J. R. (2012) Intramolecular chiral communication in peptide-dendron hybrids, *Org. Biomol. Chem.* 10, 2377-2379.

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List of Abbreviations

1D	one dimensional
2D	two dimensional
3D	three dimensional
α	alpha
Å	Angstrom
A	Adenine or Alanine
Ac	acetyl
A ^D	dendron-modified alanine
AFM	atomic force microscopy
Anal.	analyzed
bp	boiling point
b	broad (IR and NMR)
bola	bolaamphiphile
β	beta
<i>n</i> -Bu	normal-butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
¹³ C	carbon

°C	degrees Celsius
C	Cytosine
calcd.	calculated
CCl ₄	carbontetrachloride
CD	circular dichroism
CDCl ₃	deuterated chloroform
CH ₂ Cl ₂	dichloromethane
CHCl ₃	chloroform
CH ₃ CN	acetonitrile
CMC	critical micelle concentration
(COCl) ₂	oxalyl chloride
δ	chemical shift in NMR
ΔG°	Gibb's free energy
d	doublet (spectra); day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(N,N-dimethylamino)pyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
E	Glutamic acid
EDCI	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride

ee	enantiomeric excess
EI	electron impact
EPR	enhanced permeability and retention
equiv.	equivalent
ESI	electrospray ionization
ESION	extremely small iron oxide nanoparticles
Et	ethyl
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
FITC	fluorescein isothiocyanate
Fmoc	fluorenylmethyloxycarbonyl
FTIR	fourier transform infrared spectroscopy
g	gram(s)
G	Guanine
[G1]	1 st generation of dendron
GDP	guanosine diphosphate
GTP	guanosine triphosphate
H or ¹ H	proton
H ₂	hydrogen
h	hour(s)

Hg	mercury
HPLC	high performance liquid chromatography
IR	infrared
<i>J</i>	coupling constant in Hz (NMR)
k	kilo
K ₂ CO ₃	potassium carbonate
KOH	potassium hydroxide
L	liter(s)
Lys	lysine
lit.	literature
m	milli; meter(s); multiplet (NMR)
μ	micro
M	moles per liter
<i>M</i>	left handed helix
MALDI	matrix assisted laser desorption ionization
Me	methyl
MeOH	methyl alcohol
MgSO ₄	magnesium sulfate
MHz	megahertz
min	minute(s)
mol	mole(s)

mp	melting point
MS	mass spectrometry; molecular sieves
m/z	mass to charge ratio (MS)
N	equivalents per liter
NaBH ₄	sodium borohydride
NaH	sodium hydride
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
OAc	acetate
<i>p</i>	para
P	packing parameter
<i>P</i>	right handed helix
PBr ₅	phosphorus pentabromide
Pd	palladium
Pd-C	palladium on carbon
PDH	peptide-dendron hybrid
pH	-log[H ⁺]
Ph	phenyl
PPh ₃	triphenylphosphine
ppm	parts per million

pyr	pyridine
q	quartet (NMR)
rt	room temperature
s	singlet (NMR); second(s)
SEM	scanning electron microscopy
sept.	septet (NMR)
SOCl ₂	thionyl chloride
t	triplet (NMR)
<i>t</i> or <i>tert</i>	tertiary
TEG	tetraethylene glycol
TEM	transmission electron microscopy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	Tetramethylethylenediamine
UV	ultraviolet
V	Valine

Chapter 1

Self-Assembly: Driving Forces and Pathways to Advanced Functional Nanomaterials

1.1 Introduction

Intermolecular forces in nature allow simple molecules to converge together to form more complex organized micro- and nanoscale structures in a process called “self-assembly.”^[1] The self-assembly of many different types of components have been explored for decades starting with one of the most famous examples; the self-assembly of DNA duplexes.^[2] The understanding of how molecules aggregate has advanced greatly, but coaxing these molecules into an organized aggregate such as helical fibers, rods, sheets, micelles, spheres, and tubes is still challenging.^[3]

Designing a molecule to aggregate and assemble into an organized structure will rely on the exploitations of multiple types of inter- and intramolecular interactions. These interactions or forces are hydrogen bonding, electrostatic repulsion and attraction, hydrophobic effect, and C-H $\cdots\pi$ stacking.^[1] Having one or multiple of these interactions built into a molecule may result in an organized aggregate under certain conditions.

Proteins are polymers that utilize rigid amide bonds in the backbone along with versatile repeating segments, each having a residual component to fold or assemble into a stable conformation.^[4] Under ambient conditions, proteins will fold into one conformation, and with environmental change, can rearrange into a different conformation. An example of this is the protein hemoglobin.^[5] Hemoglobin has two states, T (Tensed) and R (Relaxed). When the blood is at a more alkaline pH the protein becomes relaxed allowing the absorption of more oxygen. As the cells undergo metabolism, carbon dioxide in the blood increases which lowers the pH. The Hemoglobin transforms into a tensed state, which decreases the absorption of oxygen and increases the affinity for carbon dioxide. Using pH change, hemoglobin can interchange between two kinetic forms. To understand these types of transformations in more complex biological systems, it is crucial that developing molecules that lead to self-assembly are responsive to environmental change. This chapter will introduce a few important molecular attraction mechanisms and explore these forces and how these forces can be balanced to control the transformations of assemblies into kinetic states that are not at equilibrium through a selective pathway.

1.2 Static and Dynamic Self-Assembly

In nature, the organized assembly of matter can be seen everywhere. Many of the organized units require energy in order to cooperate and maintain form. The solar system is an organized unit in a non-equilibrated state. If the motion of the orbiting matter were

to cease, the sun will pull the planets in and absorb the matter. The solar system will have equilibrated to a non-dynamic state or a static state. Another example of a dynamic assembly is a school of fish. The fish spend energy to swim with the school of fish for many reasons including protection from predators.^[6] Dynamic assemblies in the

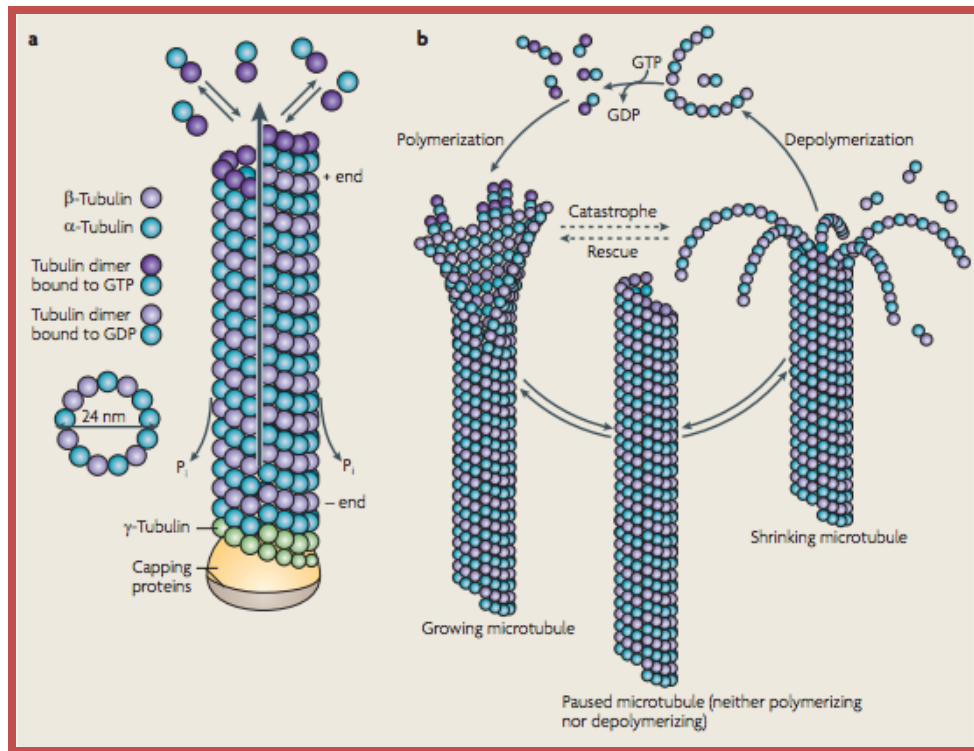


Figure 1.1: Description of microtubule self-assembly. α -Tubulin and β -Tubulin dimerize when bound to GTP. The tubulin dimer bonded to the GDT is incorporated to the microtubule polymer upon dephosphorylation of GTP to GDP. If energy ceases to put into the system via GTP to GDP dephosphorylation, the microtubule will undergo a catastrophic collapse.^[7]

molecular scale are seen in living cells. Microtubules are important to cell structure, mitosis, meiosis, and organelle movement.^[7] These polymers are made of α - and β -tubulin bounded together with an energy source, guanosine triphosphate (GTP). Microtubules are not stable and will fall apart into the monomeric tubulin pieces if GTP

is not continuously supplied. In other words, the microtubules are in a state of non-equilibrium and energy must be dissipated to maintain the assembly (Figure 1.1).

Most assembled structures on the micro- and nanoscale form an energetically stable equilibrated minimum structure. Much research has been done to pre-engineer monomeric molecules that spontaneously form advanced structures such as tubes and woven fibers.^[8] These materials have found uses in many areas, especially in the biomedical sector in the form of cancer chemotherapeutic delivery and cellular regeneration gels.^[9] These structures are possible through tuning the inter- and intramolecular hydrogen bonding, π -stacking, electrostatic, and hydrophobic forces. In the following sections, each force will be described, as well as how they are utilized in self-assembling processes.

1.2.1 Hydrogen Bonding

Hydrogen bonding occurs between hydrogen attached to an atom with a greater electronegativity value (proton donor, D) and an electronegative atom with a free lone pair of electrons (proton acceptor, A). The strength of a hydrogen bond depends on the dipole moment between the bond of the hydrogen donor atoms and the lone pair on the proton acceptor.^[10]

The strength of a hydrogen bond is not the only variable in self-assembly. The effectiveness of hydrogen bonding in self-assembly has been greatly enhanced when used in donor-acceptor arrays. Our DNA self-assembles using two different donor-acceptor

array systems: Guanine – Cytosine (G – C) and Adenine – Thymine (A – T) (Figure 1.2). To examine the strength between the two D – A arrays, poly G – C and poly A – T DNA strands have been sheared apart using an AFM tip and a gold surface. One strand of the DNA was mounted to the gold surface and one strand was mounted to the AFM tip.

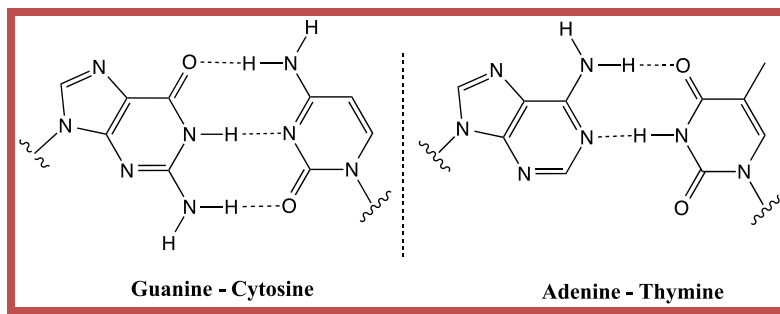


Figure 1.2: The hydrogen-bonding between DNA nucleotide pairs.

The tip was monitored, as it was raised away from the gold surface and stopped when the helix broke. The force needed to shear the poly G – C DNA was 235 pN greater than the poly A – T DNA.^[2] The number of hydrogen bonds in the array drastically strengthens or weakens the interactions of the molecules.

Additional attractive and repulsive interactions can be made in an array between opposing adjacent acceptors or donors. This effect has become known as the Jorgensen Model. These types of interactions were observed long before the model but had not been realized.^[11] Jorgensen et al. used Guanine - Cytosine and Uracil - 2,6-Diaminopyridine pairs systems and examined them using computational studies. The G – C array was found to be lower in energy than the Uracil - 2,6-Diaminopyridine array by 10.7 kcal mol⁻¹. The so-called secondary interactions created between a neighboring

donor increased the association of the dimers (Figure 1.3). Secondary interaction between

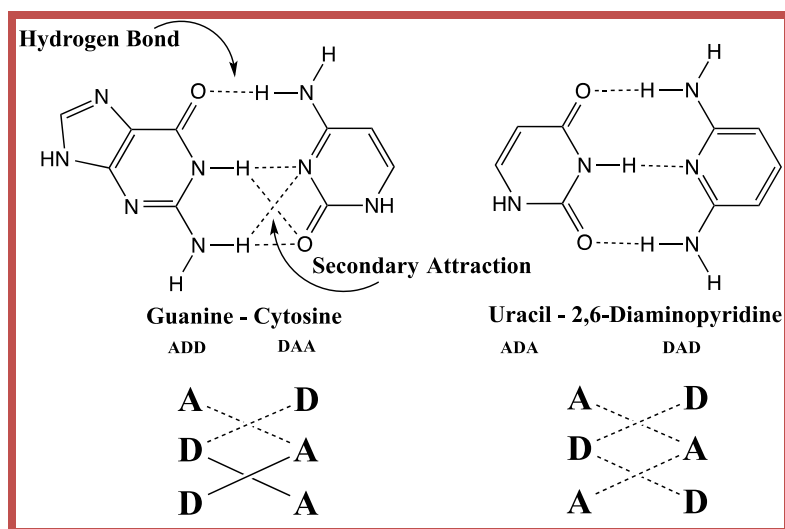


Figure 1.3: Example of secondary hydrogen-bonding between RNA nucleotides.

Compound	K°_{dim} [M^{-1}]	$-\Delta G^{\circ}_{\text{dim}}$ [KJ Mol^{-1}]
1.2	530	15.5 ± 0.5
1.4	2×10^4	24.5 ± 0.3
1.5	170	12.7 ± 0.5
1.6	2×10^5	30.2 ± 0.5

Table 1.1: The dimerization constants and free energies for compounds 1.2, 1.4, 1.5, and 1.6.

these dimers was later proven experimentally.^[12] From this data and other studied dimers a method was developed to predict the strength of a dimerized array. For each hydrogen bond the strength of the array was increased by $1.88 \text{ kcal mol}^{-1}$ and for each repulsive and attractive force the association strength increased or decreased by $0.7 \text{ kcal mol}^{-1}$.^[13]

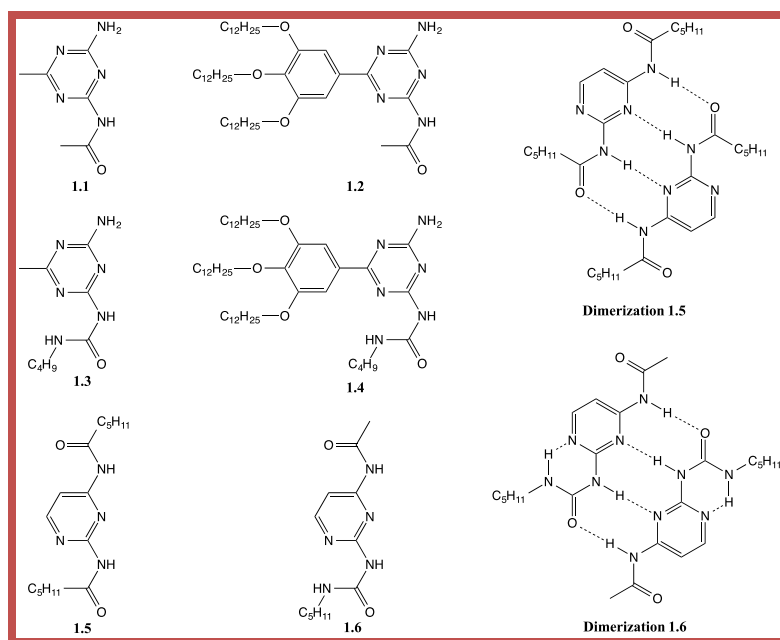


Figure 1.4: Arrays that can undergo hydrogen-bonding to yield dimers (left). Examples of dimers (right).

The strength of the hydrogen bond arrays has been observed acting as reinforcement when the molecule was prearranged in a more rigid conformation. It was determined that all examined molecules undergo hydrogen bonding and the urea based systems gave much stronger coordination when compared to their amide counterparts (Figure 1.4). Comparing the dimerization of compounds 1.5 and 1.6, determined by x-ray crystallography, the urea has an additional hydrogen bond to the aromatic nitrogen.

Through NMR and IR analysis, the dimerization constants and the Gibb's free energy was resolved (Table 1.1). The dissociation constants and Gibb's free energy value differ significantly between the compounds containing amide or urea. This example displays the importance of molecular design and preorganization in order to adjust the self-assembly.

Self-assembled polymers have been created utilizing hydrogen bonded arrays. Thermoplastic elastomers have similar properties as cross-linked rubbers, but when heated, became a liquid due to the crosslinks breaking. This effect can be done using

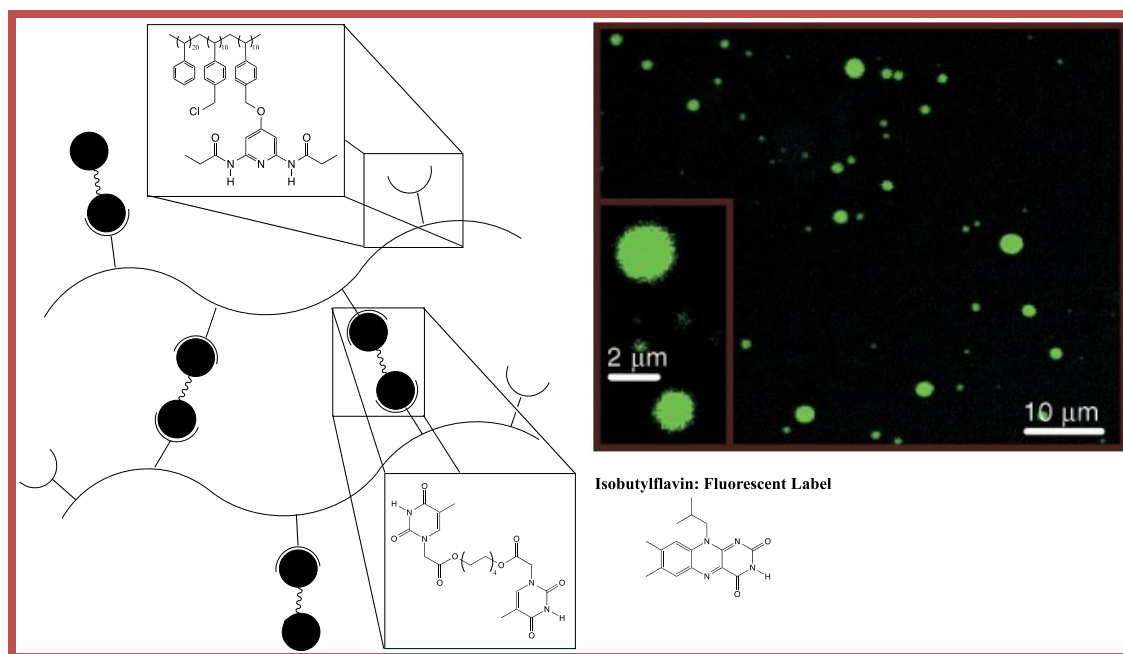


Figure 1.5: Polymers could be cross-linked through hydrogen-bonding arrays. When doped with hydrogen-bonding fluorescent tag, spherical particles were observed. ^[14]

dipole interactions, but these polymers have been created using weak intermolecular hydrogen bond crosslinking.^[15] Stronger crosslinking of polymer chains have been accomplished using arrays. The use of different array systems can yield different properties and assemblies such as dynamic temperature dependent spheres that convert to vesicles (Figure 1.5).^[14]

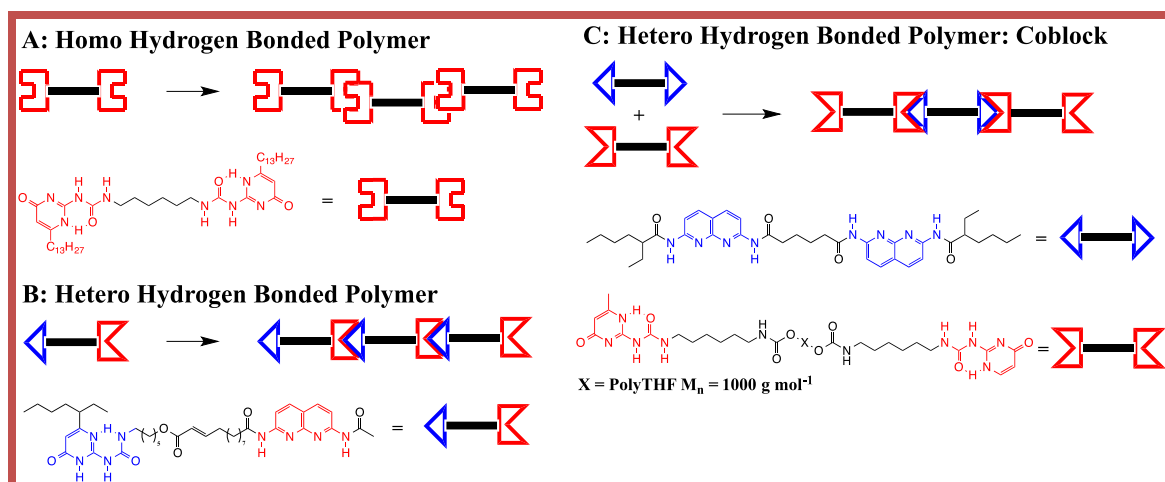


Figure 1.6: Polymers forms through hydrogen bonding. A: Homo hydrogen bonded polymers. B: Hetero hydrogen bonded polymer. C: Coblock hydrogen bonded polymer.

Traditionally, polymers are synthesized through covalent bonds, but two hydrogen-bonding interaction motifs with a linker has been used to form non-covalent polymers (Figure 1.6). Creating polymer type materials using hydrogen bonding not in prearranged conformations, but single hydrogen bonds, results in the creation of liquid crystal matrices.^[16] When stronger interactions are used in the form of hydrogen bonding arrays, polymer type assemblies form.^[17] Using highly prearranged hydrogen bonding arrays that have a strong affinity to one another has resulted in the assembly of supramolecular polymers.^[18] These types of polymers are assembled using homocoupling^[19] and heterocoupling^[20] array systems.

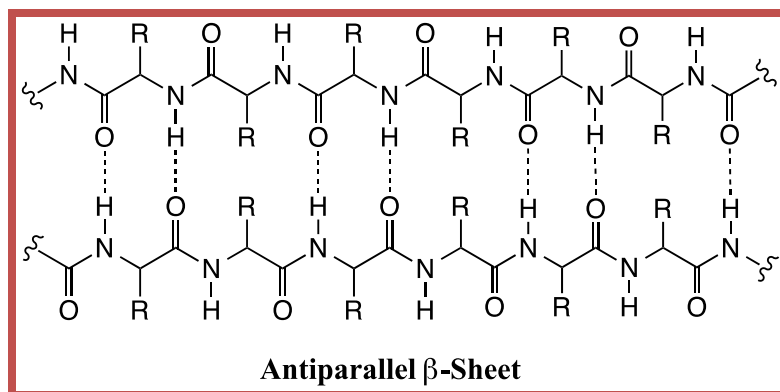


Figure 1.7: The hydrogen bonded configuration of antiparallel β -sheets.

Peptide β -sheet formations are very similar to array hydrogen bonding discussed above. Instead of the array containing 2-4 hydrogen bonds, a β -sheet can have many more hydrogen bonds along a peptide polymer. A β -sheet is formed through a series of hydrogen bonds between two amides. The amide hydrogen and the amide carbonyl oxygen can form a hydrogen bond (Figure 1.7). β -Sheet formation is found in many biological protein structures.^[21] In the past few decades, chemists have been creating self-assembled structures using synthetic peptides that form β -sheets. These assemblies yield diverse structures including rods,^[22] tubes,^[23] fibers,^[24] and belts.^[25]

1.2.2 π -Stacking

π -Stacking is a crucial force in protein folding, guest-host coordination, and self-assembly of supramolecular structures.^[26] π -Interactions may form between the π -orbitals of an aromatic ring and an electropositive s or p orbital. A great example where

multiple types of π -interactions occur can be seen between acetylcholinesterase and the anti-Alzheimer drug Aricept®.^[27] This complex yields π - π stacking, positive N- π , and

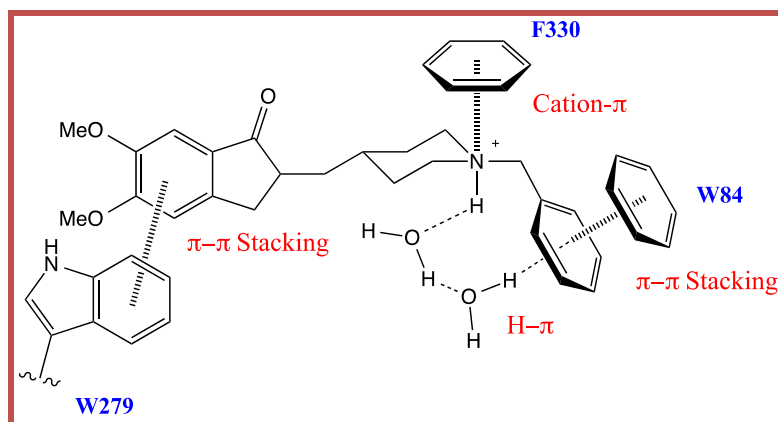


Figure 1.8: The π interactions between Aricept® and the protein acetylcholinesterase.

H- π interactions (Figure 1.8).

The two most energetically favorable arrangements for π - π stacking are parallel displacement and T-shaped edge-to-face. A configuration also seen but not the most favorable is the Eclipsed face-to-face configuration. All three configurations have been observed in nature, especially the parallel-displacement and T-shaped edge-to-edge orientations (Figure 1.9). The amino acids with aromatic residues within 34 proteins, 60% were involved in π -interactions.^[28] The preferred arrangement of these amino acids are parallel displacement.^[29]

The distance of π -interacting species are typically between 3.4 to 3.8 Å.^[30] One

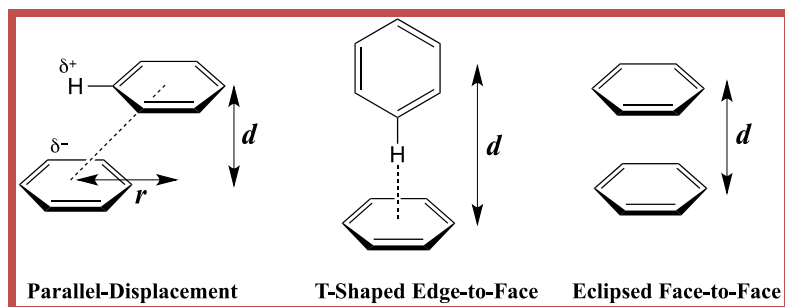


Figure 1.9: Common π - π stacking configurations.

of the shortest distances observed between two π -systems was the coordination of inhibitors of Aldose Reductase (Figure 1.10).^[31] Screening various inhibitors, it was realized the electron withdrawing meta-nitro group played a critical role in the binding affinity to the enzyme when comparing to the inhibitor exhibiting a pyridine ring. The nitro group allowed for greater π - π stacking with the tryptophan residue 111 and the bonding affinity was one magnitude larger. Hydrogen bonding was also observed

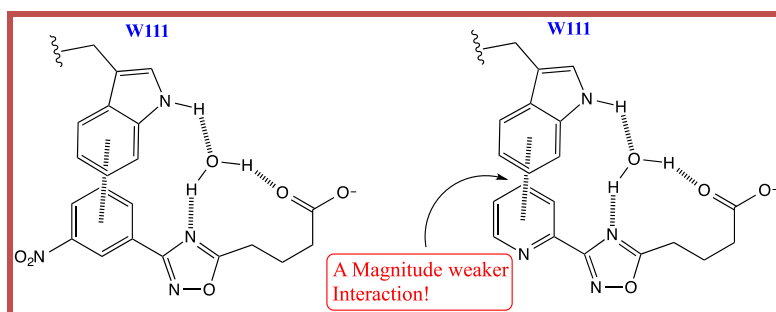


Figure 1.10: The electronegativity of the nitro group causes the aromatic ring to become electron deficient. The pyridine ring is more electron rich, weakening the π -interactions between pyridine and the tryptophan.

between the nitro group and the enzyme active site, which also helped to improve binding affinity, but in it is important to note that π - π stacking enhances hydrogen bonding as seen in the calculations of stacking DNA and RNA bases.^[32]

Molecular models have been synthesized to explore the importance of electron densities of π - π stacking aromatics. To study the T-shaped face-to-edge π -interactions, research groups have looked at models based off of a Tröger base backbone.^[33] In this model, one fixed aromatic ring (face ring) can interact with another aromatic ring that is connected to a linker to allow free rotation (edge ring) to give two possible outcomes: a folded state and a non-folded state (Figure 1.11 Left). When various substituents were added to the rings, the ratio of the fold state and the non-folded state changed. The folded state was most favorable when the face ring featured an electron-donating group, allowing for the electron rich ring to interact with the electropositive hydrogen.

A face-to-face model can be achieved using a triptycene core. In this model, the aryl arms are free to either interact or not by forming a syn- or anti- conformations respectively.^[34] Aromatic rings with electron withdrawing, neutral, or donating substituents were incorporated into the model, which gave large number examples for examination (Figure 1.11 Right). It was concluded that face-to-face π - π stacking was

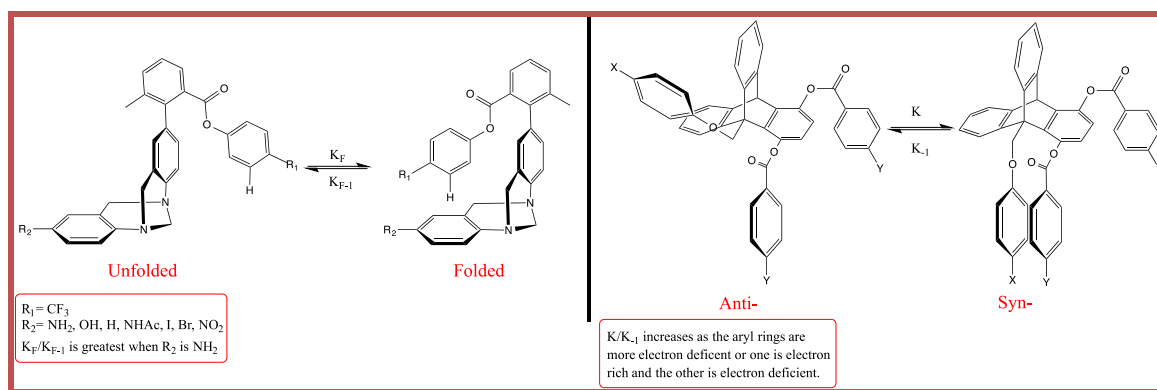


Figure 1.11: Two fixed systems to study T-shaped π -stacking (Left) and edge-edge π -stacking (Right).

achieved in examples where both aryl groups were electron deficient or one aryl group was electron rich and the other electron deficient.

With knowledge gained from these models, molecules that undergo self-assembly utilizing π - π stacking can be designed more effectively through the use of electron deficient aryl systems. A number of examples take advantage of the induced π - π stacking through the use of fluorinated aromatic systems have been reported.^[35] A one to one mixture of perfluorinated benzene and benzene forms crystals with a significantly higher melting point than crystals of benzene or perfluorinated benzene alone, suggesting enhanced π - π interactions. The crystal structures of the one to one crystals stack with a face-to-face geometry with a distance of 3.4-3.8 Å give a column shaped crystal.^[36] This is due to the favorable electron rich - electron poor π -orbital overlap or quadruple electrostatic interaction. Through computational studies, the displaced face-to-face configuration is the most stable, unlike benzene-benzene stacking which is known to be T-Shaped.^[37] Even though this is debated^[38], the F-H hydrogen bonding would also help

explain the observed face-to-face configuration instead of T-shaped configuration.^[39] Electron deficient aryl systems have seen and continue to see use in guest-host systems,^[40] self-assembly,^[41] protein folding,^[42] catalysis,^[43] and medicinal chemistry.^[31]

1.2.3 Hydrophobic Effect

The hydrophobic effect drives the association of minimally charged organics together in polar solvents such as water. Alkanes have little interaction with each other but when introduced to a polar environment, the alkanes will aggregate and develop a dehydrated core. This illustrates the rule “like dissolves like.” The aggregation of hydrocarbon species is favored, and it therefore has a ΔG° of formation less than zero. The enthalpy change, at room temperature, is often small so aggregation is entropy driven.

Research shows that the folding of proteins follows an entropy driven association process.^[44] Over the last 15 years, research on foldamers focused on understanding how to control the folding of proteins and bioconjugates with different properties, not found in nature, through the design of artificial oligomers that give only one major secondary

structure.^[45] These types of oligomers are also known as

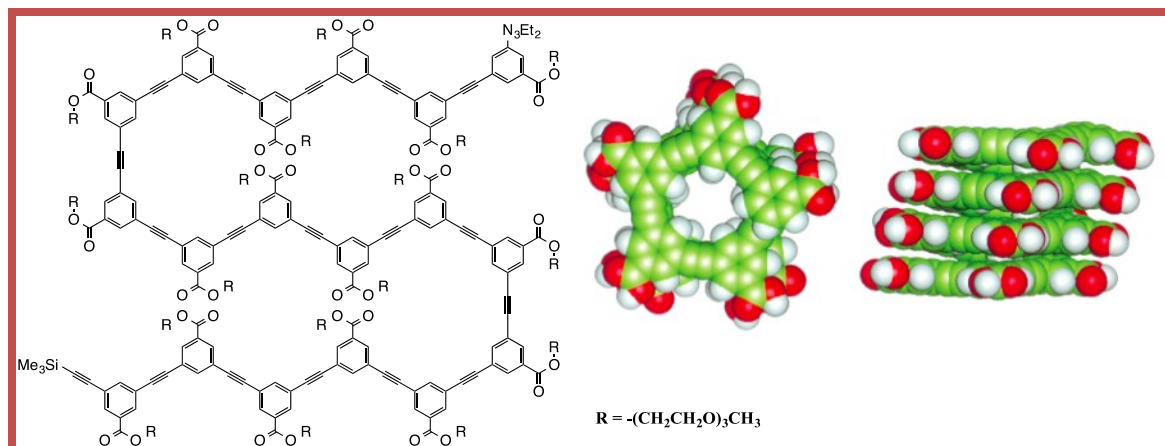


Figure 1.12: The folding of an oligomer due to the hydrophobic effect; the hydrophilic TEG groups surround the structures hydrophobic core.

foldamers. Many foldamers have been developed that give one dominated secondary structure with each one having either a peptidomimetic backbone,^[46] a nucleotidomimetic backbone,^[47] or an abiotic backbone.^[48]

Nelson et al. synthesized triethylene glycol substituted phenyl acetylene oligomers with the number of segments ranging from 2 to 18 (Figure 1.12).^[48c] They determined that when 8 or more segments were used, a helical structure was formed when in a polar solvent like acetonitrile. When dissolved in a solvent with less polarity such as chloroform the assembly destabilized. This assembly was observed using UV and NMR spectroscopy. The hypochromic effect was observed in the disassembly of DNA and the oligomers with 8 segments or longer experienced the same effect.^[48c]

Since hydrocarbons dissolve poorly in water, the formations of organized assemblies are limited. To overcome this, a hydrophilic head group can be designed into

the molecule to increase solubility. A molecule with one hydrophilic end and a hydrophobic end are known as amphiphiles or surfactants. Amphiphiles play a major role in biological systems in the form of phospholipids, which make up the surface of cells. Phospholipids are known to form sphere bilayer assemblies when dissolved in water. The walls of the assembly consist of two regions: the hydrophilic exterior and the hydrophobic interior (Figure 1.13).^[49] This type of order is driven by the hydrophobic effect where non-polar groups aggregate to form a “greasy” fluid volume in order to be free from water.

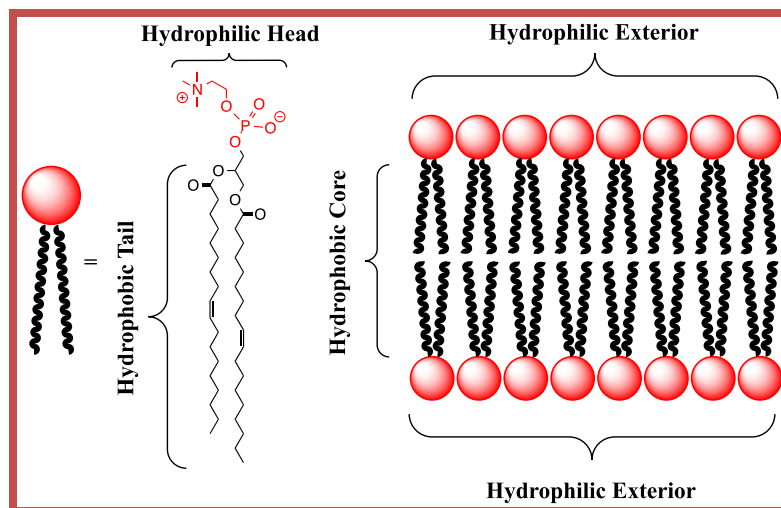


Figure 1.13: Self-Assembly of a biological amphiphilic surfactant.

Amphiphiles are developed in order to produce assemblies with interesting properties. Amphiphiles with two polar head groups that flank the hydrophobic region are known as bolaamphiphiles. These types of amphiphiles tend to be more robust to elevated temperatures and are common in the makeup of archaebacteria monolayer

membranes.^[50] Synthetic bolaamphiphiles that yield similar assembled structures in the form of vesicles,^[51] sheets,^[52] layers,^[53] fibrils,^[52, 54] and tubes^[41] have interesting properties designed into the molecule such as electron donor and acceptors to study the effect of electron transfer within the assembly. A very interesting property is that bolaamphiphiles assemblies can produce hydrogels, which has potential pharmaceutical applications.^[55]

1.3 Directionality of Amphiphilic Self-Assembly

Self-assembly of monomeric units that are programmed to orient and diverge in a particular way is a powerful bottom up method for producing advanced nano-structures. Self-assembly is an achievable goal for almost all types of amphiphiles, but to give direction to produce advanced structures such as helical tapes, belts, rods, and tubes requires additional directionality built into the monomer. Such forces that program the monomer to give an advanced assembly are steric and hydrophobic interaction, π - π stacking, and hydrogen bonding. This section will explore ways of programming monomers to give a certain type of nanostructure.

The formation of a variety of structures can be predicted as long as the amphiphile is non-crystalline and the hydrophobic tail is an alkyl chain. The structures can be predicted using the formula $P = v/a_0l_c$, where P is the packing parameter, v is the volume of the hydrophobic chain, a_0 is the surface area of the polar head, and l_c is the length of the chain. Depending on the value P , an assembled shape can be assigned: $0 - 0.33 =$

Spherical Micelle, $0.33 - 0.50$ = Cylindrical Micelle, $0.50 - 1.0$ = bilayer vesicle, ~ 1.0 = bilayer, and > 1.0 = Reverse Micelle (Figure 1.14).^[56]

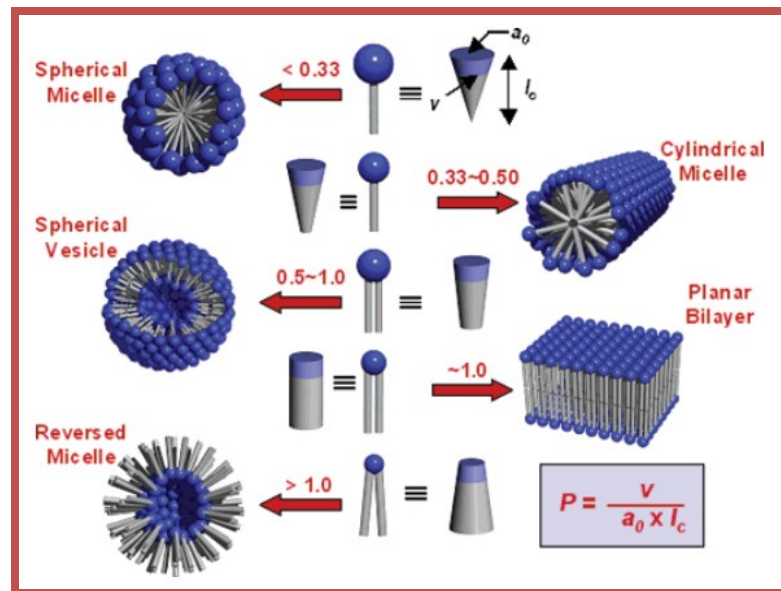


Figure 1.14: The different assemblies formed from simple amphiphiles. The assembly morphology depends on the surface area of both the hydrophilic head group and the hydrophobic tail.^[56]

Micelles are the simplest amphiphilic assembly that can form. These small structures have a hydrophilic surface that sits on and shields a fluid hydrophobic interior in aqueous solvent. These thermodynamic systems are dynamic and the monomers can interchange with one another and only form when above a critical temperature (Krafft Point) and at a critical micelle concentration (CMC).^[57] If the temperature drops below the Krafft point, the electrostatic interactions intensify and the micelle will fall apart, creating ununiformed aggregates.

When the amphiphile concentration is high enough and energy is added to dissolve the material, a kinetically stable vesicle can form. The vesicle or liposome is a

sphere or ellipsoid made up of a bilayer of amphiphile monomers. Like the micelle, simple vesicles have a surface of polar head groups but are found both on the outside and the inside. Vesicles can also be observed with multiple layers and can be as large as 10 microns.^[58]

The mechanism that leads to the formation of tubular structures (both micellar and hollow bilayer) is not completely understood. One of the first hypotheses mainly focused on the electrostatics on the surface of the tube. De Gennes et al. first developed this model, which stated that electrostatic repulsion created curvature, thus giving the tubular shape.^[59] If the electrostatics were a dominant force for the determination of the curvature of the tubes surface, electrolytes in the solution should affect the diameter and curvature of the assembly. Yager et al. examined this and concluded that electrolytes did not affect the diameter of the tube samples, thus the electrostatic repulsions do not play a major role in tube formation.^[60]

1.4 Chiral Effects of Amphiphilic Self-Assembly

There is strong evidence that the tubular shape and size is associated with the tilt of the amphiphile within the packing, or the amphiphile is unable to align with each other perpendicularly due to strain from chirality.^[61] The most accurate way to predict the dimensions of the tube is described in Figure 1.15. The continuum elastic theory involves two parts: the assembly structure and how the monomers pack in one system (the microscopic dimensions) and the longer-length-scale degrees of freedom that can be

related to the macroscopic folding process of assemblies. This theory assumes two conditions about the structure of the tube. First, the chirality of the monomer is absolute. If the enantiomer is used, the structure should yield a ϕ with the opposite sign and provide a mirror imaged structure. Second, the packing is crystalline. The chiral transfer of assemblies on the micro scale has been researched extensively, but examining on how this chiral transfer effects the overall macro morphology proves to be more difficult.^[61]

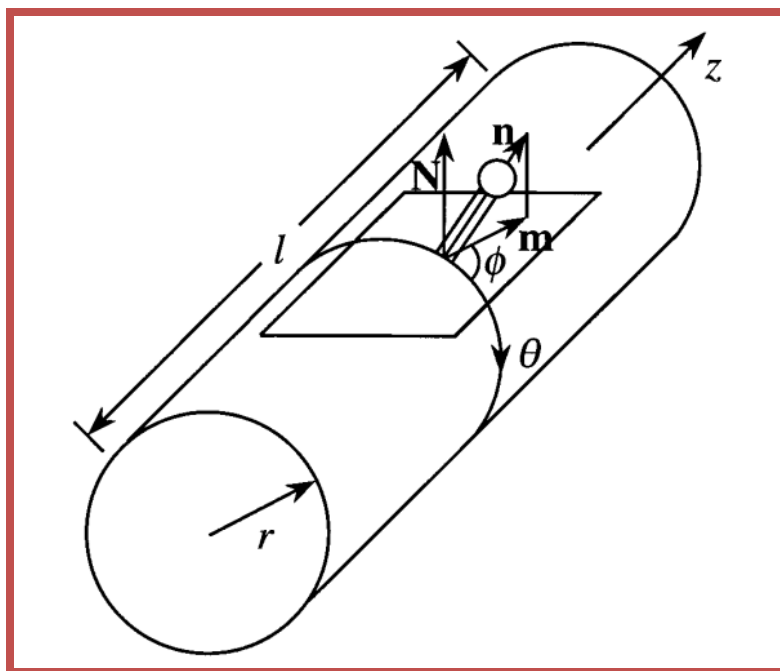


Figure 1.15: Diagram displaying the different amphiphilic angles and how they relate to the dimensions of a rod assembly.^[61]

Stupp et al. touched on this with amphiphilic peptides that featured varying bulky groups on the hydrophobic tail. Amphiphiles that had a non-bulky group, the supramolecular structure was a linear micellar tube. As the tail group induced more steric interactions the linear tube developed into a helical coil. The trend observed was

increasing sterics in this region, which yielded a super helix with decreasing left handed helical pitch. This report demonstrated chiral transfer from the monomer to the helical nature of the super helix.^[62]

There have been examples where chirality of the monomer unit doesn't control the handedness of the assembly. Achiral amphiphiles can provide interactions with both handed chiralities in the same sample. This is associated with unfavorable orthogonal arrangement of the monomers, so there is a 50:50 chance where the tilt angle screws to the right or left. The same phenomenon has been observed with chiral amphiphiles as well. There have been some discrepancies to the continuum elastic theory, but for most examples, chirality is an important factor when it comes to the formations of tubes.

1.5 The Role of Intermolecular Forces in Amphiphilic Assemblies

A chiral amphiphile that is long and narrow and has the capability to hydrogen bond allows micelle morphology elongation and form micellar rods or fibers. Often, hydrogen bonds from chiral groups morph in shape from a 3D assembly to a 1D assembly. Fuhrhop et al. recorded a wonderful example on how complex self-assembled

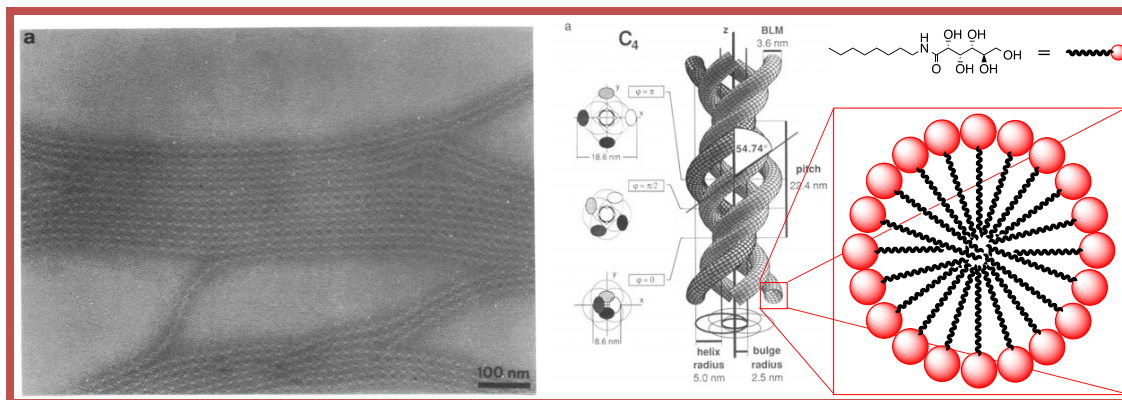


Figure 1.16: TEM of the self-assembly of N-octylgluconamide amphiphile (Left). Dimensions of the assembly (Right).^[8a]

material can be obtained from a simple monomer unit, N-octylgluconamide (Figure 1.16).^[8a] Fuhrhop et al. determined that hydrogen bonding between the amide groups supported the growth of the fibers into a right-handed quadruple helix after annealing the sample to 70°C by using TEM and solid state NMR analysis. The chirality of the helix is due to the chirality of the monomer. When the opposite enantiomer was used, the left-handed quadruple helix formed and a racemic mixture of the two did not form helices. Hartgerink et al. expressed the importance of hydrogen bonding in the core of the

amphiphile.^[63] A series of peptides were examined using CD. By selectively was eliminated. When these hydrogen bonds were neutralized, assembly was hindered. methylating a number of secondary amides in the core of the peptide, hydrogen bonding

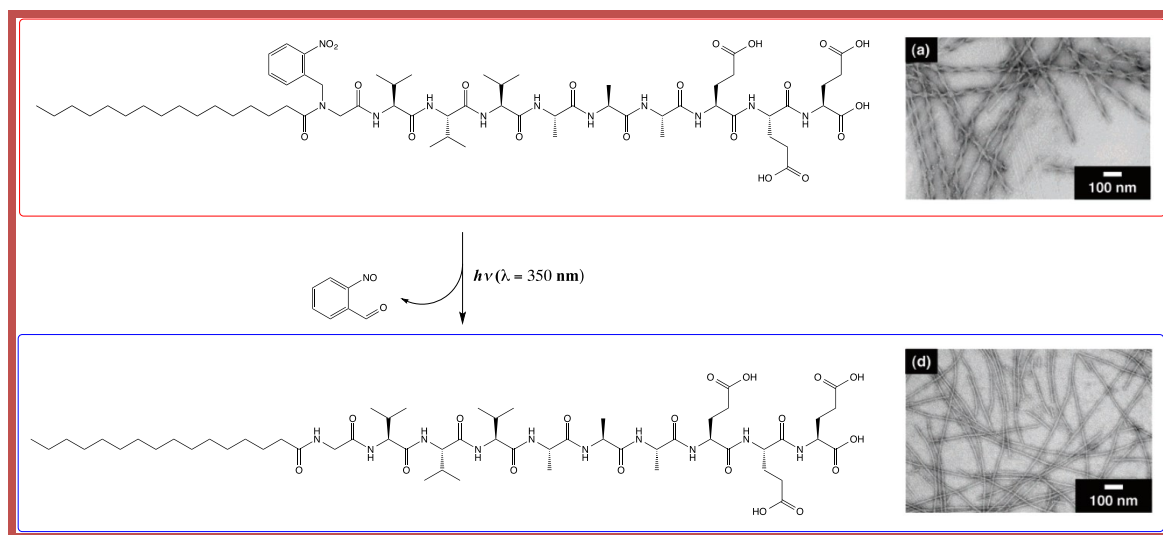


Figure 1.17: UV cleavage of the *o*-nitrobenzyl group changing the morphology of the assembly due to the different intermolecular interactions: π -Stacking (Top) and hydrogen bonding (Bottom).

Stupp et al. utilized peptide amphiphiles to accomplish similar results. The peptide structure depicted in the red box in Figure 1.17, yielded a quadruple helix made up of crystalline fibers. The removal of the *o*-nitrobenzyl group under UV light afforded the peptide in the blue box. The addition of the inner core amide hydrogen bonding and less steric interactions changed the assembly drastically to fluid micellar fibers. One possibility for this change in morphology of the two assemblies is the π - π stacking between *o*-nitrobenzyl groups. It has been reported that π - π stacking may be the main

factor for the self-assembly of β -amyloid fibrils.^[64] Peptides containing adjacent aromatic phenylalanine side residues have yielded self-assemblies of β -amyloid fibrils.^[65] Vesicles, like micelles, can also form tubular assemblies, but are hollow. This is stabilized because just like a vesicle the molecular arrangement is in a bilayer. Tubular assemblies have been created with simple amphiphiles with diacetylene in the hydrophobic tail. The original purpose of the diacetylene was to stabilize the vesicle bilayer structure.^[66] However, tubes ended up forming instead for many lipids containing diacetylene. Not only do these amphiphiles allow hydrogen bonding between the amides, the diacetylene units provide a pathway to stabilized tube growth through π - π interactions. The evidence for this was the polymerization of the assembly. In order for the diacetylene to form polydiacetylene, each group must be 3-4 Å from one another.^[67] There are a number of examples of phospholipids^[68] and glycolipids^[69] with a diacetylene in the tail that yields helical coils and tube assemblies.

The importance of π - π stacking in these assemblies was demonstrated by Shimizu et al. by examining a series of glycolipids featuring an aryl ring in the hydrophobic tail along with a varying number of alkenes (Figure 1.18). Focusing on the saturated lipid and the mono-alkene lipid, a ribbon to tube mechanism was realized. In a solution with 100% saturated lipid, a twisted assembly was observed. As the percentage of the mono-alkene lipid increased, tubes formed.^[70] In the saturated hydrophobic region of the bilayer, the linear arrangement of the hydrocarbon tail was organized and allowed only weak interaction with the aryl groups. As the concentration of alkenes increased in the

hydrophobic region, the organization was disturbed and strong π - π stacking occurred and as a result tubes were formed. The example showcased π - π stacking as a driving force

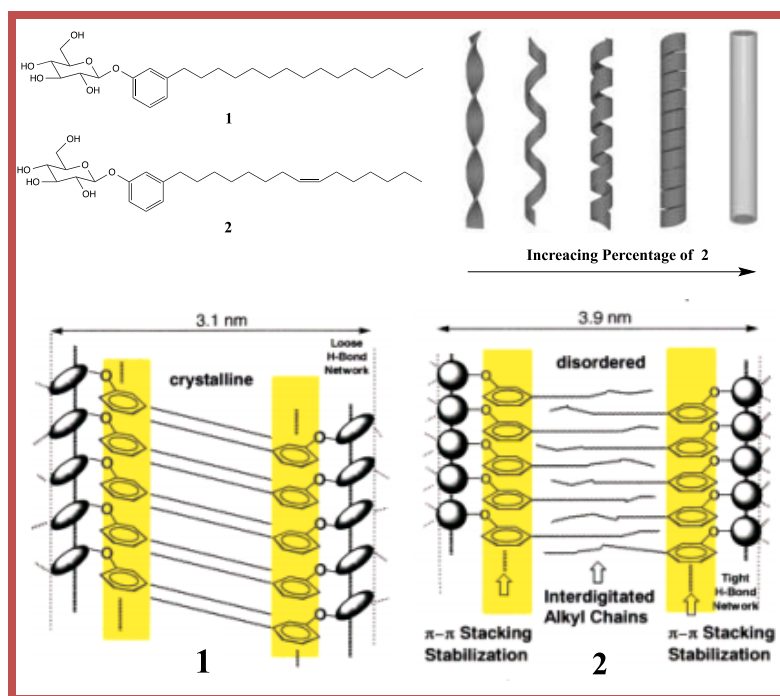


Figure 1.18: The alkene in the hydrophobic tail allows for a more ordered assembly. The increase of compound 2 allows nanotubes to form due to more loose hydrogen bonding and a more crystalline π - π stacking network.

toward tubular architecture instead of an amide hydrogen bond.^[71] Soon after, tube assemblies were created using a dimer of phenylalanine.

The surface forms spontaneously due to thermodynamic stability in aqueous environments. These systems are also dependent of physiological conditions such as pH, concentration, salts, and temperature, which may cause different morphologies.

1.6 Stimuli Responsive Self-Assembly

Amphiphilic molecules containing a variety of attractive and repulsive forces may reach equilibrium in certain conditions to yield an organized nanostructure. If the conditions change, the original equilibrated state will not be at an energetic minimum and the strength of the attractive and repulsive forces shift resulting in a new nanostructure at a different energy level. This is known as stimuli responsive self-assembly. Stimuli responsive self-assembly are attractive for applications for drug delivery,^[72] controlled release,^[73] nanoreactors,^[74] supramolecular polymers,^[75] and detection.^[76] The assemblies can be affected through varying stimuli such as pH change, thermal conditions, and light.

1.6.1 pH Responsive Self-Assembly

Due to their cancer chemotherapeutic drug delivery potential, pH stimulated nanoparticles are interesting because of the appeal for a material to absorb a drug and release with a change in protonation states. The pH within a cancerous tumor is lower than normal tissue due to the increase of metabolic induced lactic acid buildup.^[77] A nanoparticle that contains absorbed or encapsulated medication in the slightly basic blood stream, and can undergo a change that will release the medication within the more acidic tumor is an attractive feature.

One method to developing an amphiphile that is pH sensitive would be to protect using an acid or basic sensitive hydrophilic group. Klaikherd et al. developed a

polymeric amphiphile that forms micelles with a diameter of about 100 nm at pH=6.^[78] The micelles were able to absorb water insoluble Nile Red dye within the hydrophobic core. The hydrophobic end of the amphiphile has acetal protected alcohols. When the pH is adjusted to a more acidic condition the acetal group hydrolyzes, deprotecting the polar alcohol functionality (Figure 1.19). The assembly is disrupted due to the lack of a

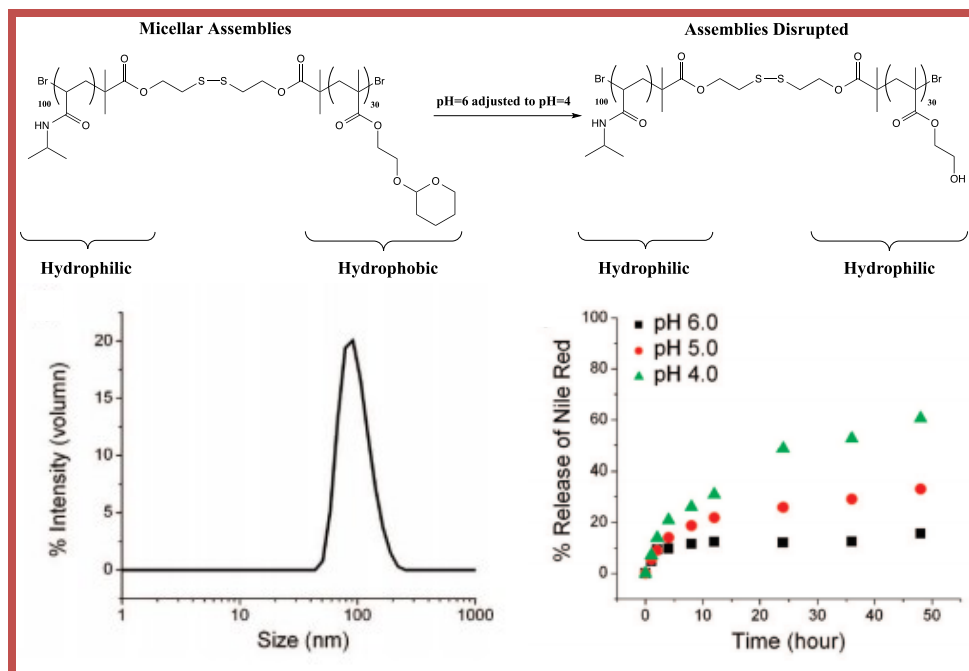


Figure 1.19: Irreversible hydrolysis of the pH sensitive acetal group converting the hydrophobic end of the polymer to hydrophilic (Top). DLS size measurement of the assembly at pH = 6.0 (Bottom Left). Time dependent release of Nile Red Dye at various pH conditions (Bottom Right).^[78]

hydrophobic effect resulting in the release of the Nile Red dye. One drawback to the releasing system is that solubility at 40°C decreasing substantially. The body temperature for humans is about 37°C.

Assemblies may also be sensitive to pH change through weakening and strengthening electrostatic and hydrogen bonding interactions. When the viologen amphiphile is dissolved in water vesicles form.^[79] The positively charged amphiphile can

form a 1 to 1 co-assembly with the negatively charged pyrene **2** through compatible electrostatic forces (Figure 1.20). The co-assembly forms long non-linear fibers at pH=9. The pyrene allows for π - π stacking occurring which gives directionality to the nanostructure resulting in a 1D assembly. When to pH conditions where adjusted to pH=10 the non-linear fibers change to straight fibers. The X-ray ORTEP revealed a

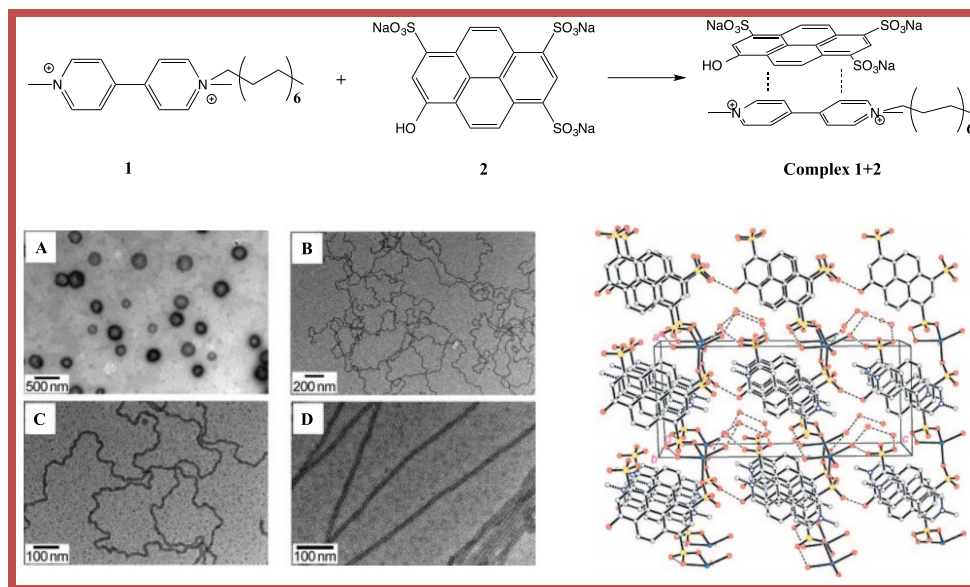


Figure 1.20: Complex formation of pyrene and viologen (Top). Self-assembly of viologen in water (A), viologen-pyrene complex at pH = 9.0 (B,C), viologen-pyrene complex at pH = 10.0 (D). ORTEP of the viologen-pyrene complex in water at pH = 9.0 (Bottom right).^[79]

network of hydrogen bonding between the hydroxyl and sulfate group on the pyrene. Wang et al. hypothesized that the increase in pH cause the deprotonating of the hydroxyl group close to the surface of the assembly and created electrostatic repulsion within the tangled structure and straightens out.

More advanced pH sensitive assemblies have been produced. One such system the authors coined as “pH-Sensitive Magnetic Nanogrenades” (PMAs).^[80] At

physiological pH, Ligand A and Ligand B co-assembly in the presences of extremely small iron oxide nanoparticles (ESION) to yield micelles with the chlorin e6 group on the inside. The size of the micelles were determined to be about 60 nm using TEM. (Figure 1.21 D) The size of the nanoparticle allowed for the acumination with in a tumor in vivo by exploiting the EPR effect. Once inside the tumor the pH decreases and the negatively charged particle surface becomes positively charged through the protonation of the imidazole groups, which causes the micelle to swell. (Figure 1.21 C) Both the size and the positively charged nanoparticle promote internalization due to the negatively charged cells.^[81] Once internalized, the pH drops further to less then 6.5 and the micelle is disrupted. With radical initiator “chlorin e6” free in the cell, a laser with a wavelength of 670 nm was used to irradiate the chromophores resulting in the production of free radical oxygen, which kills the cancer cell via a non-pathway dependent means.

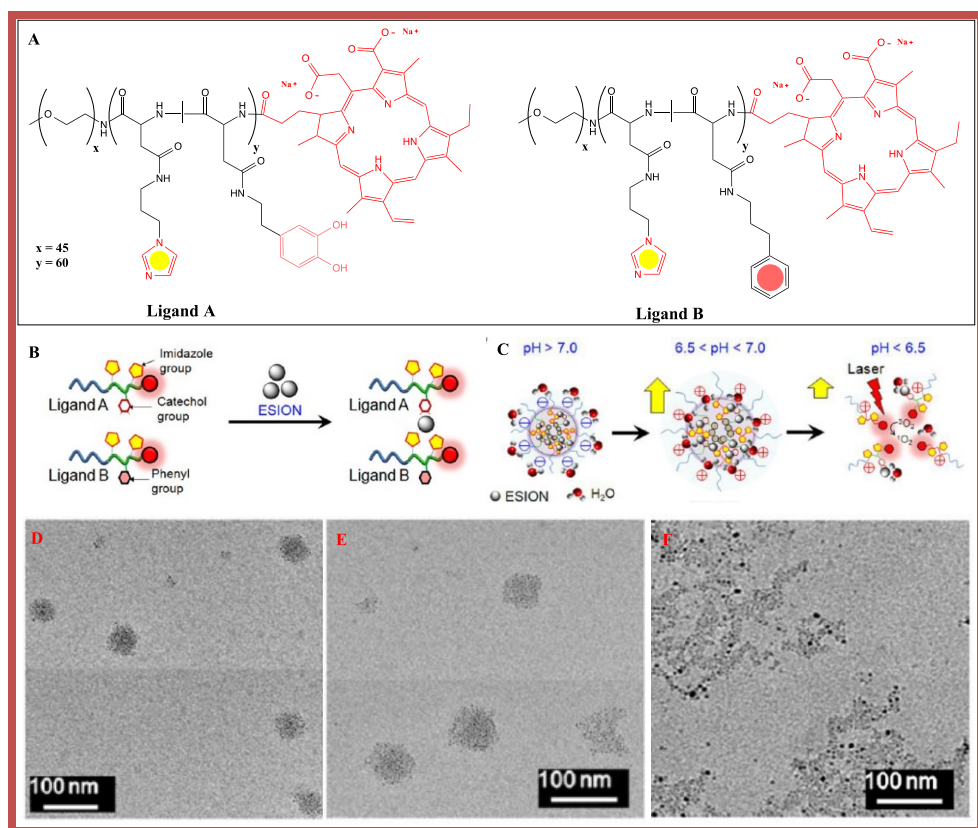


Figure 1.21: Structures of polymer Ligand A and B (A). Self-assembly mechanism (B) and pH stimulus mechanism of the nano-grenade (C). TEM of assemblies at $\text{pH} = 7.4$ (D), 6.8 (E), 5.5 (F).^[80]

1.6.2 Thermal Responsive Self-Assembly

Hydrogels have shown promise in not only drug delivery, but as cell regenerative scaffolds for tissue engineering applications.^[82] An attractive quality for a 3D cell matrix are materials that can dissolve in water while remaining a liquid and later become a gel by adjusting the temperature slightly. There are two mechanisms in which gelation can occur thermally: gelation through cooling the solution or through heating the solution. When a gel forms upon cooling, the intermolecular interactions are reestablished thus

forming a network of attractive forces.^[83] Gelation via heating the solution is driven through the hydrophobic effect. The solubilized material contains a hydrophobic region that can be encapsulated by water molecules at lower temperatures, but when the temperature is increased, the water molecules dissipate resulting in the reestablishment of the hydrophobic intermolecular attraction.^[84]

Gelation upon cooling allows for the intermolecular interactions to form and self-assembly is facilitated. Jeong et al produced poly(ethylene oxide) (PEO) and poly(L-lactic acid) (PLLA) tri-block polymers (PEO-PLLA-PEO) that form micellar assemblies at low concentrations.^[85] When the concentration was increased, the micelles were able to interact and formed a gel network at 37°C. The gel network was disrupted at 45°C and was a non-viscous solution. Fluorescein isothiocyanate (FITC) labeled dextran with an average molecular weight of 20,000 was allowed to absorb into the micelle at 37°C. The gel was heated to form an injectable solution, and injected into a mouse. Once in the mouse the solution cooled to 37°C and gelled. The release of the FITC labeled dextran was monitored and was a linear release over a 12-day period. This system may be used for the slow release of larger proteins such as insulin.

Most gelling systems that are formed through heating, result in isotropic networks. One of the first known materials that gels when heated to yield isotropic network of fibers was a lipophilic cobalt (II) 1,2,4-triazole complex (Figure 1.22).^[86] The mechanism of gelation was a change between an octahedral geometry at lower temperatures and a tetrahedral geometry at higher temperatures. The authors hypothesize

that the tetrahedral geometry allows for more fragmentation of the assembly resulting in a gel. When cooled the octahedral geometry allows a linear assembly without fragmentation.

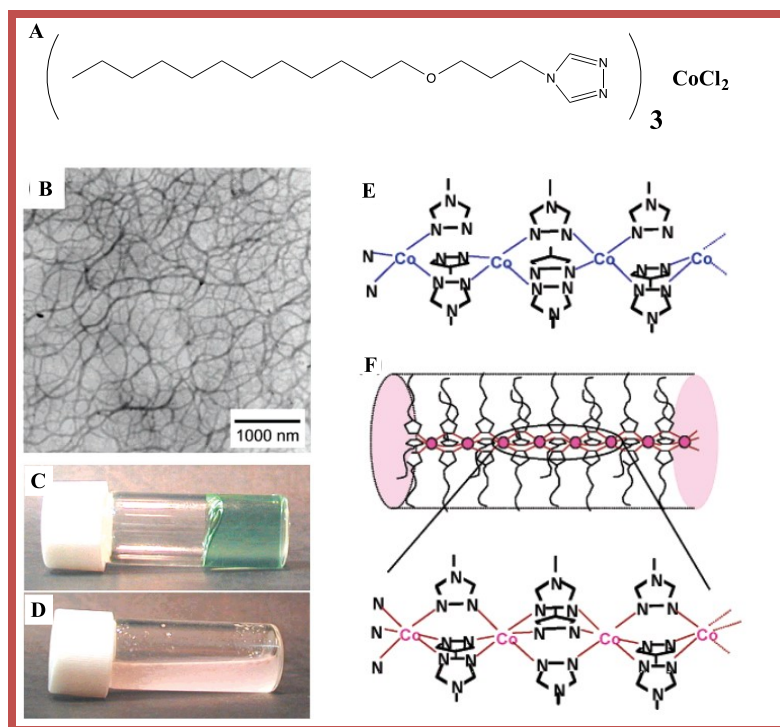


Figure 1.22: Lipophilic cobalt (II) 1,2,4-triazole (A). TEM of the gel (B). Lipophilic cobalt (II) 1,2,4-triazole at 30°C (C, E) and at 10°C (D, F).^[86]

Huang et al. developed an oligoether dendrimer attached through an imidazole linker to a linear aromatic penta-*p*-phenylene rod that assembles into long linear fibers that form an isotropic network in aqueous solutions at 10°C.^[87] If the solution is heated to 30°C, the fibers reorganized and arrange next to one another yielding a nematic gel. The heating is believed to enhance the hydrophobic effect by allowing the oligoether dendrimer to become more hydrophilic. The fibers were then able to form with a highly

organized core of π - π stacked penta-*p*-phenylene rods (Figure 1.23). The authors were then able to introduce cells to the solution at 10°C and upon heating to 37°C the cells were supported into a 3D gel matrix. The gel was shown to be cytocompatible and allowed for cell growth to give clumps of cell colonies after 2 days.

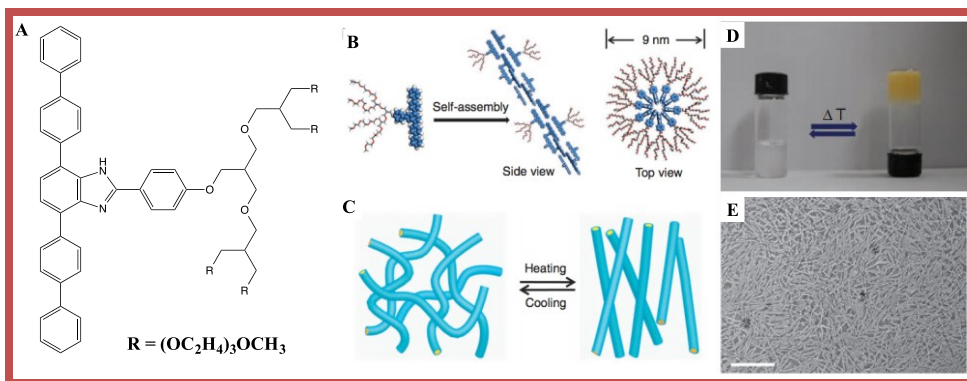


Figure 1.23: Amphiphilic dendrimer structure (A). Self-assembly mechanism (B). Cartoon depicting the morphology change during the heating and cooling cycle (C). Self-supporting gel in vial upon heating (D). TEM of the hydrogel (E).^[87]

1.6.3 Ionic Responsive Self-Assembly

Detection and identification of species in solution is important for environmental pollution such as heavy metals mercury, arsenic, and lead. Self-assembly may be used as a method of detection. Quinoxalinone derivatives were found to form gels were exposed to mercury (II) salts in methanol and acetic acid (Figure 1.24).^[88] Also, mercury could also be detected at concentrations as low as 10 ppb using UV. Examining the hydrogel using SEM revealed robust 1D fibers with varying widths that had a breaking stress of 100 Pa. Beyond detection, the assembly was found to absorb 99% of the mercury in a

river water sample, which could lead to a method of remediation of contaminated water systems.

Giving an additional directional stimulus may also be done through the use of metal chelation. Song et al. developed a bola amphiphile with a good electron donor



Figure 1.24: Reaction of quinoxalinone with mercury forms a hydrogel (Left). SEM of the hydrogel (Right).^[88]

dipyridine group in the center of the molecular structure (Figure 1.25).^[89] The pure bola in water solution assembles to give micelle structures with a diameter of 23 nm. When copper (II) was added to the solution, the dipyridine group coordinated. The assembly morphology changed from a disperse micelles to micelluar aggregates. The addition of the copper (II) was monitored by UV and NMR spectroscopy to determine the number of possible coordinating coppers ions. As the copper (II) was titrated to a 1:1 ratio the absorbance of 265nm decreased and 325 nm increased indicating that the metal is coordinating to the dipyridine group. Proton NMR analysis verified that coordination is taking place and the NMR peaks cease to change past a 1:1 ratio. The aggregation

process was found to be reversible upon the addition of EDTA and the monodispersed micellar assembly system was recreated.

Another example of ionic species stimulating the structure of an assembly involves adding a counterion of the opposite charge to influence the chiral helical twist of the assembly. Ethylene-1,2-bis(dimethylalkylammonium), a cationic gemini surfactant, formed nanosheets without any helical twist.^[90] When chiral counter anions such as *l*-tartrate and *d*-tartrate were added to the solution the nanostructure twisted to the

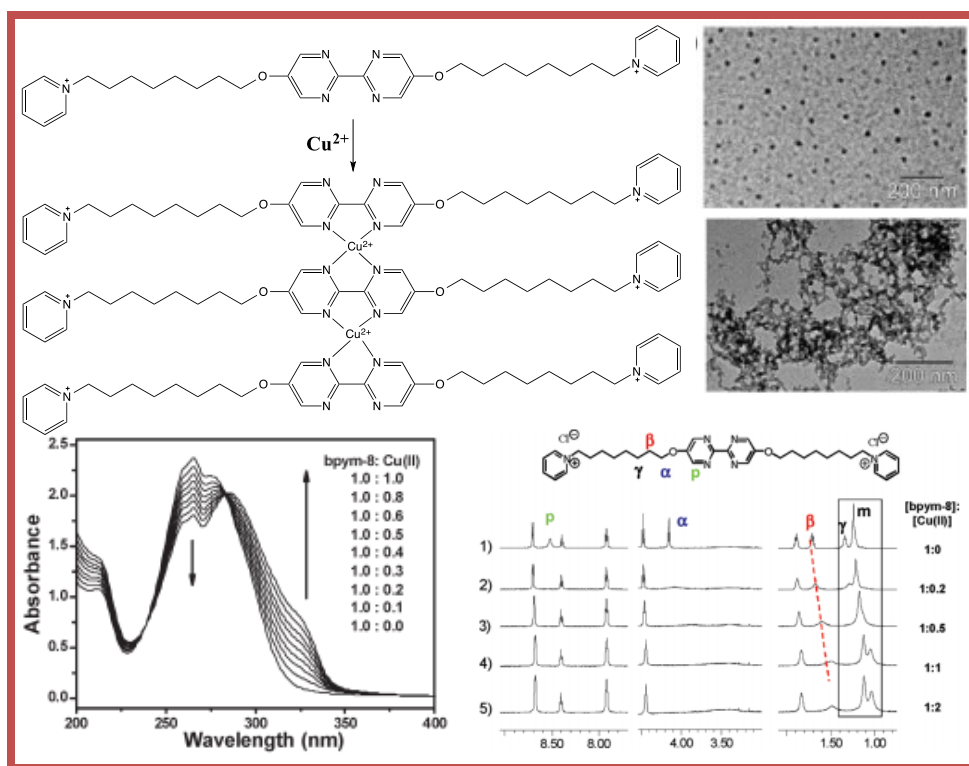


Figure 1.25: Coordination mechanism of Copper (II) and the dipyrindine bola. Before the addition of Copper (II) micelles were observed, and after the addition of Copper (II), the assemblies are disrupted (Top). UV and NMR of the addition of Copper (II). NMR stopped changing after a 1:1 ratio addition (Bottom).^[89]

handedness of the tartrate. The *l*-tartrate yielded left handed helical tapes and the *d*-tartrate gave left handed helical ribbon. The helical ribbon aged into tubes. Simple achiral surfactants may be influenced through the electrostatic interaction of a chiral ion, which will cause a change in morphology. The following example shows that ionic interactions can provide an additional interacting factor. The counterion can allow for assembly growth, aggregation, and chiral bias.

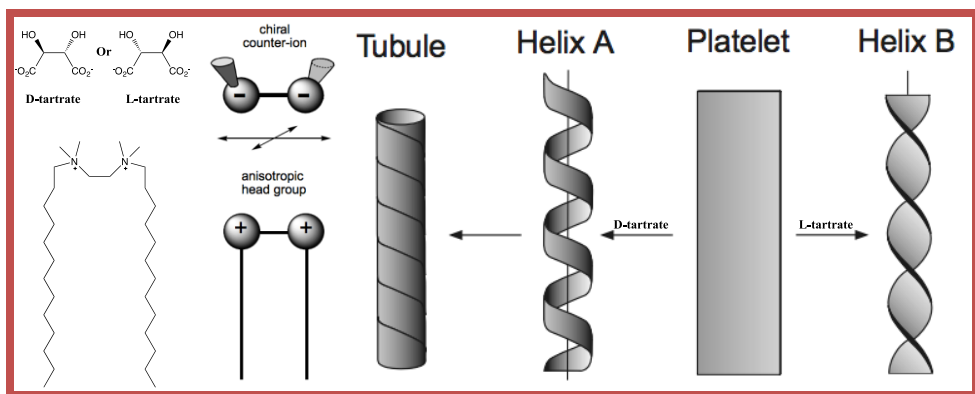


Figure 1.26: Gemini amphiphile can electrostatically interact with D- or L-tartrate (Left). Morphology changes depending on the chirality of the counterion (Right).^[90]

1.6.4 Light Responsive Self-assembly

Releasing mechanisms heavily involve uncontrollable conditions in a biotic system such as pH. Photosensitive assemblies can be controlled through external means. Azobenzene derivatives can be in a *cis* or *trans* conformation depending on the wavelength of light used to excite the azo double bond. Decyl triethylamine bromide amphiphiles with azobenzene have been synthesized and did show assembly-altering effects upon irradiation.^[91] If the centralized azobenzene is *trans*, the linear amphiphile

results in micellar nanostructures. The micelle assembly can be irradiated with UV radiation at 254 nm, *cis* conformation was formed resulting in the disruption of micelle.

Azobenzene amphiphile co-assembled with poly(ethylene glycol)-block-poly(acrylic acid) through electrostatic interactions and the nanostructure can change reversibly between a vesicle and non-assembled material (Figure 1.27).^[92] When the solution is irradiated with UV light, the azobenzene is in the *cis* conformation, which does not result in an organized assembled structure. If the system is irradiated with visible light the *trans* conformation is favorable yielding a vesicle. These simple azobenzene-amphiphile systems can encapsulate different dyes, which includes, sodium 1-pyrenesulfonate and sodium 1-pyrenesulfonate. When the nanostructures are disrupted with UV irradiation the dyes are released.

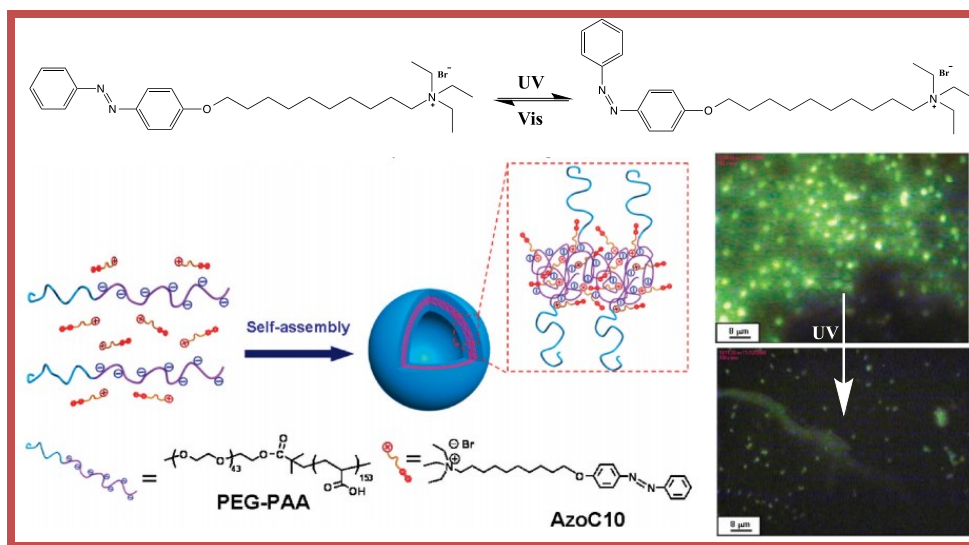


Figure 1.27: *Cis* and *trans*-azobenzene amphiphiles (Top). Nanostructure morphology (Bottom left). Dye release visualized with fluorescence microscopy (Bottom right).^[92]

The co-assembly of *trans*-azobenzene cyclodextrin was realized in the 1990's.^[93] This host-guest relationship can be used in light sensitive self-assembly where the interacting *trans*-azobenzene can be converted to the disruptive *cis*-azobenzene. Using a very similar compound to cyclodextrin, hydrophobic pillar[6]arene, Yu et al. describes the same behavior between the *trans*- and *cis*-azobenzenes but in organic solvents.^[94] With an azobenzene amphiphile (4-bromomethylazobenzene), they used the pillar[6]arene this increase the size of the hydrophobic head group when the azobenzene is in the *trans* configuration (Figure 1.28). To change the dynamics of the amphiphile, the *cis* configuration can be formed and the pillar[6]arene will slip off. In the report, *trans*-4-bromomethylazobenzene in chloroform: acetonitrile (10:1), the amphiphile self-assembled into small solid spheres with a diameter of about 78 nm. The pillar[6]arene was introduced to the solution and formed a host-guest complex resulting in the disruption of the solid spheres to give random aggregates. When the solution was irradiated with light at 365 nm to yield the *cis*-azobenzene, which forces the pillar[6]arene to slip off. This allowed for large vesicles to form with a diameter of about 4500 nm. The authors hypothesize that when the pillar[6]arene slips off, make up the inner and out surfaces with the azobenzene amphiphile buried in the middle between the to surface layers. These large vesicles can be converted back to irregular aggregates with 435 nm light.

1.7 Pathway-Dependent Self-Assembly

Stimuli responsive assemblies, as with most assemblies, are static. Stimuli responsive materials change due a change in the environment and reach a new equilibrium. Dynamic self-assembly forms structures not at equilibrium via a kinetic pathway. Nanoscale assemblies that are created through certain pathways using kinetic control are becoming an attractive research area to develop adaptive materials. These

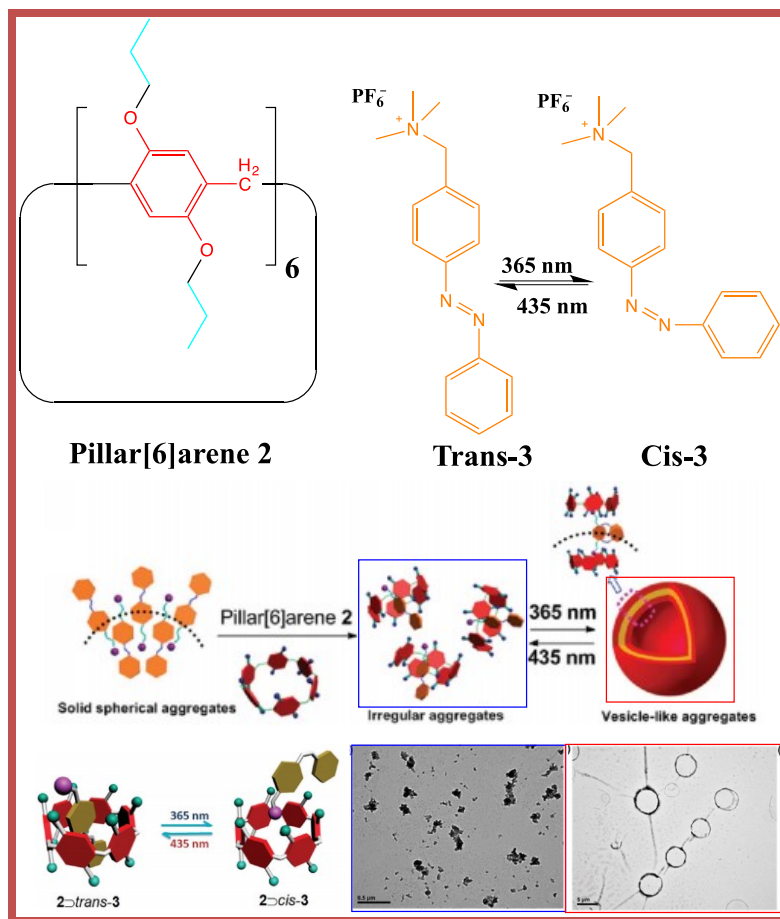


Figure 1.28: Structure of pillar[6]arene and trans- and cis-azobenzene amphiphiles (Top). Self-assembly process of trans-azobenzene amphiphile, co-assembly of the trans-azobenzene with pillar[6]arene before and after UV irradiation (Bottom).^[94]

pathways are a change in the conditions, such as solvent adjustments, to allow

transformation irreversibly. Characteristics of assemblies in non-equilibrium are: non-prescriptive, system-generated, propagation in time/length, additive, and competitive.^[95] Merocyanine dyes aggregate into centrosymmetric dimers due to strong dipolar interactions.^[96] These dimers then self-assemble into ordered nanorods in THF:dichloromethane (70:30) (Figure 1.29). When chirality is introduced into the molecule, the chirality is expressed in the supramolecular assembly as helical grooves along the nanorod realized with AFM.^[97] The nanorods have structural complexity and is patterned which suggests a non-equilibrium system. The merocyanine dye in CD displayed initially a negative bisignlet indicating an *M* helicity of the centrosymmetric dimers (H1 Assembly). The sample over time showed a slow *M* to *P* (H1 to H2 Assembly) transition

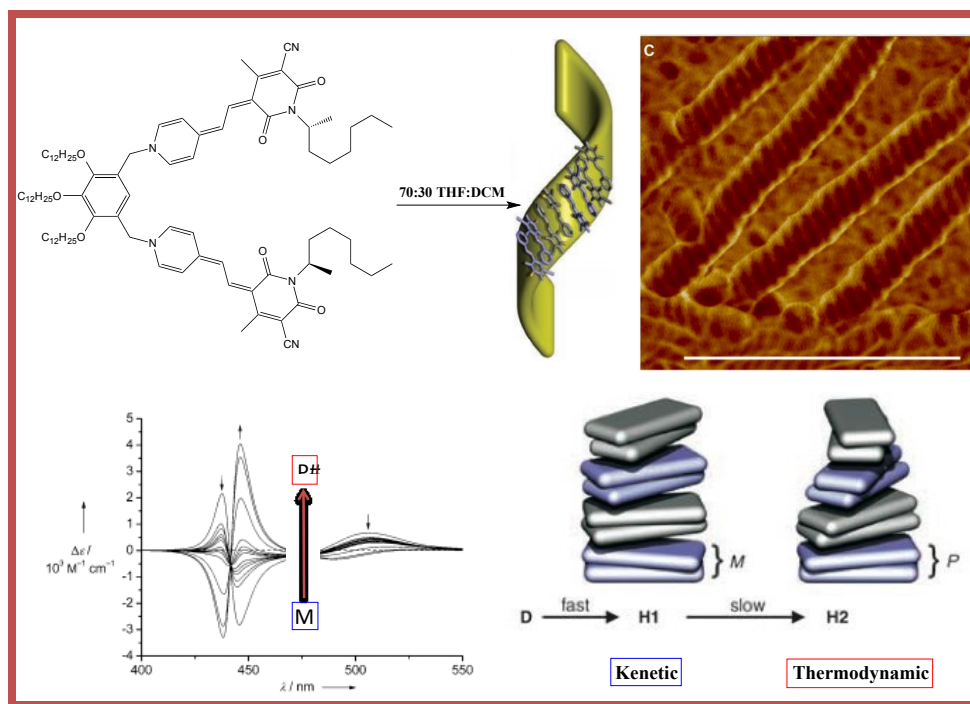


Figure 1.29: Morphology of the merocyanine dye assemblies (Top). CD and the helical configurations of the merocyanine dye dimers (Bottom).^[96]

to give a totally inverted CD bisignet. The authors explain this phenomenon as a slow kinetic to thermodynamic transition.

Trapping kinetic states remains a challenge and is a rare occurrence in self-assembly. Yamamoto et al. found that hexabenzocoronene amphiphiles assemble into nanocoils in THF, and this intermediate assembly transitioned into nanotubes (Figure 1.30).^[98] To trap the nanocoil kinetic intermediate norbornene was coupled onto the end of the hydrophilic PEG chains. This material did not form ordered assemblies in THF but in dichloromethane after the diffusion of diethyl ether vapor at 15°C. These nanocoils also transformed into nanotubes slowly at 25°C in five days. Using Grubb's catalyst, the norbornene can undergo Ring Opening Metathesis Polymerization (ROMP). When the polymerized nanocoil was heated the coil remained thus locking the kinetic state

Locking the kinetic state is a challenging task and an important step toward artificial nanoscaled dynamic self-assembly, but the ability to control the transformation to another kinetic state is desired. In order to trap kinetic intermediates in a non-covalent fashion, strong intermolecular interactions must be present. Amphiphilic coblock polymer systems that have strong hydrophobic interactions and display slow dynamics have shown the formation of kinetic assemblies.^[99] Colloidal gold with azobenzene thiosurfactants have also shown kinetically locked assemblies through light induced self-assembly.^[100] Kinetically locked assemblies created from small monomers are rare due

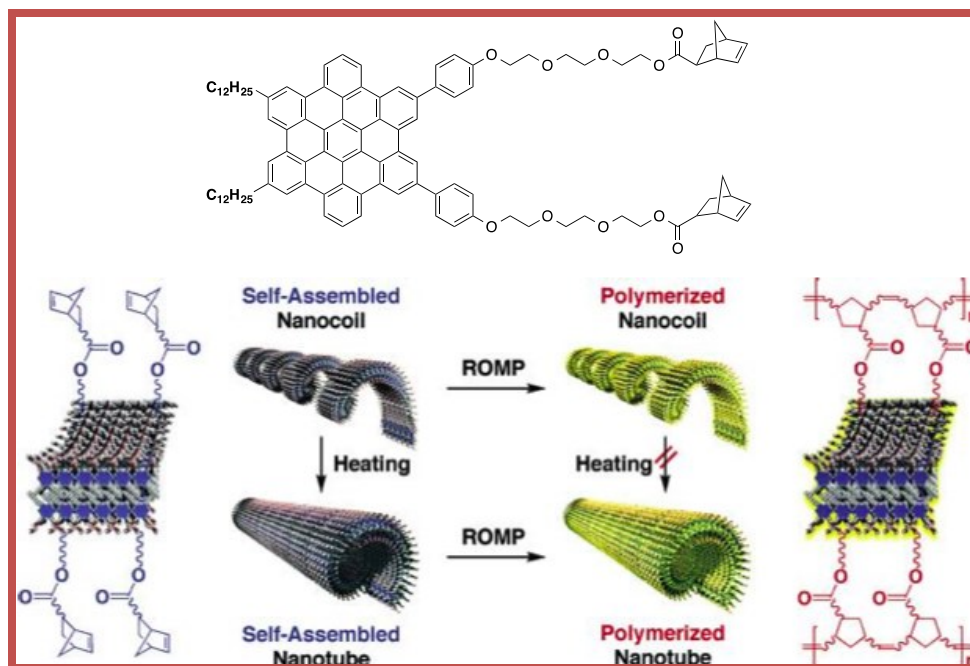


Figure 1.30: Self-assembly of hexabenzocoronene amphiphiles to nanocoils and nanotubes, and locking the nanostructures through ROMP. ^[98]

to the lack of intermolecular strength. Tidhar et al. developed a simple amphiphile with multiple types of interacting groups on the molecule (Figure 1.31).^[101] The amphiphile is capable of hydrogen-bonding, sulfur-platinum interactions, π - π stacking, and van der Waals interactions. The molecule in THF minimally aggregates. THF disrupts enough of the intermolecular interactions where self-assembly does not occur. When water is

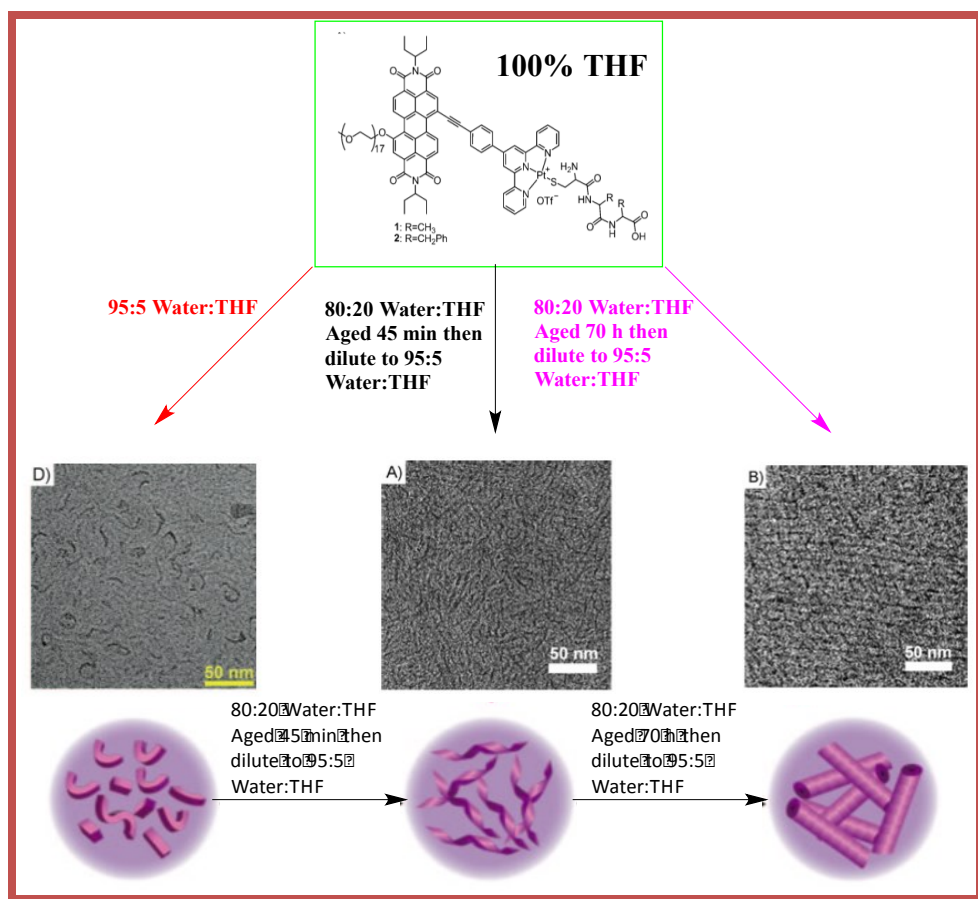


Figure 1.31: Self-assembly in water:THF (95:5) yields small aggregates. When THF concentration is increased the self-assembly process progresses to tubes, but can be “paused” by adding water to make the original 95:5 water:THF solution. ^[101]

added to this solution to give a 95:5 water:THF solution, the intermolecular interactions are strengthened and assemble to small aggregates. The same THF solution was diluted to 80:20 water:THF solution and aged for 45 minutes, followed by a 95:5 water:THF adjustment, resulted in stable helical nanocoils. With the nanocoils in to the same conditions and the smaller aggregates, the nanocoils do not change over time. The 80:20 water:THF sample was aged longer (70h), then the solution was adjusted to 95:5 water:THF and a nanotube assembly was observed. This assembly was again stable to

these conditions. The same assembly progression was observed starting with the small nanostructures in 95:5 water:THF solution. When the sample was diluted with THF to give a 80:20 water:THF solution, the helical coils formed in 45 minutes and the nanotubes were formed when aged longer to 70 hours. When water is added to the solution, morphology transition is stopped by reinstating the hydrophobic interactions π - π stacking and van der waals. With the more THF in the solution the π - π stacking and van der waals interactions weaken, while the hydrogen bonding strengthens. The monomer organization becomes more dense while pivoting about the hydrogen-bonds and forming

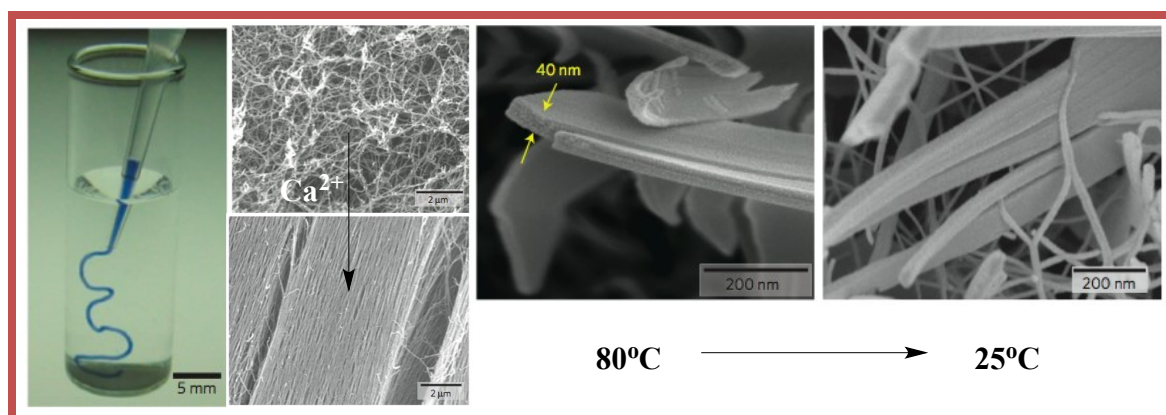


Figure 1.32: The heated peptide amphiphile added to a solution with calcium salt yields a robust structure such as a “noodle”. This is from the fibers straightening out into bundles (Left). SEM of a heated sample showing plaque made from bunched up fibers and of a cooled sample showing the plaque breaking up (Right).^[102]

the nanotube. This is one of the smallest molecules that assembles into nanostructures that undergoes pathway dependent self-assembly.

The peptide amphiphile (C₁₆H₃₃)-V₃A₃E₃-COOH was developed by the Stupp group and undergoes self-assembly to give fibers formed through β -sheet hydrogen

bonding.^[102] It was discovered that added calcium chloride to the amphiphile solution and heated to 80°C then cooled back to 25°C, the viscosity of the solution increased four fold. The TEM of the amphiphile before the heat treatment revealed fibers (Figure 1.32). When heated to 80°C, the nanostructures were plaque shaped assemblies. Examining the plaque structures using SEM, the plaque is made up of parallel fibers. When the sample was cooled, the plaque broke up in fiber bundles all aligned in the same direction. Internally the β -sheet hydrogen bonding had a parallel configuration before the heat treatment and an antiparallel configuration after the heat treatment. Due to the large increase in the viscosity and the irreversibility of the materials, the peptide solution without salt was heated to 80°C and slowly injected into a calcium chloride solution. When injected, the solution transforms to a strong gel and a “noodle” can be formed. This technology can produce cellular wires for biological applications involving cell regeneration of the spinal cord.

1.8 Conclusion

A “bottom-up” approach to fabricate nanoscaled materials is an efficient way to advance areas such as biomedical, sensors, and optoelectronics fields. Over the past few decades, many different self-assembly processes and systems have been developed through the incorporation of one or two interacting properties built into the molecule. With the careful control of these intermolecular interactions through strategic molecular design, stimuli responsive self-assembly has resulted in interesting properties and

advanced applications in the environmental sciences, chemotherapeutics, and cell regeneration. Most self-assembly research results have provided in depth knowledge of equilibrated systems. Even with many decades of study, laboratory produced self-assembly cannot mimic adaptive self-assembly found in nature. The development of pathway dependent self-assembly to produce materials not at equilibrium could lead to dynamic self-assembly that more closely mimics nature.

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Chapter 2

Intramolecular Chiral Communication in Peptide-Dendron Hybrids

(Adapted from “Intramolecular chiral communication in peptide-dendron hybrids” *Org.*

Biomol. Chem. 10, 2377-2379.)

2.1 Introduction

Proteins are important for the regulatory cellular and biological functions in organisms. Organisms, in dynamic environments, need regulatory proteins to maintain homeostasis. Allosteric proteins adapt in the presence of external stimuli through small perturbations within the structure as a whole, and switches on and off protein functions in response.^[103] Synthetic oligomers that responded to stimulus display a nonlinear fashion.^[104] The functions of proteins evolve from the structural cooperativeness that influences the conformational equilibrium of protein subunits.^[105] Few synthetic systems behave like proteins where external stimuli result in a nonlinear transfer of information in a form as chirality amplification. Subunits of a folded synthetic system interact through noncovalent intramolecular interactions and follow a phenomenon known as the

“majority rule”^[106] or the “sergeants and soldiers effect” (Figure 2.1).^[107]

Dendrimers are monomolecular branched molecules with repeating subgroups that can fold into spherical micelle-like unimolecular molecules. The name “Dendrimer” comes from two Greek words ‘dendra’ and ‘meros’ which both translate to ‘tree’ and ‘part’.^[108] Unlike self-assembled amphiphilic micelles that may become structurally unstable in most conditions, large dendrimers have a covalently locked hydrophobic core with hydrophilic arms that can interact with solvents and dissolved species without destroying the integrity of the structural shape. Dendrimers are non-equilibrating

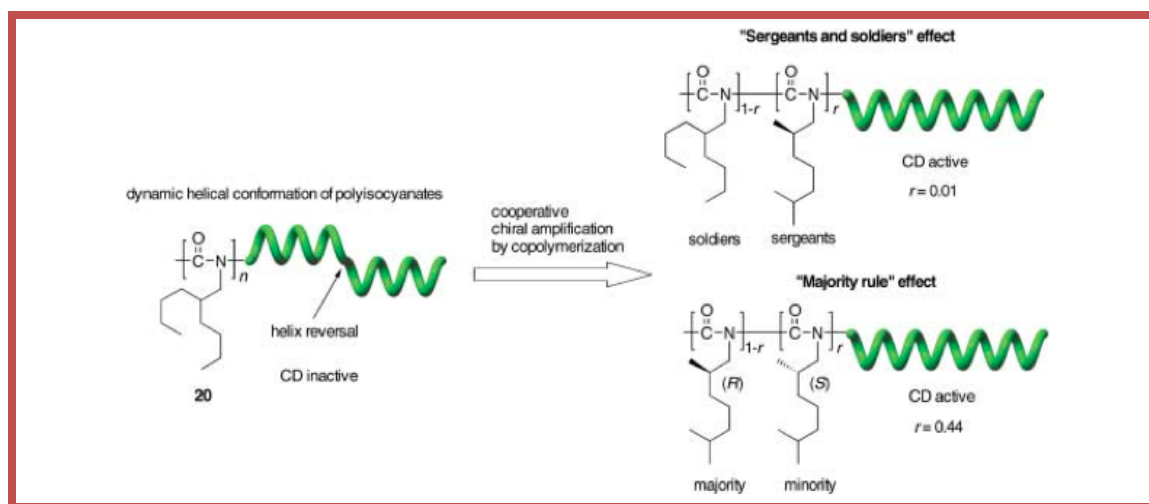


Figure 2.1: Examples of the “Majority rule” and the “Sergeants and soldiers” effects.^[103]

structures with a CMC of zero theoretically.^[109] Also, higher generation dendrimers provide a more spherical structure and may mimic many global proteins while minimizing complex folding variables.^[110] Applications that utilize dendrimers have been developed in research areas including biomedical^[111], materials in the form of polymers^[112], light harvesting devices^[113], solid supports^[114], and catalysts.^[115]

The Parquette group has been interested in cooperative inter- and intramolecular interactions in large ridged macromolecular dendrimers.^[116] Molecular cooperativeness is a concept where small chiral bias from one unit will amplify with multiple interacting units intra- and intermolecularly. In the case of dendrimers, the terminal groups will exert a small chiral bias and as the dendrimers increase in generations, the bias will become larger.^[117] With changes in the conditions, the chirally biased equilibrium may change and cause small perturbations throughout the dendrimer resulting in a chiral switch. This chapter will discuss the research that led to the design and results of peptide-dendrimer hybrids (PDHs) that exhibit the transfer of chiral information and intramolecular chiral amplification.

2.2 Peptide-Dendrimer Hybrid Design

Dendrimers with highly flexible branches will result in low or no transfer of information from either the core or terminal ends, and fail to adopt a dominant conformation.^[118] A successful way to decrease the flexibility of the dendrimer arms is to introduce hydrogen bonding. Pyridine-2,6-dicarboxamides have the ability to have multiple conformations, but due to intramolecular hydrogen bonding, the *syn-syn*

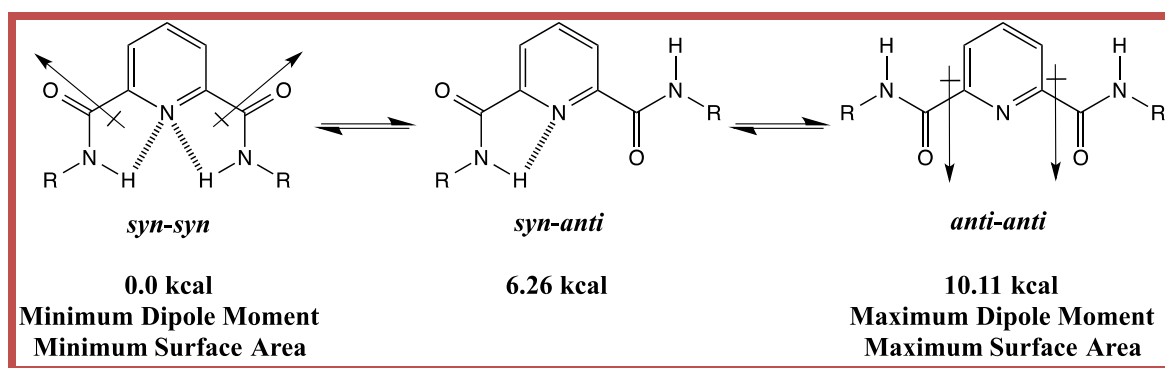


Figure 2.2: The different conformations of pyridine-2,6-dicarboxamide: *syn-syn*, *syn-anti*, *anti-anti*.

syn-syn conformation is preferred by 10.11 kcal (Figure 2.2) because of the minimization of the dipole moment and surface area.^[119] The *syn-syn* conformation forces the substituents attached by the amide bond to become sterically crowded. To relieve sterics, the arms will move out of the pyridine plane resulting in an *M* or *P* conformation.^[120]

The stability of the *syn-syn* conformation of the pyridine-2,6-dicarboxamide provides the rigidity to allow the dendrimer arms to prefer a helical bias. Introducing a chirality source to the branch terminus has shown a transfer of information to the

dendrimer core. Dendrimers with chiral branches, acylated (1*S*,2*S*)-(+)-thiomicamine, shows a helical bias in CD spectroscopy with increasing generations **G0**–**G3** in dichloromethane (Figure 2.3).^[121] Dendrimer **G1** did not show a CD signal at 316 nm due to a fast *M*–*P* conformation equilibrium. In hydrophobic solvents the hydrogen bonds

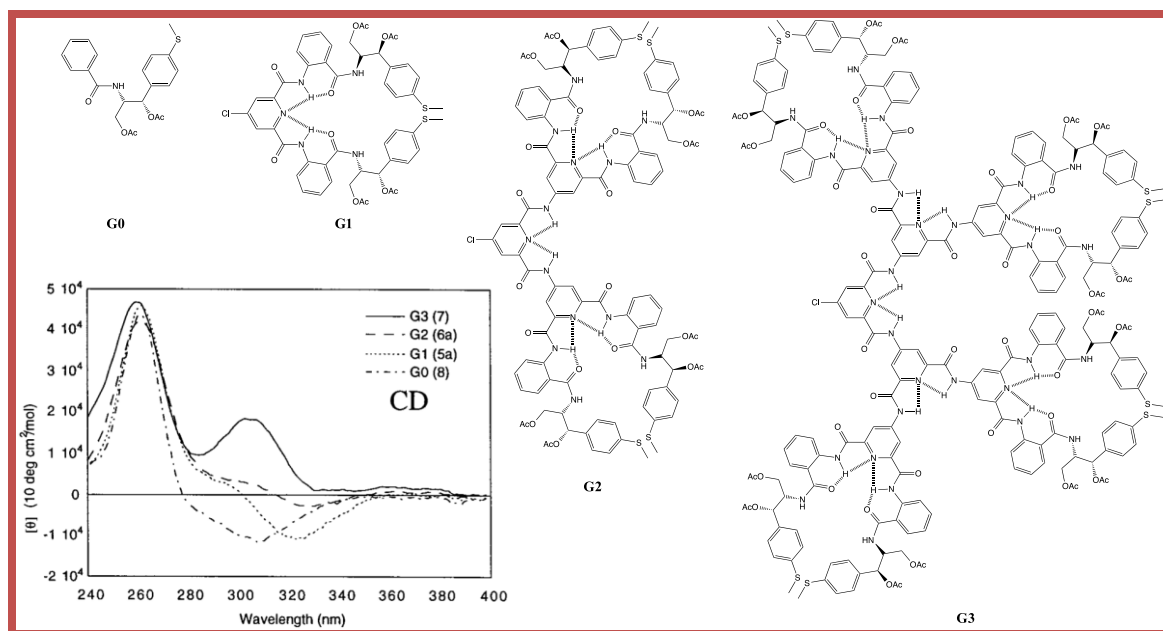


Figure 2.3: The 2-acylamino benzamide control (**G0**) and pyridine-2,6-dicarboxamide dendrimer generation molecules with 2-acetamido-*N*-methylbenzamide arms (**G1**–**G3**). CD spectrum displaying an increase of helical bias as the dendrimers become larger.

for **G2** are strong due to an increase of the CD signal at 316 nm when the dichloromethane was doped with hexanes. When doped with ethanol, the helical bias deteriorates suggesting weaker hydrogen bonds and increases arm flexibility. **G3** maintains the helical bias in all solvents studied. The helical bias is driven by the larger number of chiral terminal groups and resists change because of the increased intramolecular repulsions and interactions.

Polar solvent tends to disrupt hydrogen bonding, but globular proteins can stabilize these attractions. Globular proteins create a hydrophobic environment by folding and decreasing surface area, which increases core density.^[122] Replacing the acylated (1*S*,2*S*)-(+)-thiomicamine with a chiral pentaethylene glycol ether will increase

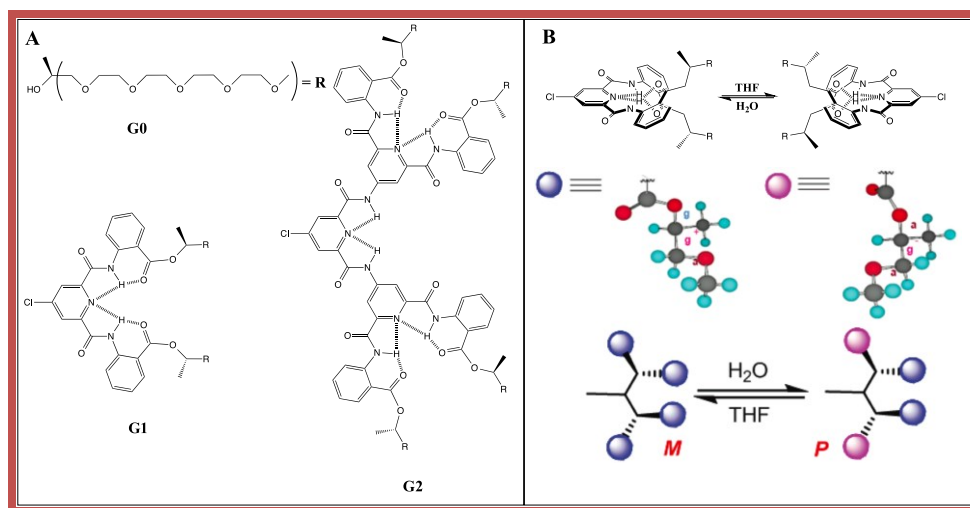


Figure 2.4: Molecular structures of dendrimers with chiral pentaethylene glycol arms (A). Visual of the chirality switch process (B).

water solubility of the dendrimer (Figure 2.4 A). The **G1** and **G2** PEGalated dendrimers displayed a negative 316 nm signal that indicates an *M* helix in CD spectroscopy.^[117] The packing interactions of the dendrimers allows for chirality transfer to the anthranilate. In the organic solvent THF, **G1** maintains the *M*-helical chirality. Interestingly for the **G2** dendrimer, THF causes a helical switch observed in CD as a positive singlet. IR analysis and computational calculations determined that the PEG groups were acting as a trigger (Figure 2.4 B). In water, the conformation of the first ethylene group in the PEG chain and the chiral methyl group is equally both anti-gauche-

anti and gauche-gauche⁺-anti. In THF the conformation changes to gauche-gauche⁺-anti. Depending on the conformation, the PEG group shifts the equilibrium to an energetically more favorable state, which is observed as a *M* to *P* chiral switch.

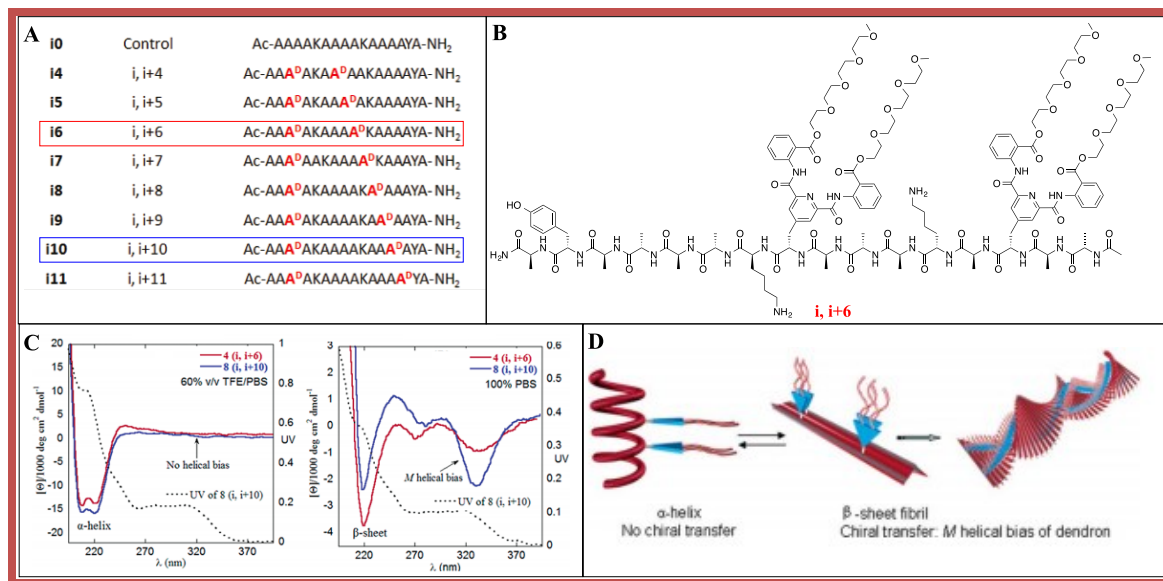


Figure 2.5: PDHs examined (A). Molecular structure of an *i, i+6* PDH (B). CD spectra of **i6** and **i10** in 60% TFE/PBS and 100% PBS (C). Models of the secondary structures of the examined PDHs (D).

A series of alanine rich with achiral pyridine-2,6-dicarboxamide-TEG dendrimers residues were examined to explore information transfer between the dendrimers and the peptide backbone intramolecularly (Figure 2.5 A).^[123] Alanine rich peptides are known to form stable α -helix secondary structures with 3.7 amino acid residues per rotation.^[124] The hypothesis was chiral transfer from the peptide backbone to the achiral **G1** dendrimer would occur followed by intramolecular dendrimer-dendrimer chiral amplification especially for the **i4** (*i, i+4*) PDH, where the dendrimers are extending out from the same side of the α -helix. CD spectroscopy of 60% TFE/PBS solutions of PDHs

displayed a α -helical secondary structure seen as the two 222 nm and 208 nm local minima signals, but did not show any helical bias of the dendrimers with the absence of the 316 nm signal. Therefore, the dendrimers are not interacting and amplifying chiral information. The α -helix secondary structure deteriorates in 100% PBS and random coil was observed in CD for all the PDHs except for **i6** and **i10** which has β -sheet secondary structure. Interestingly, a negative CD couplet at 316 nm indicating chiral amplification was observed. TEM revealed fiber nanostructures. When the dendrimers are at the $i, i+6$

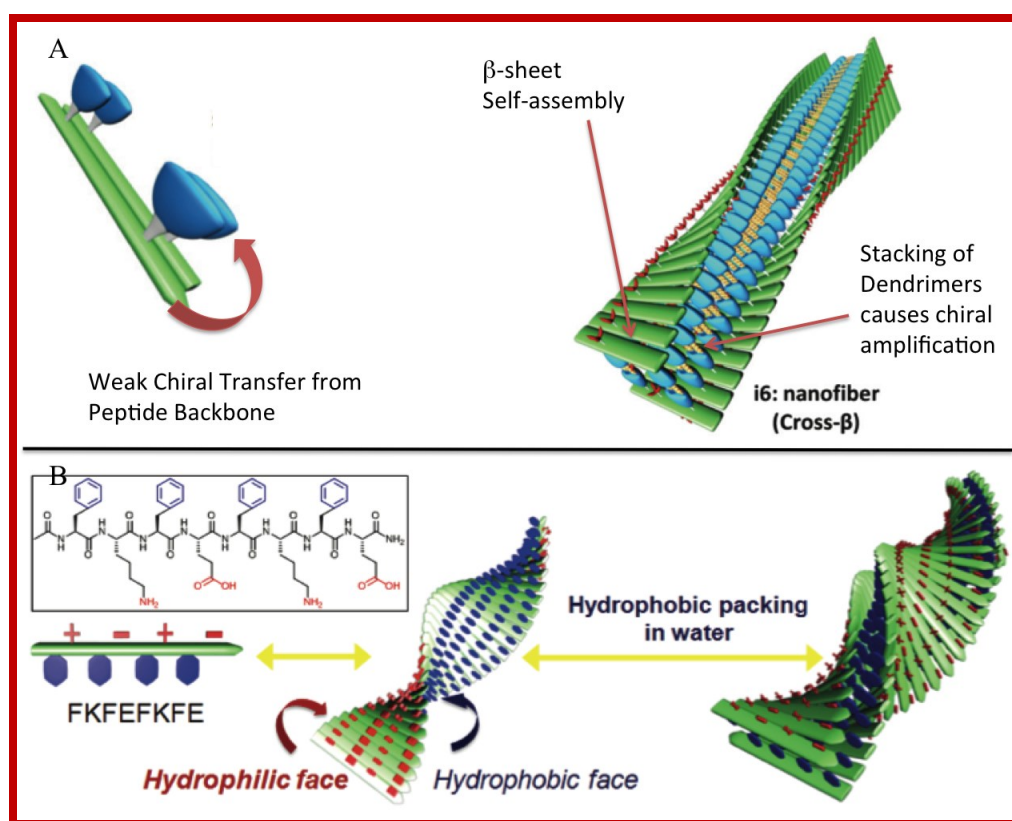


Figure 2.6: Chirality is transferred from the peptide backbone to the dendrimer and the chirality is amplified due to dendrimer stacking in the β -sheet fiber (A).

and i , $i+10$ positions, they are on the same face of the peptide backbone. This allows hydrophobic regions of aligned dendrimers to form in a bilayer as the β -sheet forms. The aligned dendrimers interact and transfer chiral information from the chiral peptide backbone (Figure 2.6 A).

β -Sheet forming peptides can be stabilized with alternating polar and non-polar amino acid residues, observed in natural isolated compounds.^[125] The polar and non-polar residues create an amphiphilic effect. When the polar residues are evenly positively and negatively charged, the net charge in aqueous solution is zero, minimizing electrostatic repulsion. A peptide with repeating units of FKFE will form β -sheet readily in aqueous solutions.^[126] This peptide has the criteria described above: alternating polar/non-polar amino acid residues and a net charge of zero (Figure 2.6 B).

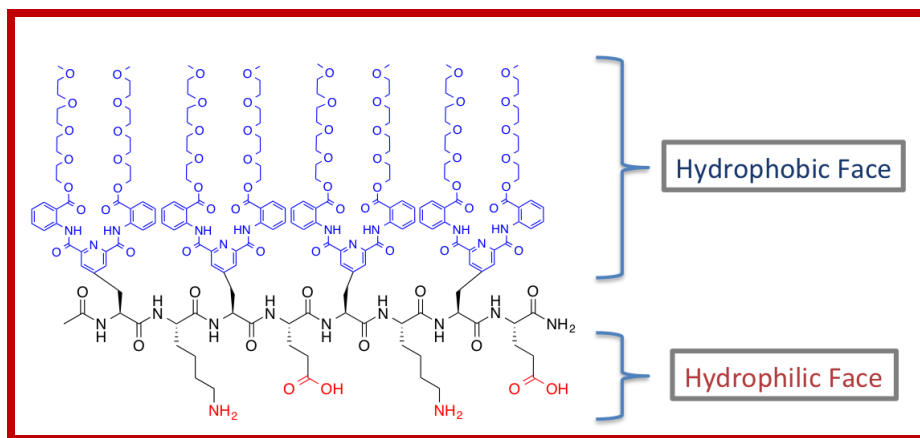


Figure 2.7: Design of alternating polar/non-polar PDHs.

The FKFE model was modified and the phenylalanine was replaced with the **G1** achiral dendrimer. Our hypothesis was that the PDHs with alternating dendrimers and polar residues would promote a fiber assembly with β -sheet secondary structure (Figure 2.7).

Four molecules were analyzed: G1 amino acid **1**, tetra-peptides **2** and **3**, and octa-peptide **4** (Figure 2.8). None of the PDHs produced β -sheet fibers due to intramolecular steric interactions, but chiral helical bias and chiral *M* to *P* switching behavior similar to larger G2 and G3 dendrimers was observed. Reported in the following will be the discussion of alternating polar/non-polar PDHs that respond to external stimuli and displays intramolecular non-linear chiral amplification.

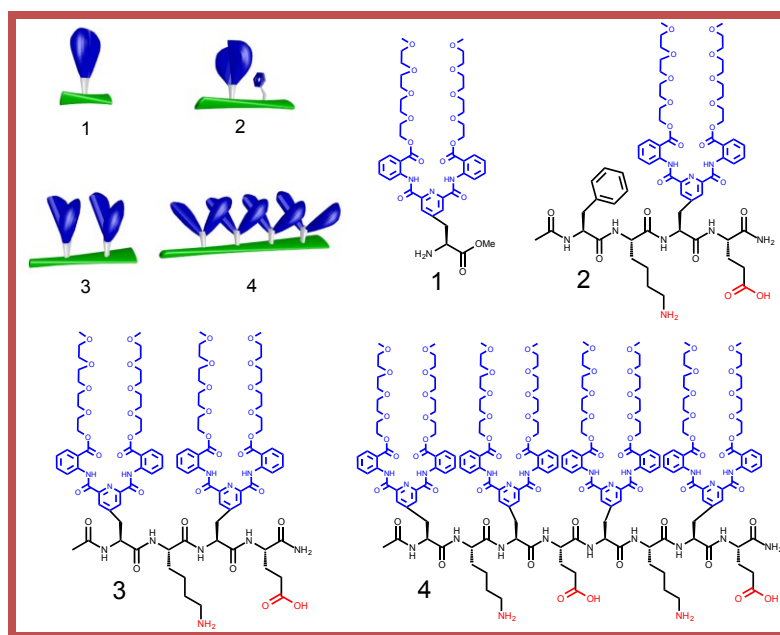


Figure 2.8: Models representing the PDHs and molecular structures of PDHs.

2.3 Results and Discussion

The conformational properties of dendrimers **1-4** were investigated by CD and IR spectroscopy (Figure 2.9). The negative couplet at 204 nm observed for all three PDHs

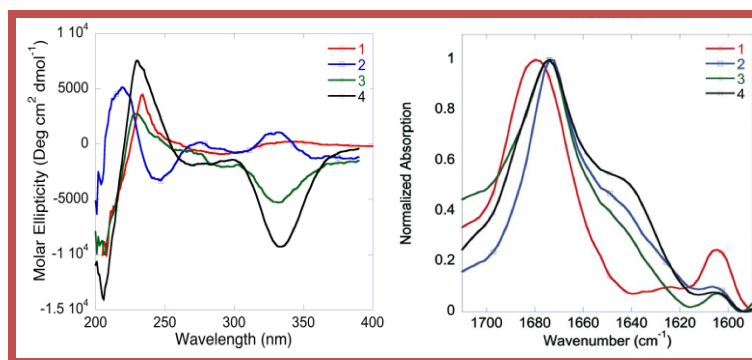


Figure 2.9: CD of PDHs **1-4** (10 μ M) (left). IR of PDHs **1-4** (10 mg/mL) (Right)

2-4 indicates that the peptides adopt a random coil conformation. IR spectroscopy confirms the random coil conformation with a 1640 cm^{-1} absorption. The expected β -sheet conformation most likely cannot form due to both intra- and intermolecular steric hindrance causing inadequate intermolecular packing.^[123] An α -Helical state was also not observed. Computational studies have demonstrated that entropy loss occurs from side chain fluctuations, causing stability reducing sterics.^[127] Therefore both α -helical and β -sheet secondary structures are destabilized in the PDH structures.

The dendron control **1** lacked the anthranilate π - π^* absorption at 316 nm in the CD spectrum, which does not express helical bias.^[117] Chiral groups alone at the four position on the pyridine ring does not transfer chirality information to the dendrimer arms.^[128] In contrast, PDHs **2-4** exhibited excitonic couplets centered at 316 nm,

indicating chiral helical bias of the dendron side chains (Figure 2.9). The presence of a phenylalanine residue adjacent to the dendron in PDH **2** caused a *P* helical bias seen as a positive couplet. Increasing the number of adjacent dendrimers on the peptide backbone resulted in an increasing *M* helical bias. PDH **3** displayed a weak negative couplet while PDH **4** showed a negative couplet with an intensity increase of around double. Although the dendrimers were first generation molecules, the helical bias represented second and third generation dendrimers.

Helical bias was observed when PDHs formed β -sheet fibers with good dendron-dendron packing. In PDH **4** dendron-dendron packing can occur through intramolecular interactions or intermolecular packing through aggregation. PDH **4** was examined at very low concentrations where aggregation would be unlikely. Samples at 100 μ M and 10 μ M in water both displayed negative couplets with the same molar ellipticity intensity (Figure 2.10). The minimal change supports that intramolecular dendrimer packing was occurring. PDH **4** also exhibits a 316 nm negative excitonic couplet in THF, ethanol, and dichloromethane in both 100 μ M and 10 μ M concentrations. Typically organic solvents would degrade the hydrophobic dendrimer interactions and chiral amplification would be

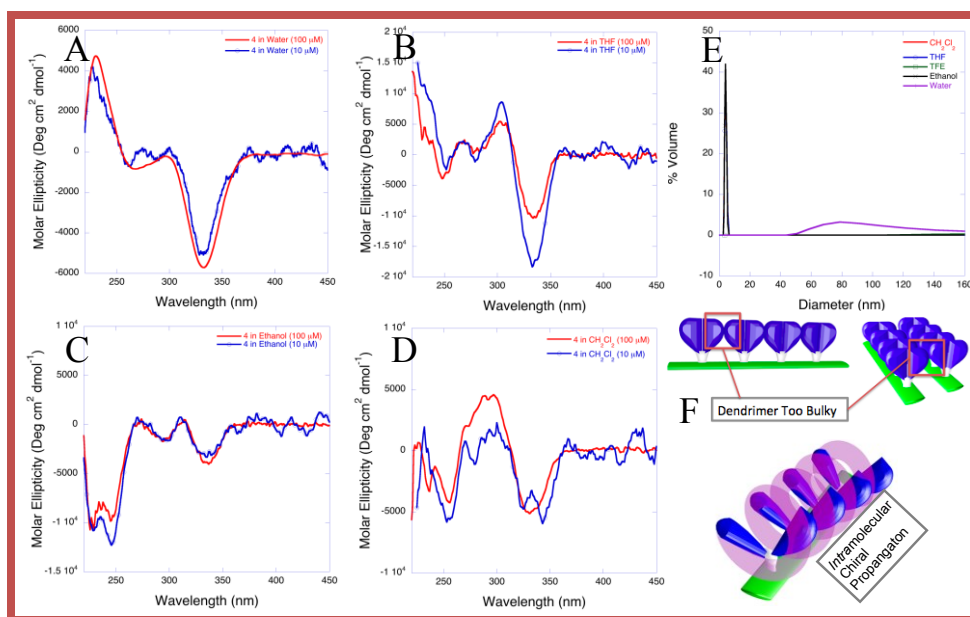


Figure 2.10: Concentration dependent analysis of PDH **4** (100 μM (red) to 10 μM (blue)): Water (A), THF (B), Ethanol (C), Dichloromethane (D). DLS measurements in water, THF, Ethanol, Dichloromethane, and TFE at 1 mM (E). Due to intra- and intermolecular steric hindrance, β -sheet self-assembly is unlikely; therefore the dendrimer helical bias is caused through intramolecular dendron-dendron stacking (F).

minimalized. In the case of PDH **4**, the dendrimers are prearranged and are linked through covalent bonds instead of β -sheet hydrogen bonding; organic solvents do not affect the dendrimer-dendrimer interactions. DLS measurements also show minimum aggregation in all solvents. 2D-NOESY experiments in [*d*₈]THF did not reveal any close contacts between adjacent dendrimers in PDH **4**. The dynamics of the conformational state was too fast for a broadening of the NMR spectrum and to see a NOE between neighboring dendrimer protons. PDH **4** was also examined with fluorescence spectroscopy. In water and TFE, the emission (440 nm, excited at 316 nm) intensity decreased, signifying that the dendrimer chromophores are strongly interacting.^[129]

These observations along with the progressive trend going from **1-4** support a process in which chirality information transfer occurs by the intramolecular packing of the dendrimer residues.

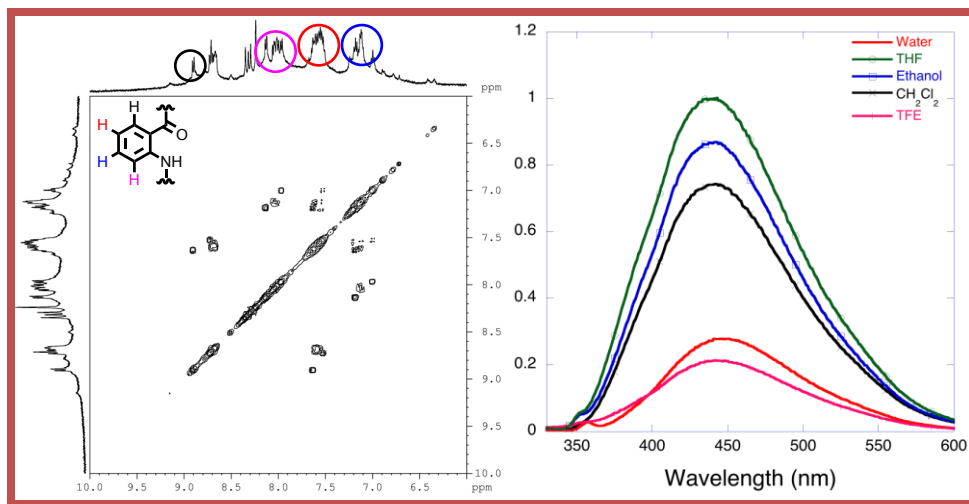


Figure 2.11: 2D-NOESY of PDH **4**(left). Fluorescence emissions (440 nm, excitation at 316 nm) of PDH **4** (Right).

In water, PDH **4** did not display any β -sheet secondary structure according to IR. The quenching of the fluorescence emission in TFE was interesting because TFE is known to disrupt interactions, especially in systems that undergo self-assembly, and proteins.^[130] However, peptides that are unorganized have a tendency to adopt an α -helical secondary structure in 50% TFE-water due to the strengthening of *i*, *i*+4 hydrogen bonding.^[131] PDHs **2** and **3** were analyzed by CD spectroscopy in TFE and a 316 nm couplet intensity decreased (Figure 2.12 A and B). Alternatively, PDH **4** in TFE resulted in a couplet of the opposite chirality or an *M* to *P* helical switch (Figure 2.12 C). The chirality source for the achiral dendrimers changes from the peptide backbone, therefore,

induced intramolecular hydrogen bonding may affect the dendrimer interactions resulting in the chiral switch. A titration study revealed that the *M* to *P* helical switch occurs between 20%-30% TFE in water (Figure 2.12 D). Interestingly, TFE-water solutions were found to form nanospheres with TFE surface.^[132] These nanospheres are believed to insert between hydrophobic groups and stabilize hydrophobic interactions.

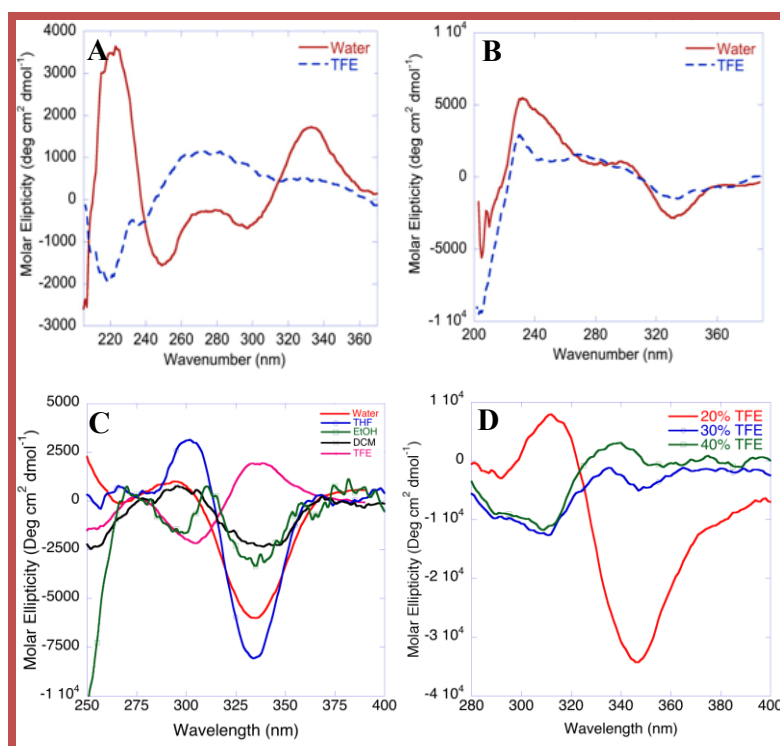


Figure 2.12: PDH 2 and 3 in water (red) and TFE (blue) (10 μM) (A and B). PDH 4 in varying solvents (10 μM): Water (red), THF (blue), Ethanol (green), Dichloromethane (black), TFE (pink) (C). PDH 4 TFE titration in water (10 μM) (D).

The helical switch observed for PDH 4 in solvents water and TFE manifests from the peptide backbone. The peptide backbone can also be affected through a pH change in water. The polar residues can be charged or uncharged depending upon the pH. At a low

pH, the glutamic acid residue will be protonated making the net charge of the peptide positive. As the pH increases, the glutamic acid will be deprotonated creating a neutral charged peptide. The peptide will become negatively charged at a high pH when the lysine residue and the glutamic acid are both deprotonated. Similarly in TFE, PDHs **2** and **3** show little change from pH=3 to pH=11 (Figure 2.13 A and B). In PDH **4** the helical bias was very sensitive to pH change (Figure 2.13 C). The helical bias was strongest at pH=3, but was minimal at pH=11. The nonlinear response to external stimuli was due to the intramolecular cooperation between the dendrimer subunits.

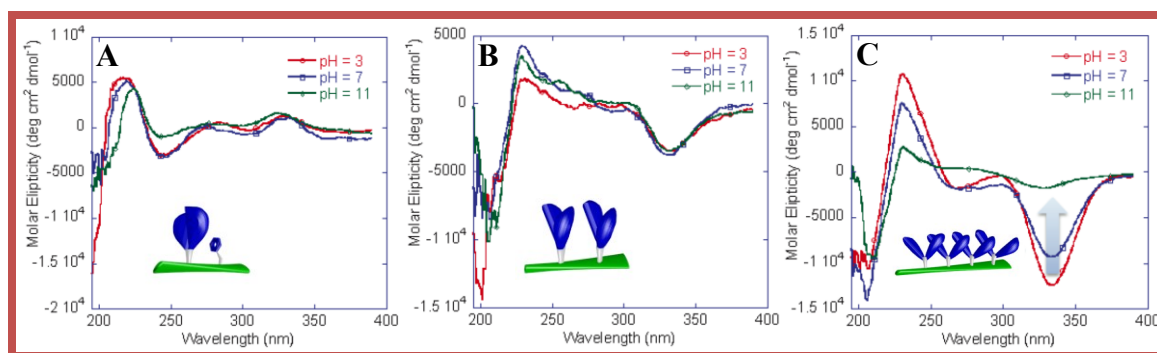


Figure 2.13: PDHs **2** (A), **3** (B), **4** (C) at pH=3 (red), pH=7 (blue), pH=11 (green).

2.4 Conclusion

PDHs that underwent self-assembly and form fibers exhibited peptide to dendrimer chiral transfer, and displayed a helical bias due to intermolecular interactions. PDH **4** was found to be sterically hindered and self-assembly was not detected. However, peptide to dendrimer chiral transfer and amplification was observed as the number of dendrimers increased. It appears that intramolecular dendrimer stacking was

taking place and was effected by external stimuli. PDH **4** was responsive to TFE where an *M* to *P* helical transition occurred in solutions 20% TFE-water to 30% TFE-water. Also, PDH **4** was responsive to pH change. Both PDH **2** and **3** did not show significant responsiveness in TFE or with pH change, which suggests nonlinear intramolecular cooperation between the dendrimer subunits and the chirality of the dendrimers manifest from the TFE and pH sensitive peptide backbone.

2.5 Methods and Experimentals.

General Methods

Fourier transform-infrared (FTIR) spectra were obtained on a FTIR spectrometer (Shimadzu, IRAffinity-1). Circular dichroism (CD) spectra were taken at 25°C with an AVIV 202 CD spectrometer or Jasco J-815 CD spectrometer. Fluorescence spectroscopy were taken using a Shimadzu RF 5301pc using a cuvette with 1 cm path length at 25°C. Dynamic light scattering (DLS) measurements were take with a model ZEN3600 spectrometer (Malvern Instruments Ltd.) at 20°C. All reactions were performed under a nitrogen atmosphere. The adjusted of pH was done with 0.2 M NaOH or HCl solution for CD studies. Water used was HPLC grade and passed through membrane filter (0.02 µM) before use. THF used was HPLC grade. Dichloromethane, ethanol, and 2,2,2-trifluoroethanol (TFE) solvents used were distilled under nitrogen.

Peptide Preparation

All peptide-dendron conjugates were manually prepared using Fmoc solid-phase peptide synthesis on rink amide resin (loading ca. 0.30 mmol/g). Amide-coupling steps were accomplished with standard techniques for all amino acids: natural Fmoc-amino acid, 1,3-diisopropylcarbodiimide (DIC), and 1-hydroxybenzotriazole (HOBt) (500 mol% each relative to resin) in 1:1 DMF/DCM for 1 h. For **1** the reaction conditions were DIC, HOBt (300 mol% each relative to resin) in 1:1 DMF/DCM for 12-18 h at ambient temperature. Piperidine (20%) in DMF was used for Fmoc removal. The peptide-dendron hybrids were cleaved from the resin by the treatment of TFA/water (95:5) at room temperature for 2 h. The TFA was removed under vacuum. The residue was diluted in water, lyophilized, and purified by reverse-phased HPLC on a preparative Waters XBridge C8 column or a preparative Varian Dynamax C18 column eluting with a linear gradient of CH₃CN/water (30/70 to 100/0 over 30 minutes (XBridge) or 30/70 to 90/10 over 30 minutes (Dynamax), 0.1 % TFA) and stored as lyophilized powders at 0 °C. Peptide purity was assessed by analytical reverse-phase HPLC and the identity was confirmed using ESI mass spectrometry.

Circular Dichroism (CD) Spectroscopy Measurement.

CD spectra were recorded on an AVIV 202 CD or Jasco J-815 CD spectrometer under a nitrogen atmosphere. Experiments were performed in a quartz cell with a 1 mm path length over the range of 190-400 nm at 25 °C. CD spectra were taken routinely at peptide

concentration around 10 μM or 100 μM in water, THF, DCM, ethanol, and TFE. The pH dependent CD spectra were taken in water at a concentration of 10 μM at 25°C. The pH was adjusted using 0.2 M NaOH or HCl solutions with the aid of a calibrated pH meter.

Fourier Transform Infrared (FTIR) Spectroscopy Measurement

All FTIR spectra were collected on a Shimadzu FTIR spectrometer at ambient temperature. The instrument was continuously purged with CO₂-free dry air. Interferograms were recorded between 1700 and 1600 cm⁻¹ at a resolution of 1 cm⁻¹, and a total of 32 scans were averaged. Samples for FTIR were dissolved in D₂O (about 10 mg/mL) and analyzed in a transmission cell having CaF₂ windows and a 0.025 μm path length. Samples dissolved in THF, DCM, ethanol, and TFE (about 10 mg/mL) were analyzed in a NaCl cell. The data were analyzed using IRsolution software.

Dynamic Light Scatter (DLS) Spectroscopy

DLS solutions (1 mM) were prepared with double distilled water, THF, DCM, ethanol, and TFE solvents. DLS measurements (12-14 averaged measurements per sample) were done at 20 °C with a Malvern Instruments Ltd. model ZEN3600 spectrometer equipped with a 633 nm laser and an optical detector for a back scatter angle of 173°. Known solvent parameters setup (refractive index and viscosity) and analysis was done using the software DST (NANO) to obtain the % volume of observed signals.

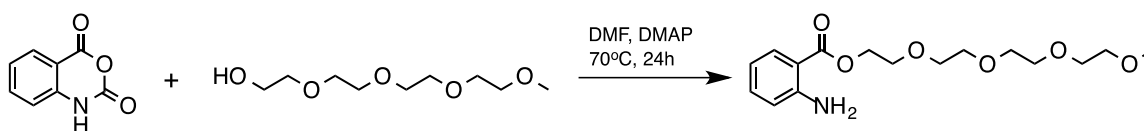
Fluorescence Spectroscopy

All data were collected using a Shimadzu RF 5301pc spectrometer. The sample was excited at 316 nm and measured in solvents water, THF, DCM, ethanol, TFE at a concentration of 10 μ M with a path length of 1 cm. The software used to collect and analysis the data was RFPC.

Nuclear Magnetic Resonance

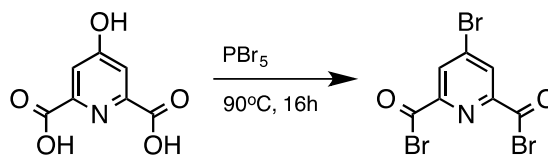
Compound **4** was analyzed by ^1H -NMR in degassed THF- d_8 using a Bruker DPX-500 instrument.

Synthetic Experimentals^[123]



2.1

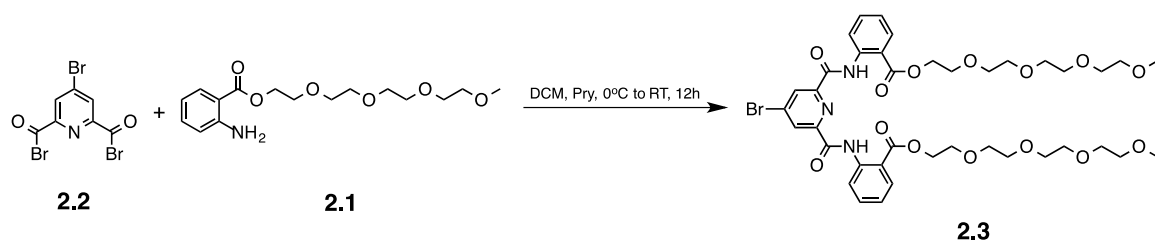
Anthranilate (2.1): Methyl tetraethylene glycol (13.0 g, 62.4 mmol) was dissolved in 60 ml of dry DMF and isatoic anhydride (10.7 g, 65.8 mmol) and DMAP (0.857 g, 7.02 mmol) were added, and the solution was stirred at 70°C for 24 h. The reaction mixture was cooled to room temperature, and the solvent was removed by short path distillation under vacuum. The residue was purified by flash column chromatography (1% MeOH in EtOAc) yielding a light yellow oil (13.8 g, 42.2 mmol, 68%). ¹H NMR (400 MHz, CDCl₃) δ 3.40 (s, 3H), 3.53 (m, 2H), 3.64 (m, 10H), 3.81 (m, 2H), 4.41 (m, 2H), 5.70 (br s, 2H), 6.82 (t, *J* = 8 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H).



2.2

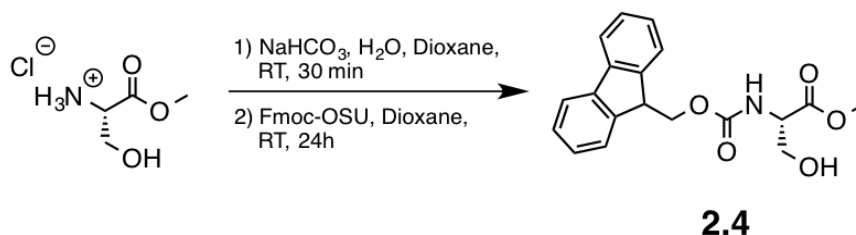
4-Bromopyridine-2,6-dicarbonyl bromide (2.2): A flask was charged with phosphorous tribromide (62.0 g, 229 mmol) and bromine (36.6 g, 229 mmol) was added

dropwise over a 20 min period to yield the yellow phosphorous pentabromide solid. Dried chelidamic acid (10.6 g, 59.5 mmol) was added to the phosphorous pentabromide and the solid mixture was heated to 90°C for 16 h over nitrogen with a base trap outlet. The residue was cooled to room temperature and extracted three times with CHCl₃ (100 mL). The combined organic layers were concentrated. The POBr₃ was removed by Kügelrohr distillation. The residue was purified by sublimation affording the product as white needle crystals (9.51 g, 25.6 mmol, 43%). ¹H NMR (250 MHz, CDCl₃) δ 8.38 (s, 2H).



Br-[G1]-TEGMe (2.3): [G0]-TEGMe (**2.1**) (3.40 g, 10.4 mmol) and 4-dimethylaminopyridine (136 mg, 1.07 mmol) were dissolved in a mixture of dichloromethane (15 mL) and pyridine (6 mL). 4-Bromopyridine-2,6-dicarbonyl bromide (**2.2**) (1.83 g, 4.93 mmol) was then added to the reaction mixture at 0°C resulting in a color change from light yellow to brown and formation of a white precipitate. After stirring at room temperature for 12 h, dichloromethane was added (100 mL) and washed with water (3 x 100 mL), 1 M HCl (2 x 100 mL), saturated sodium bicarbonate solution (2 x 100 mL) and brine (100 mL). The organic layer was dried (Na₂SO₄) and concentrated to give a brown oil. Purification by flash column chromatography (2%

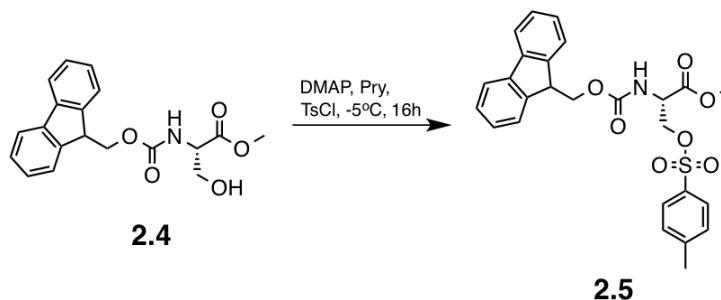
methanol-ethyl acetate) to yield a pale yellow oil (3.50 g, 4.04 mmol, 82%). ^1H NMR (400 MHz, CDCl_3) δ 3.35 (s, 6H), 3.58 (m, 28H), 4.20 (t, $J = 4.4$ Hz, 4H), 7.20 (t, $J = 7.6$ Hz, 2H), 7.63 (t, $J = 8.4$ Hz, 2H), 8.11 (d, $J = 8.0$ Hz, 2H), 8.58 (s, 2H), 8.71 (d, $J = 8.4$ Hz, 2H); 12.62 (s, 2H).



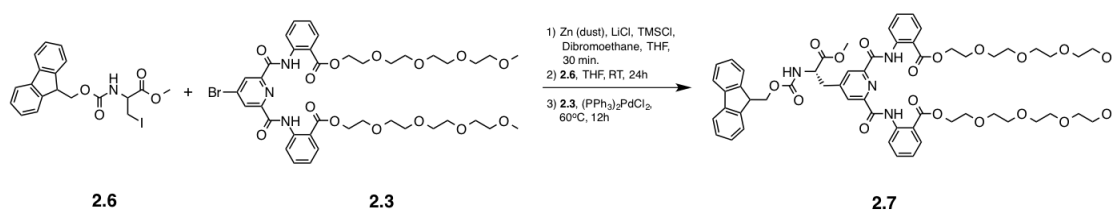
***N*-(9-Fluorenylmethyloxycarbonyl)-*L*-Serine methyl ester (Fmoc-Ser(OH)-OMe)**

(2.4): A flask was charged with sodium bicarbonate (9.42 g, 112 mmol), water (15 mL) and Dioxane (30 mL). *L*-Serine methyl ester hydrochloride in a mixture of dioxane (10 mL) and H_2O (5 mL) was added to the flask slowly. The reaction mixture was stirred for 30 min at RT. *N*-(9-Fluorenylmethoxycarbonyloxy) succinimide (15.7 g, 46.5 mmol) in dioxane (60 mL) was added dropwise over 2 min to the previous mixture. The reaction mixture was left at room temperature for 24 h, and poured into water (150 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with water (1 x 100 mL), brine (1 x 100 mL) and dried over magnesium sulfate, then concentrated in vacuo to give oil. Crystallization from Et_2O gave a white solid (13.94 g, 88%). ^1H NMR (250 MHz, CDCl_3) δ 1.96 (s, 1H), 3.80 (s, 3H), 4.0 (m, 2H), 4.24 (t, $J =$

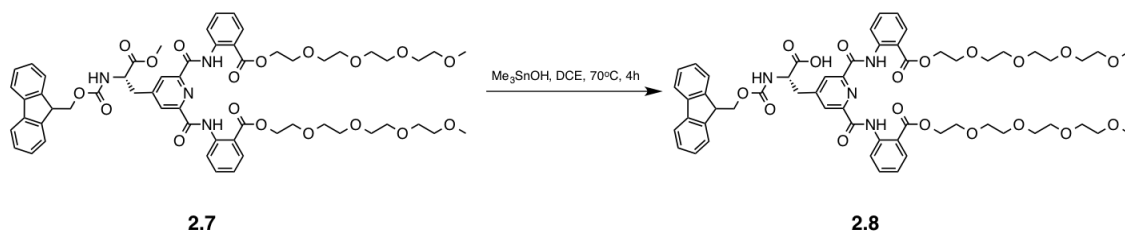
3.3 Hz, 1H), 4.45 (m, 3H), 5.70 (d, $J = 2.0$ Hz, 1H), 7.32 (t, $J = 3.7$ Hz, 2H), 7.42 (t, $J = 3.6$ Hz, 2H), 7.61 (d, $J = 5.6$ Hz, 2H), 7.77 (d, $J = 3.7$ Hz, 2H).



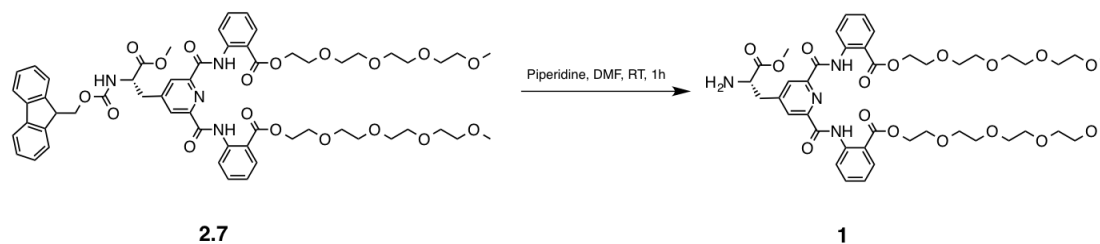
Fmoc-*L*-Ser(OTs)-OMe (2.5): Fmoc-*L*-Ser(OH)-OMe (**2.4**) (13.94 g, 40.8 mmol) and 4-dimethylaminopyridine (615 mg, 4.84 mmol) were dissolved in dry pyridine (70 mL) and cooled to -5°C . *p*-Toluenesulfonyl chloride (25.8 g, 135 mmol) was added to the solution and the resultant yellow reaction mixture was stirred under nitrogen for 16h and poured into ice water and the aqueous mixture was extracted into ethyl acetate (3 x 100 mL). The combined organic layer was washed with water (2 x 100 mL), 10% KHSO_4 solution (2 x 100 mL), saturated sodium bicarbonate (2 x 100 mL) and brine (2 x 100 mL). The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure, which gave oil. Crystallization from Et_2O yielded white crystals (28.01 g, 92 %). ^1H NMR (250 MHz, CDCl_3) δ 2.33 (s, 3H), 3.71 (s, 3H), 4.18 (t, $J = 3.5$ Hz, 1H), 4.25-4.30 (m, 1H), 4.33-4.47 (m, 4H), 4.60-4.62 (m, 1H), 5.83 (d, $J = 3.5$ Hz, 1H), 7.25 (d, $J = 4.0$ Hz, 2H), 7.32 (t, $J = 4.0$ Hz, 2H), 7.41 (t, $J = 3.5$ Hz, 2H), 7.60 (t, $J = 4.2$ Hz), 7.76-7.78 (m, 4H).



Fmoc-Ser(G1)-OMe (2.7): A 25 mL pear shaped flask was dried charged with lithium chloride (19 mg) and zinc dust (41 mg, 16.67 mmol). The mixture was heated for an addition 20 min at 160°C under vacuum. When the flask was cooled to RT, Dibromoethane (2.0 μ L, 0.022 mmol) was added under nitrogen followed by trimethylsilane chloride (0.6 μ L) in THF (0.5 mL). The mixture was stirred for 30 min. A solution of Fmoc-Ser(I)-OMe (200 mg, 0.44 mmol) in THF (2.5 mL) was added to the zinc and stirred for 24 h. Dendron Br-[G1]-TEGMe (**2.3**) (159 mg, 0.184 mmol) and (Ph₃P)₂PdCl₂ (7.0 mg, 0.010 mmol) were placed in a separate 25 ml pear shaped flask under nitrogen. The zinc reagent was transferred with a syringe into the second flask and the mixture was heated to 60°C for 24h. Evaporation of the solvent gave a brown oil which was purified by flash chromatography (7/1 CH₂Cl₂/Acetone and 2% MeOH) to yield a light yellow oil (29 mg, 14%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.18 (s, 6H), 3.2-3.23 (m, 2H), 3.34-3.36 (m, 4H), 3.39- 3.45 (m, 20H), 3.54 (t, *J* = 4.5 Hz, 4H), 3.68 (s, 3H), 4.10-4.12 (m, 5H), 4.19-4.21 (m, 2H), 4.53-4.54 (m, 1H), 7.18-7.32 (m, 6H), 7.50-7.55 (m, 2H), 7.72-7.78 (m, 4H), 7.98 *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2Hz), 8.379 (s, 2H), 8.60 (d, *J* = 8.5 Hz, 2H), 12.46 (s, 2H).



Fmoc-Ser(G1)-OH (A^D) (2.8): The Fmoc-Ser(G1)-OMe (2.7) (1.00 g, 0.893 mmol) was dissolved in 1,2-dichloroethane (5 mL) followed by addition of trimethyltin hydroxide (made by reacting trimethyltin chloride with potassium hydroxide 1:1 in dichloromethane) (0.346 g, 1.91 mmol), the mixture was heated at 70°C for 4 h. The mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate (50 mL). The organic layer was washed with aqueous citric acid (25 mL, 1.0 mM) and brine (25 mL) and then dried over sodium sulfate. Removal of the solvent in vacuo afforded the crude compound as a brown oil which was purified by flash chromatography (2% methanol in dichloromethane to 7% methanol in dichloromethane) to give Fmoc-Ser(G1)-OH (A^D) (8) as a light yellow foamy solid (0.423 g, 0.386 mmol, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.18 (s, 6H), 3.20-3.22 (m, 1H), 3.35- 3.38 (m, 4H), 3.39- 3.48 (m, 21H), 3.55 (t, *J* = 4.8 Hz, 4H), 4.10-4.12 (m, 6H), 4.23-4.26 (m, 2H), 7.078 (s, 1H), 7.22-7.32 (d, *J* = 7.2 Hz, 2H), 7.26-7.30 (m, 4H), 7.53-7.56 (m, 2H), 7.71 (t, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 8.03-8.05 (m, 2H), 8.30 (s, 2H), 8.57 (d, *J* = 8.0 Hz, 2H), 12.41 (s, 2H).



Synthesis of **1**

Fmoc protected **1** (147 mg, 0.135mmol) was added to a 5 mL round-bottom flask, followed by addition of 20% piperidine in DMF (3 ml). The mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (5/1 CH₂Cl₂/Acetone and MeOH to 5% MeOH) to afford **1** as a brown oil (116.2 mg, 98%). *R_f* 0.10 (5/1 CH₂Cl₂/Acetone 1% MeOH); ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.19 (s, 6H), 3.05-3.11 (m, 1H), 3.20-3.25 (m, 1H), 3.36-3.38 (m, 4H), 3.39-3.46 (m, 22H), 3.56 (t, *J* = 5.0 Hz, 4H), 3.65 (s, 3H), 3.77-3.79 (m, 1H), 4.13 (t, *J* = 5.0 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.31 (s, 2H), 8.63 (d, *J* = 8.0 Hz, 2H), 12.47 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 52.47, 52.55, 55.11, 59.11, 64.00, 64.35, 68.92, 70.61, 70.69, 72.03, 117.71, 121.69, 123.61, 126.21, 131.39, 134.43, 140.35, 149.41, 151.36, 162.28, 167.18, 171.33; IR (CH₂Cl₂) 3357, 3257, 2889, 1738, 1683, 1603, 1532, 1453, 1102 cm⁻¹. MALDI calcd for C₄₃H₅₈N₄O₁₆ (M+Na)⁺ 909.3746, found 909.3686.

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Chapter 3

Self-Assembly, Polymerization, and Post-Polymerization Modification of Diacetylene Functionalized Lysine-NDI Amphiphiles

3.1 Introduction

A bottom-up approach through a self-assembly process is an efficient method to develop advanced materials. Amphiphiles are found throughout nature and are often used to study self-assembly. Phospholipid amphiphiles are known to assemble into bilayers in water as seen in biological systems, and make up cell membranes.^[49] For decades, researchers have been exploiting this phenomenon to develop synthetic assemblies that form a number of distinctly shaped assemblies in the form of vesicles and micelles,^[51, 133] mono- or multi-layered films,^[53] fibrils,^[52, 54] sheets,^[52] and tubes.^[41, 134] Many technologies have been developed through the research and creation of new synthetic amphiphiles. Some of these technologies are biologically active hydrogels,^[55] drug delivery systems,^[135] and electropical devices.^[136]

Polymerization of pre-organized nanostructures can give highly organized structures with increased stability. Methods have been developed to lock assemblies in a

desired form through disulfide oxidations,^[137] disulfide ring-opening polymerization,^[138] Grubbs metathesis,^[139] and RAFT polymerization.^[140] Polymerization of highly ordered self-assembled nanostructures containing diacetylene subunits has been successful and obtained locked mono- and multilayers,^[141] vesicles, and helical type of supramolecular assemblies.^[8b, 142]

Our group has developed a series of 1,4,5,8-naphthalene-tetracarboxylic acid diimide (NDI)–lysine amphiphiles that form ordered nanotubes. Recently we reported that amphiphilic lysine-NDI-(*n*-butyl) compounds formed varying types of nanotubes depending on the functionality of the lysine head. Even though the modification of the lysine head group did not disrupt the ability for these molecules to form into organized nanostructures, the assemblies were sensitive to solvent changes. Modification of the lysine-NDI-(*n*-butyl) amphiphile, by replacing the *n*-butyl tail with a polymerizable diacetylene nonane tail, allowed for the nanostructure to be polymerized. Post-polymer modification is not new, but post-polymer modification of a polymerized organized nanostructure has rarely been reported.^[143] Herein, we report the self-assembly and polymerization of an *n*-type amphiphile, which can undergo hydrolysis while maintaining the nanostructure morphology.

3.2 Background and Research Design

Amphiphiles with a hydrophobic core flanked by two polar heads are known as bola-amphiphiles. Intermolecular interactions, such as hydrogen-bonding or π - π

stacking, assists directional assembly. 1,4,5,8-Naphthalenetetracarboxylic dianhydride makes up the desired hydrophobic core, which provides π - π stacking and also provides a scaffold that allows versatility and modification through the incorporation of diverse primary amines to the dianhydride. The Parquette group developed zwitterionic NDI-lysine bola-amphiphiles that form uniform nanotubes built from smaller ring assemblies with a diameter of 12 nm (Figure 3.1).^[41] The assembly is stabilized from the strong π - π interactions between the naphthalene cores observed in XRD where the d -spacing is 3.6 Å. The electrostatic properties of the lysine group influenced the assembly stability

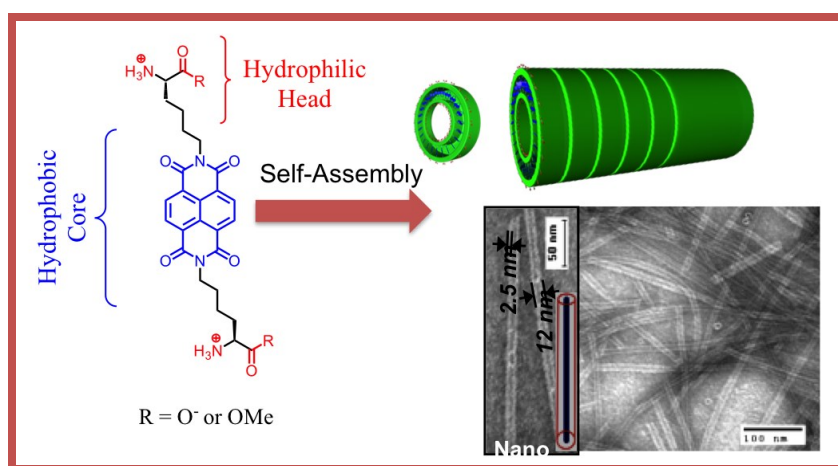


Figure 3.1: Molecular design and the self-assembly mechanism of lysine-NDI bola amphiphiles.

greatly. The nanotubes were stable with a zero net charge of the zwitterion, but if the carboxylic acid is methylated the positive charged amine disrupts the assembly.

The unsymmetrical lysine-NDI-*n*Bu amphiphile displayed greater assembly stability towards electrostatic repulsions. Like the zwitterionic bola NDI amphiphiles,

the zwitterionic unsymmetrical NDI amphiphiles form nanotubes with a diameter of 14 nm (Figure 3.2).^[144] Interestingly, electrostatic interactions did not prevent self-assembly. The carboxylic acid was converted to a methyl ester and an amide yielding a positive polar head, and a tubular assembly assembled. The methyl ester variant forms a nanotube with walls twice the width of the zwitterionic amphiphile nanotubes and the amide variant assembles into larger bilayer coils that collapse into large nanotubes with a diameter of 100 to 250 nm.

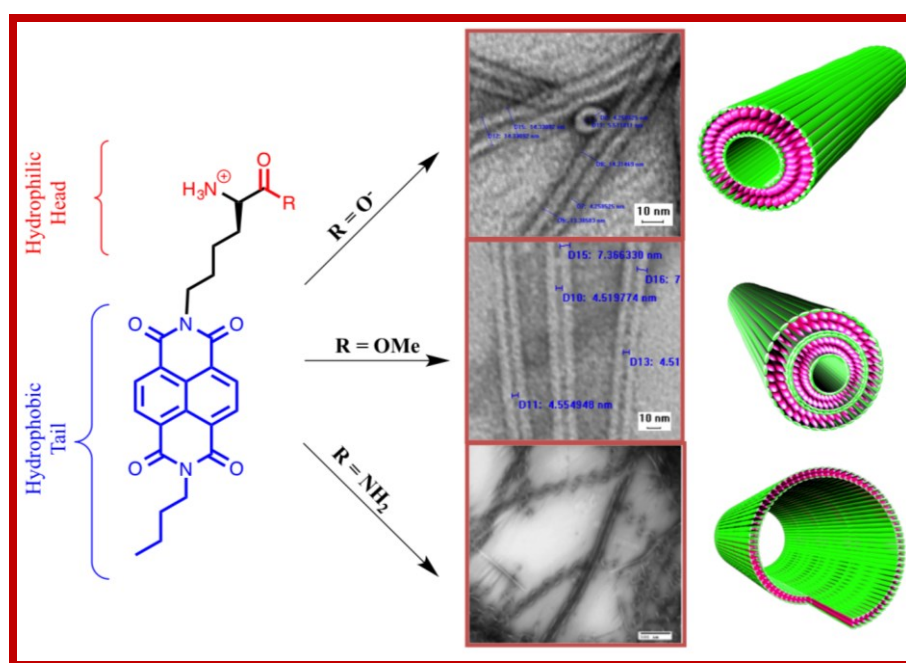


Figure 3.2: Molecular design and self-assembly of lysine-NDI amphiphiles with varying electrostatic properties.

Crosslinking assemblies are a useful strategy to stabilize the nanostructures to varying conditions. One method to crosslink or polymerize lysine-NDI amphiphilic assemblies is by light induced diacetylene polymerization. Diacetylene polymerization

has been used in crosslinking aldonamide amphiphiles, but stability of the nanostructure during polymerization tends to be dependent on the spacer between the intermolecular interacting unit and the diacetylene group.^[69] However, it seems that when the intermolecular interactions are strong, the spacer plays a smaller role. β -Sheet amphiphiles as in Figure 3.3, forms double helical assemblies.^[142e] The assembly can be polymerized without disruption of the assembly even though the spacer between peptide

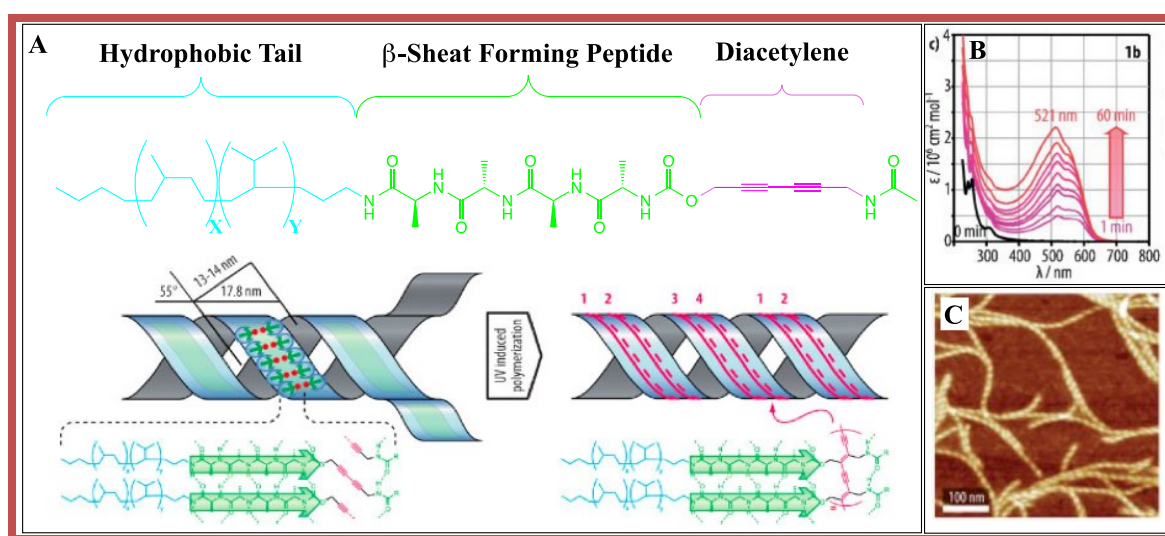


Figure 3.3: Peptide amphiphile with a polymerizable diacetylene functionality that undergoes self-assembly that forms double helical β -sheet fibers (A). UV spectrum of the polymerization (B). AFM of the double helical β -sheet fibers (C).

and the diacetylene was a methylene group. The hydrogen bonding distance within the parallel peptide strands are 3.2 to 4.0 Å, which was long enough to provide flexibility as the rigid polymer forms.^[145]

3.3 Research

Modification of the lysine-NDI-*n*Bu amphiphile to include diacetylene functionality in the hydrophobic tail can yield a polymerizable assembly through irradiation with UV light (Figure 3.4). The *d*-spacing of the naphthalene π - π interactions were comparable to the distance within β -sheet assembly, therefore the NDI amphiphilic assemblies have enough flexibility to survive the polymerization process with a methylene spacer. Also, due to the one methylene spacer between the NDI and diacetylene, polymerization should be fast because of the rigidity of the structure and the π - π stacking between the NDIs will result in the diacetylene tails lining up in a crystalline fashion. With the nanostructure polymerized, the nanotube would be stable to conditions that were normally degrading, such as heat and organic solvents. Also, post-polymer modification would be interesting and obtain materials that would not be possible through self-assembly of the related monomer. Hydrolysis of the methyl ester would be a simple way to evaluate the nanostructure stability and compare the structures with the self-assembled zwitterion species.

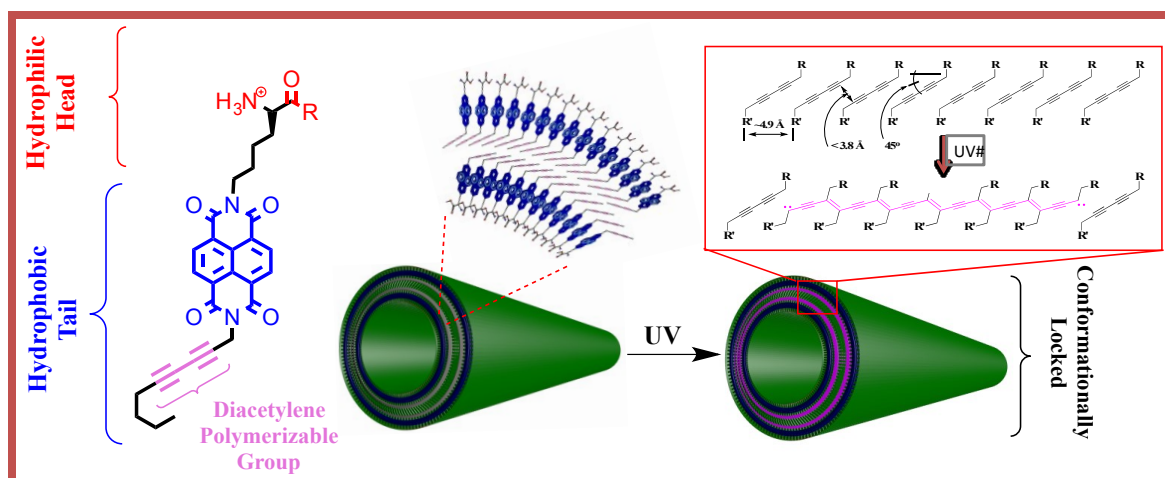
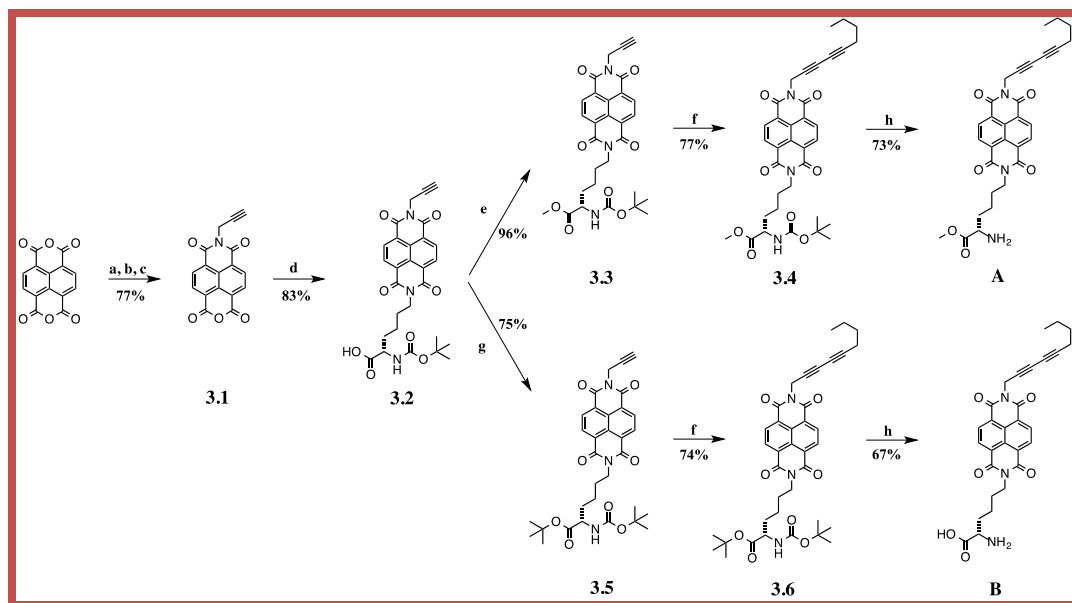


Figure 3.4: Molecular design of diacetylene NDI-lysine amphiphiles.

3.4 Synthesis

Starting material Boc-lys(propargyl-NDI)-OH **3.2** was synthesized from propargyl compound **3.1** with the addition of Boc-Lys-OH in heated DMF to 120°C for 14h and provided a yield of 83%.^[41] From **3.2** both amphiphile **A** and **B** can be produced (Scheme 3.1). To synthesize **A**, compound **3.2** was first methylated with methyl iodide in a potassium carbonate and DMF suspension. After 14h, the reaction was completed and produced the methyl ester **3.3** with a yield of 96%.^[146] Copper catalyzed (copper(II)acetate monohydrate) acetylene-acetylene cross coupling worked well in dichloroethane (Higher boiling point minimized evaporation), piperidine, and with five mole excess of 1-hexyne to give the hetero-diacetylene **3.4** with a 77% yield in 10h.^[147] The Boc protection was removed in acidic conditions (95:5 TFA:TES) to give the crude amphiphile **A** after 2h and was purified by HPLC with a yield of 73%.



Scheme 3.1: KOH, water (a). H_3PO_4 , propargyl amine, pH=6.3, 110°C , 14 h (b). Ac_2O , 110°C , 16 h (c). Boc-Lys-OH, DMF, 120°C , 14 h (d). Methyl iodide, K_2CO_3 , DMF, RT, 14 h (e). 1-hexyne (5eq), piperidine, $\text{Cu}(\text{AcO})_2$ (10 mol%), dichloroethane, O_2 , RT, 10 h (f). EDCI, DMAP, *t*-butanol, dichloromethane, RT, 16 h (g). TFA, triethylsilane (5% v/v), RT, 2 h (h).

Acetylene-acetylene copper cross coupling between **3.2** and 1-hexyne was not efficient due to the free acid in basic conditions causing precipitation and/or coordination to the copper and poisoning the catalyst. To avoid this, the carboxylic acid was converted to an acid labile *tert*-butyl ester with a yield of 75% by esterification with *tert*-butanol, DMAP and EDCI coupling reagent in dichloromethane to give compound **3.5** in 16h.^[148] The diacetylene formation, using the same procedure of **3.4**, proceeded much more efficiently, yielding compound **3.6**. Both the *tert*-butyl ester and Boc protecting groups were removed using TFA:TES (95:5) solution in 2h to give the crude amphiphile **B** that was purified with HPLC and achieved a 67% yield. After protecting group removal, amphiphiles **A** and **B** are light sensitive in water and will polymerize. To prevent

premature polymerization of this material, TFE should be used to dissolve the amphiphiles and then purified on the HPLC. The TFE will prevent self-assembly to organized nanotubes and the diacetylenes tails will not be properly oriented to undergo polymerization.

3.5 Results and Discussion

Compound **A** was soluble in neutral water due to the positive charge produced from the protonated amine. Zwitterion **B** has a formal charge of zero and a large crystalline lattice energy resulting in very low solubility in water at neutral conditions.^[149] At pH of 11, compound **B** was soluble enough to obtain solutions at low concentrations (50 μ M).

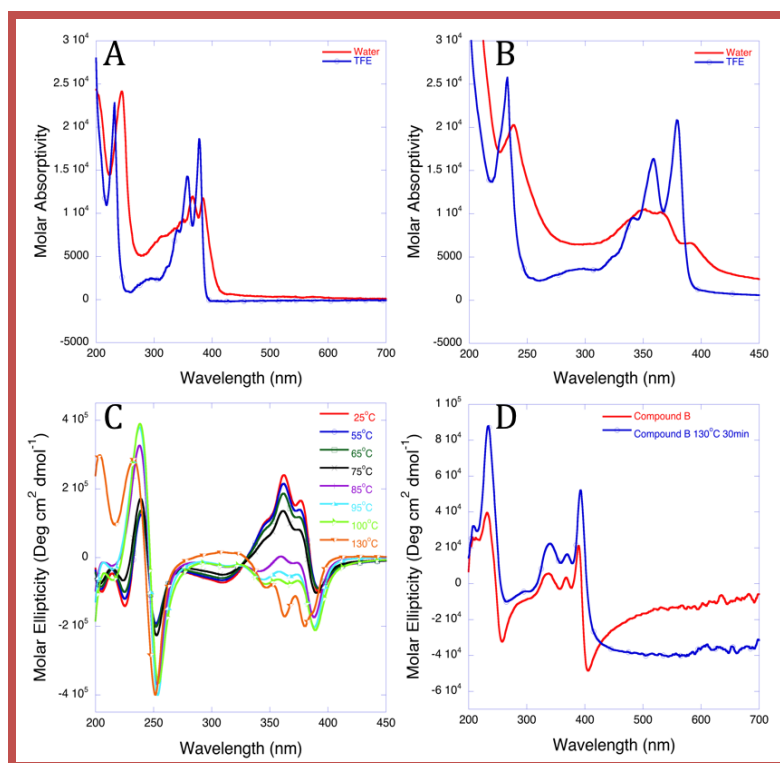


Figure 3.5: UV-Vis of **A** (aged for 12h at 5 mM) in TFE and water (0.30 mM) (A). UV-Vis of **B** in TFE and water (0.05 mM) (B). Temperature dependent CD of **A** (1 mM) (C). Temperature dependent CD of **B** (0.05 mM) (D).

Initially, the amphiphiles were analyzed by ultra-violet spectroscopy (UV) in TFE and water (Figure 3.5). The NDI chromophore π - π^* band I (300 nm to 400 nm) and band II (220 nm to 280 nm) were observed as intense sharp absorbance.^[144] When **A** and **B** were dissolved in water, the intensities of band I decreased in intensity and a red shift of bands I and II occurred indicating *J*-type aggregation of the NDI.^[150] The red shift of compound **A** was 6 nm while compound **B** had a larger shift of 10 nm.

Long-range NDI organization was examined with CD in water. Both compound **A** and **B** displayed cotton effects in the corresponding π - π^* NDI I and II absorbance

regions. Compound **A** shows a negative excitonic couplet cotton effect, which indicates that NDI adopts on *M*-helix. When the solution was heated (2 mM at 130°C in a pressure

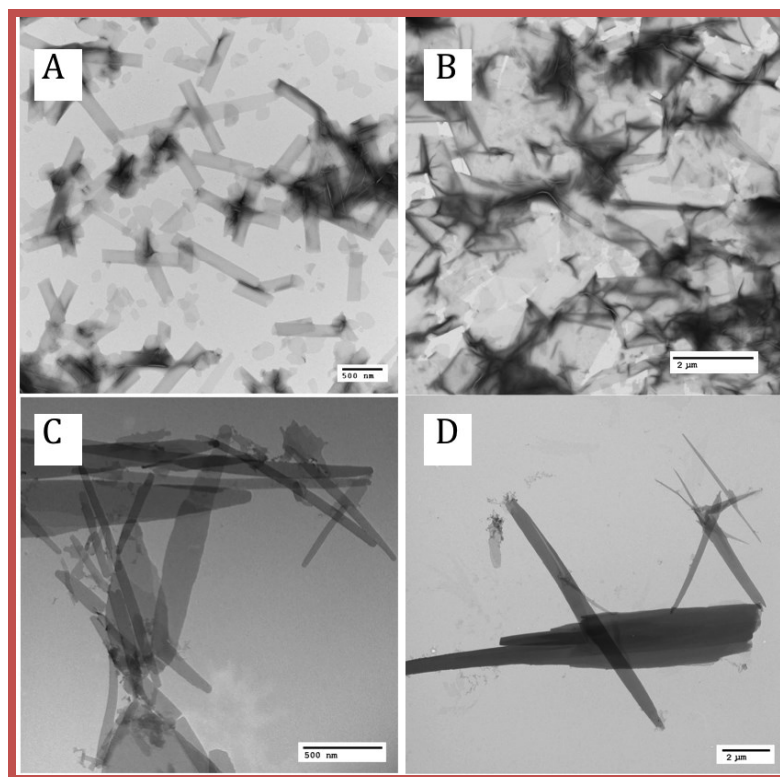


Figure 3.6: TEM of **A** (aged (12h) and examined at 4 mM; carbon-coated grid and stained with 2% (w/w) uranyl acetate negative stain) (A) and **A** heated to 130°C for 30 min (B). TEM of **B** (0.05 mM) (C) and compound **B** heated to 130°C for 30 min (D).

tube for 30 min), the negative signature became more pronounced at 242 nm and the band I signals between 330 nm and 390 nm flip from a positive signal to a negative signal (Figure 3.5 C). Also, the solubility decreases as the solution undergoes prolonged

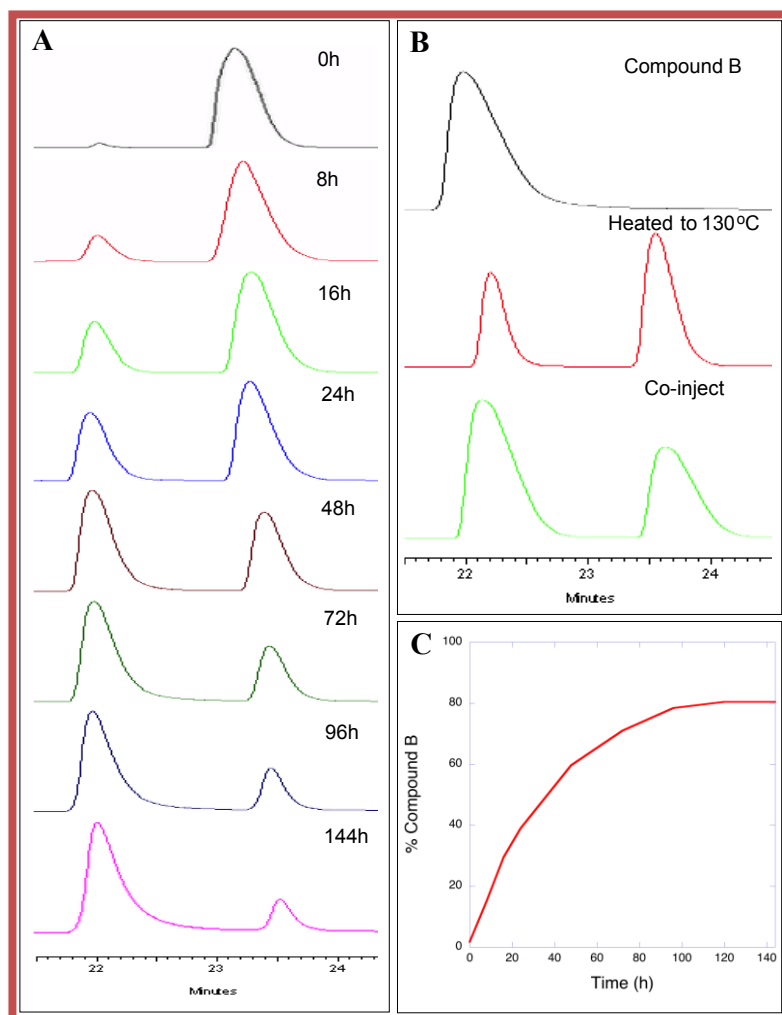


Figure 3.7: Time dependent hydrolysis of compound **A** at neutral pH and room temperature (2 mM) (A). HPLC traces of **B**, **A** heated in a sand bath (130°C for 30 min in a pressure tube at 2 mM), and a co-injection of **A** and **B** (B). Time dependent hydrolysis of compound **A** at neutral pH and room temperature in graphic form (C).

heating treatment. Examining the TEMs of Compound **A**, nanotubes with a width of 140 nm and lengths up to 2 microns were observed with the wall width of 4 nm (Figure 3.6 A and 3.11). After heat treatment of compound **A** at 130°C for 30 min in a pressure tube, the nanotubes transformed to sheets and helical coil assemblies (Figure 3.6 B). The TEM

of compound **B** (Synthesized from 3.6) exhibits assemblies that resemble 2D sheets as well (Figure 3.6 C). Interestingly, when compound **B** was heated to 130°C for 30 minutes in a pressure tube the NDI CD signals showed minimal change other than a slight increase in intensity and the sheet nanostructures remained (Figure 3.5 D and 3.6 D).

The cause of the change in chirality of the band I region was an interesting feature that needed further exploration. At an elevated temperature, hydrolysis can take place

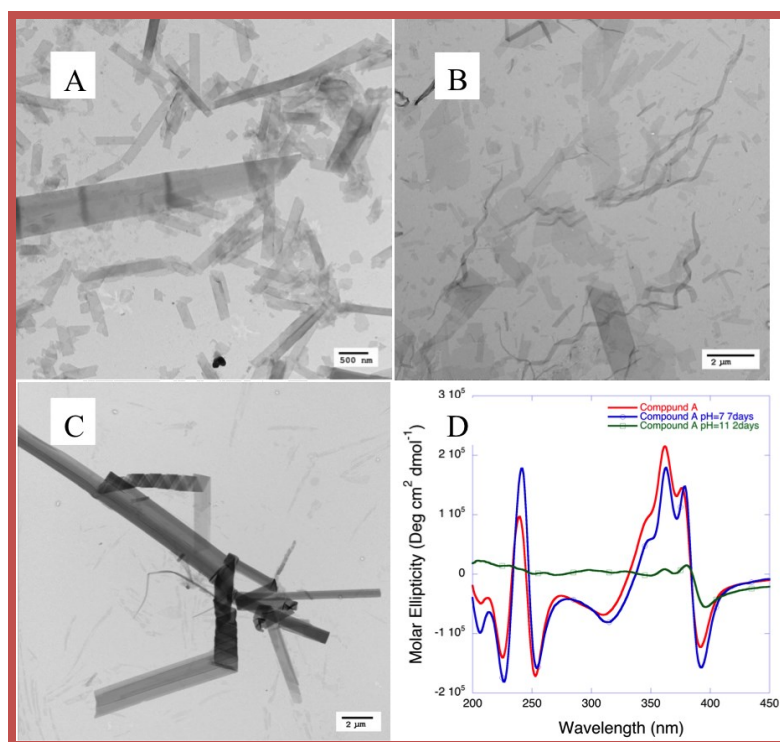


Figure 3.8: TEM of **A** aged for 7 days at pH=7 (2 mM) (A). TEM of **A** heated to 130°C for 30 min (1 mM) (B). TEM of **A** aged for 2 days at pH=11 (C). CD of the hydrolysis of **A** after 7 days at pH=7 (Blue) and 2 days at pH=11 (Green) (D).

in a reactive media such as water.^[151] Even though hydrolysis of amino acid methyl esters at neutral pH is slow, this reaction may be promoted in an assembly with protonated amines and catalyze hydrolysis of an neighboring ester. Functionalities that are regional to the labile group have been shown to effect the rate of hydrolysis.^[152] To examine hydrolysis of compound **A**, analytical HPLC was used since both the methyl ester and zwitterion retention times are known. Compound **A** was dissolved in neutral water and left in the dark at room temperature. Measurements were taken at different intervals of time and the zwitterion was detected after 8 hours (Figure 3.7). After 144 h the hydrolysis leveled off to yield 20% compound **A** and 80% compound **B**. TEM of the sample aged for seven days showed that the tubes were deteriorating and slowly converting to sheets (Figure 3.8 A). As the hydrolysis occurs, sheet formations are promoted due to the nature of compound **B**. The transformation to sheets was much slower when the hydrolysis occurs at room temperature, even after 80% of **A** was hydrolyzed. To compare, a fresh sample of compound **A** was heated for 30 min at 130°C in a sand bath, and only 37% hydrolysis conversion was observed (Figure 3.7 B). The TEM revealed that the nanotubes converted to sheets and helical coils (Figure 3.8 B).

A total conversion (>96%) to zwitterion **B** was accomplished in two ways: heating at 130°C for 4 hours in an oil bath, and aging the sample at pH=11 for 2 days at a concentration of 2 mM. Both methods resulted in large decrease of solubility and most of the material precipitated out of solution, which was expected due to the low solubility of compound **B**. The TEM images displayed nanosheets when **A** was aged at pH=11 for

two days (Figure 3.8 C). The CD spectrum decreased in intensity due to solubility, but the band I cotton effect is similar to compound **A** (Figure 3.8 D).

Diacetylene compounds are known to have a strong UV signal at ca. 500 nm and/or ca. 650 nm after UV induced polymerization.^[153] When solutions of nanotubes,

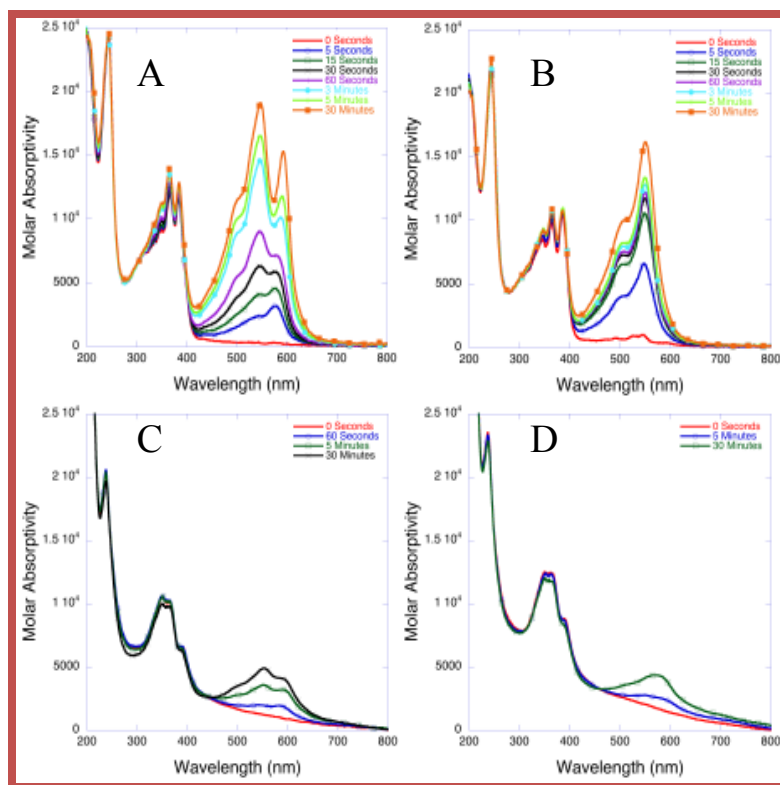


Figure 3.9: Time dependent polymerization of **A** in water (254 nm (19 W); aged at 5 mM then diluted to 0.30 mM) irradiated over a 30 min period (A), **A** heated to 130°C for 30 min in water in a pressure tube (0.30 mM), irradiated over a 30 min period (B), **B** in water (0.30 mM) irradiated over a 30 min period (C), and **B** heated to 130°C for 30 min in water in a pressure tube (0.30 mM), irradiated over a 30 min period (D).

created from **A** (300 μ M water), were exposed to UV light (254 nm, 19 W), a strong absorbance was observed at 593 nm, 540 nm, and 504 nm within 30 minutes and the solution turned a purple color (Figure 3.9 A). Previous reports have described the purple

PDA color emerge from to the 593 nm absorbance.^[154] The nanosheets (From **A** heated to 130°C for 30 minutes in a pressure tube) were also exposed to UV light for 30 minutes, causing the 593 nm absorbance to disappear and the solution turned red (Figure 3.9 B). Compound **B**, when irradiated with UV light polymerizes to give the same PDA absorbance as compound **A**: 593 nm, 547 nm, and 504 nm (Figure 3.9 C). The intensity of the PDA absorbances were not as strong. Compound **B** (50 μ M) was heated to 130°C for 30 minutes and then cooled to room temperature, followed by 30 minutes of UV irradiation to see if the behavior of **B** was similar to **A**. Once again the 593 nm absorbance disappeared and the color of the solution was red (Figure 3.9 D). Hydrolysis does not cause the change of the two PDA organizations, but appeared to be promoted with heat.

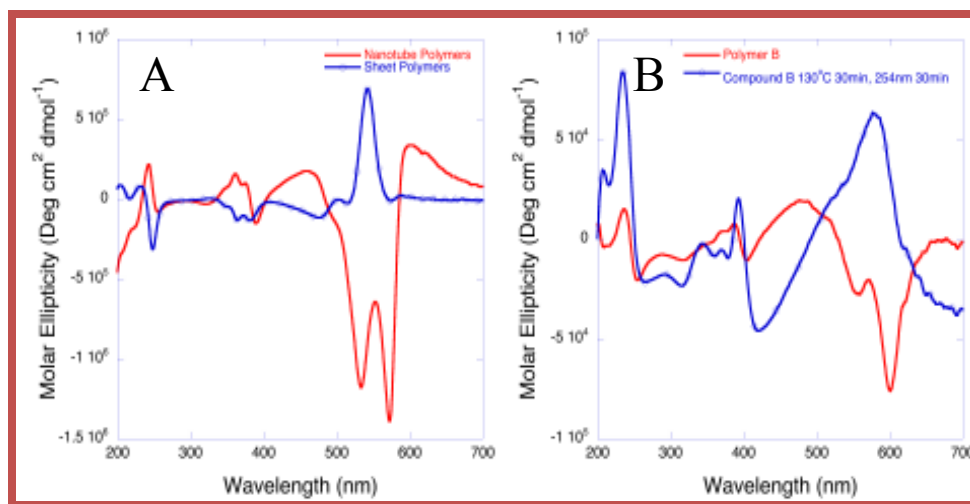


Figure 3.10: CD of polymer **A** nanotubes (aged for 12h 5 mM, diluted to 0.3 mM, and then polymerized via UV irradiation at 254 nm (19 W) for 30 minutes) and **A** heated to 130°C (Pressure tube, 30 minutes, 2 mM) to yield sheets, then polymerized (UV irradiation at 254 nm (19 W) for 30 minutes) (0.3 mM) (A). CD of polymer **B** and compound **B** heated to 130°C then polymerized (0.05 mM) (B).

The NDI chromophores of **A** (300 μ M) before heat treatment, displays a positive band I excitonic cotton effect and when irradiated with UV for 30 minutes, the polymer helicity was *M* due to the negative signals centered at 550 nm (Figure 3.10 A). When **A** was heated (130 $^{\circ}$ C, 30 minutes), a negative NDI band I excitonic cotton effect, the polymer helicity was *P* due to the positive signal centered at 550 nm. CD of polymer **B** displayed the similar effect for both preheated and heated samples (Figure 3.10 B). The NDI organization regulates the helicity of the polymer backbone. When a positive signal was observed for the NDI chromophores, a negative signal emerged from the PDA chromophores and vice versa.

In order for diacetylene materials to polymerize, the diacetylene groups must be 4.8 nm from one another. Compound **A** polymerizes quite readily, which hints that the internal organization of the monomeric units are highly ordered (Figure 3.11). XRD of the centrifuged nanoparticles from compound **A** yielded a 2Θ of 25.7, which indicates a *d*-spacing between the NDI chromophores of 3.5 $\text{\AA}$. Since the diacetylene group and the NDI have only a ridged one-carbon spacer between them and that the polymerization occurs readily, the *d*-spacing of the diacetylene should be less than 4.8 $\text{\AA}$. If the spacer

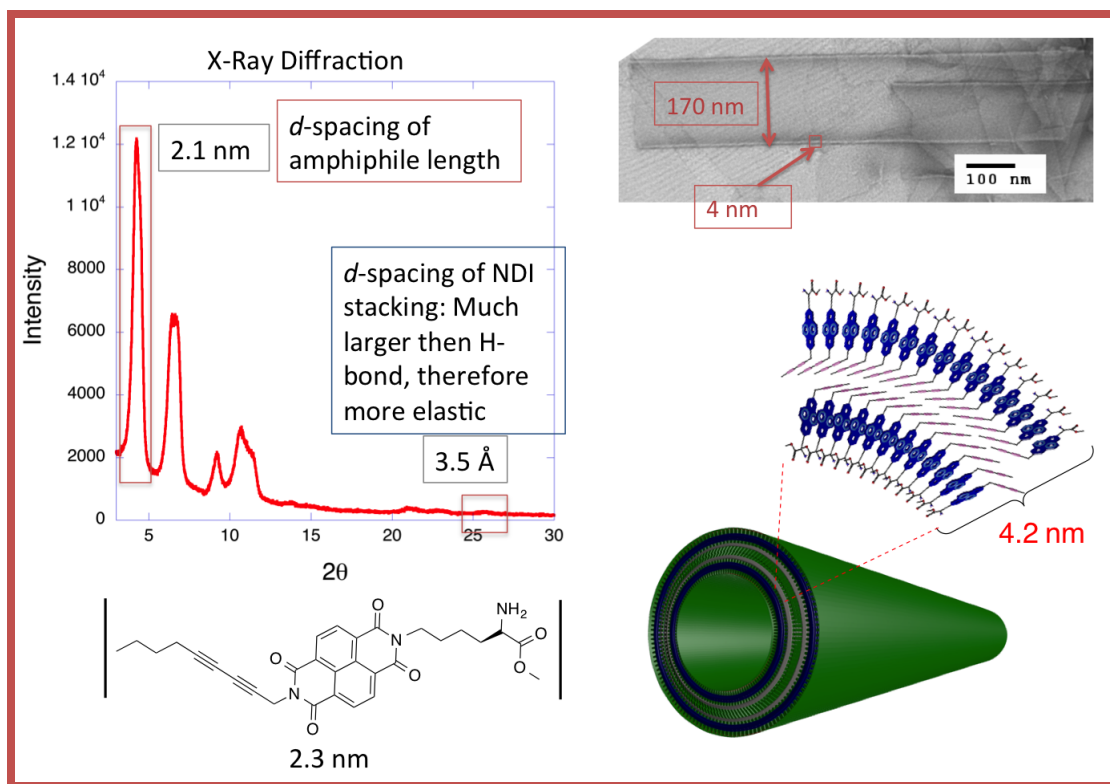


Figure 3.11: XRD of compound **A** (left) and a model of the nanotube assembly.

was larger the diacetylene groups could be further apart due to increased tail flexibility, which would slow PDA formation. The XRD also has a 2θ of 4.3, which relates to the molecular length with a *d*-spacing of 2.1 nm. This correlates with the measured bilayer tube wall thickness (~ 4 nm), but is slightly less than the calculated molecular length (2.3 nm). Since the calculated length was less than the *d*-spacing, we hypothesized that the molecular stacking was not straight, but has a slight tilt. The tilt would result in a smaller *d*-spacing value. Tilted molecules within the matrix were common in chiral amphiphilic assemblies.^[59]

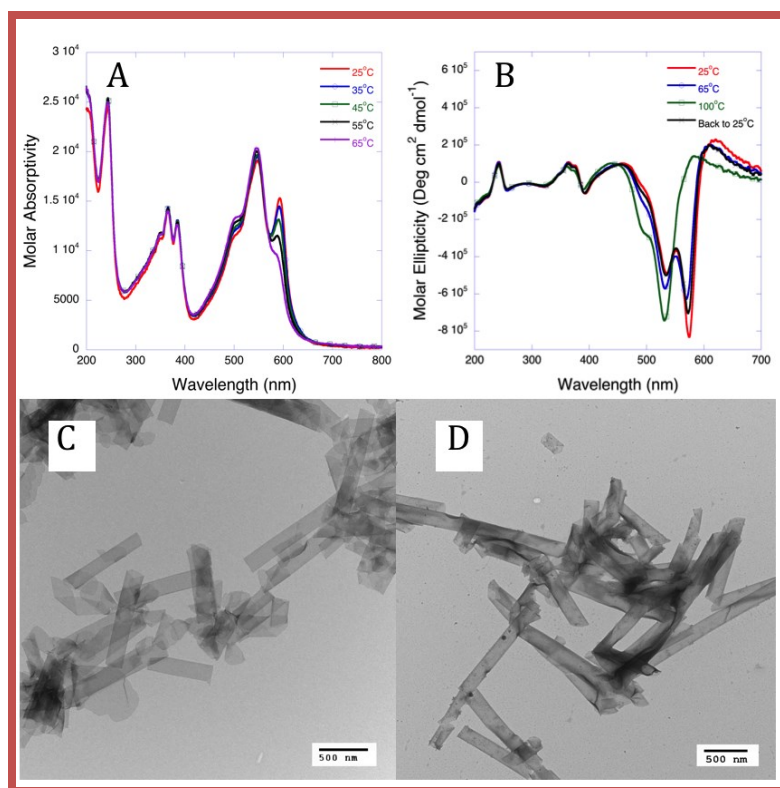


Figure 3.12: CD and UV-Vis of polymer A nanotubes aged for 12h 5 mM, diluted to 1 mM, and then polymerized via UV irradiation at 254 nm (19 W) for 30 minutes. Temperature dependent UV-Vis of polymer A (0.3 mM) (A). Temperature dependent CD of Polymer A (0.3 mM) (B). TEM of polymer A before heating to 100°C (1 mM) (C). TEM of polymer A after heating to 100°C (1 mM) (D).

Polymerized assemblies have shown improved robust characteristics toward thermal and chemical treatments.^[69, 155] The UV absorbance at 593 nm decreased and the absorbances at 547 nm and 504 nm intensified as the result of the elevated temperature (Figure 3.12 A). Also when visually inspecting the solution color, the initial purple solution changed to red. When the solution was allowed to cool, the color changed back to purple and the absorbance of 593 nm reappeared. The decrease of the 593 nm absorbance indicated the loss of conjugation within the polymer backbone.^[156] A similar

effect can also be seen in the CD spectrum where the negative excitonic cotton signal corresponding to the absorbance at 593 nm also loses intensity and while the signals at 547 nm and 504 nm intensifies. The NDI CD regions remain unchanged and suggesting the organization of the structure was stable even after 30 minutes at 100°C (Figure 3.12 B). When polymer A was cooled back to room temperature, the 597 nm absorbance

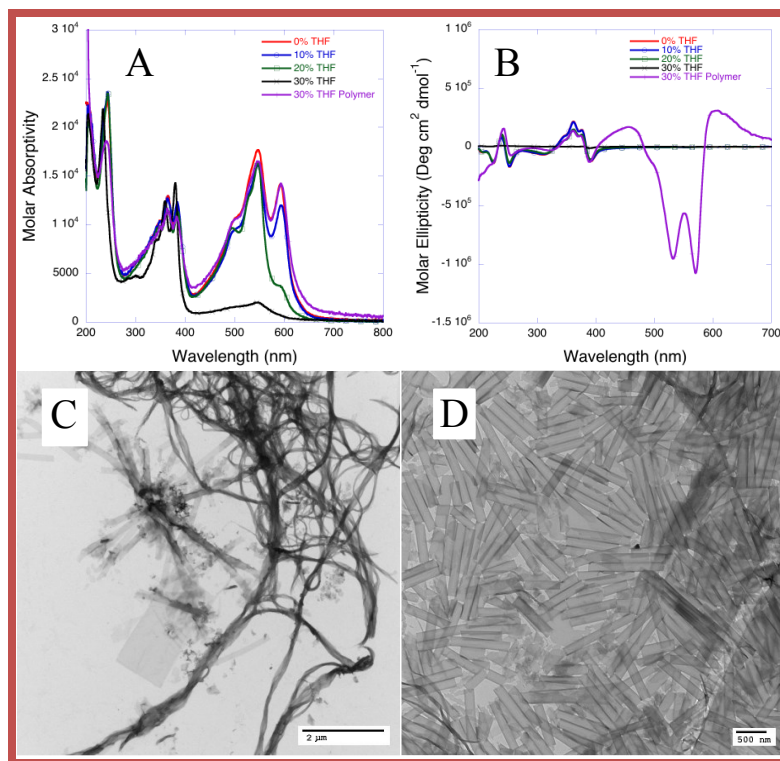


Figure 3.13: UV-Vis of time dependent polymerization of A in THF/water solutions (0% to 30%, v/v). Purple line is polymer A in 30% THF/water (v/v) (A). CD of A in increasing THF solutions. Purple line is polymer A in 30% (v/v) THF/water solution (B). TEM of A in 30% (v/v) THF/water solution (C). TEM of polymer A in 30% (v/v) THF/water solution (D).

intensified again reestablishing the lost conjugation. TEM of a sample heated to 100°C for 30 minutes at a concentration of 1 mM confirms that the nanotubes are retained (Figure 3.12 D).

The tube morphology and internal organization of compound **A** were destabilized in 30% THF/Water solution. As the percentage of THF increased in solution from 0% to 30%, the polymerization was hindered as evident by the decreased PDA absorbances centered at 550 nm (Figure 3.13 A). In 30% TFE/water solution, the PDA absorbances were significantly less intense. This indicates that the diacetylene groups were no longer adjacent to one another within the structural matrix and cannot polymerize.^[157] Compound **A** lacked a PDA CD signal (centered at 550 nm) when THF was added to 30% (v/v) while polymer **A** showed stability in THF solutions where similar CD positive couplet was observed in the band I range in 30% THF/water (v/v) solutions (Figure 3.13 B). TEM demonstrated the induced robustness of polymer **A**. The non-polymerized nanotubes were destroyed in 30% THF/water (v/v) solutions and transforms into large fibers, while the polymer retains the tube morphology (Figure 3.13 C and D).

Post-polymerization modification has been studied extensively in the literature.^[158] Development of monomers that assemble into an organized nanostructure with a lot of complexity desired properties would be very difficult because of hindering interactions that would prevent controlled self-assembly. Modification of organized assembled polymers without disruption of the morphology was an important step to develop complex advanced materials.^[159] The hydrolysis of the methyl ester for compound **A**, as stated above, was fast at elevated temperatures. In an attempt to hydrolyze the polymer, polymer **A** (1 mM) was heated to 130°C for four hours in a

pressure tube. The CD spectrum showed that the NDI organization has a signature similar to the zwitterion, but

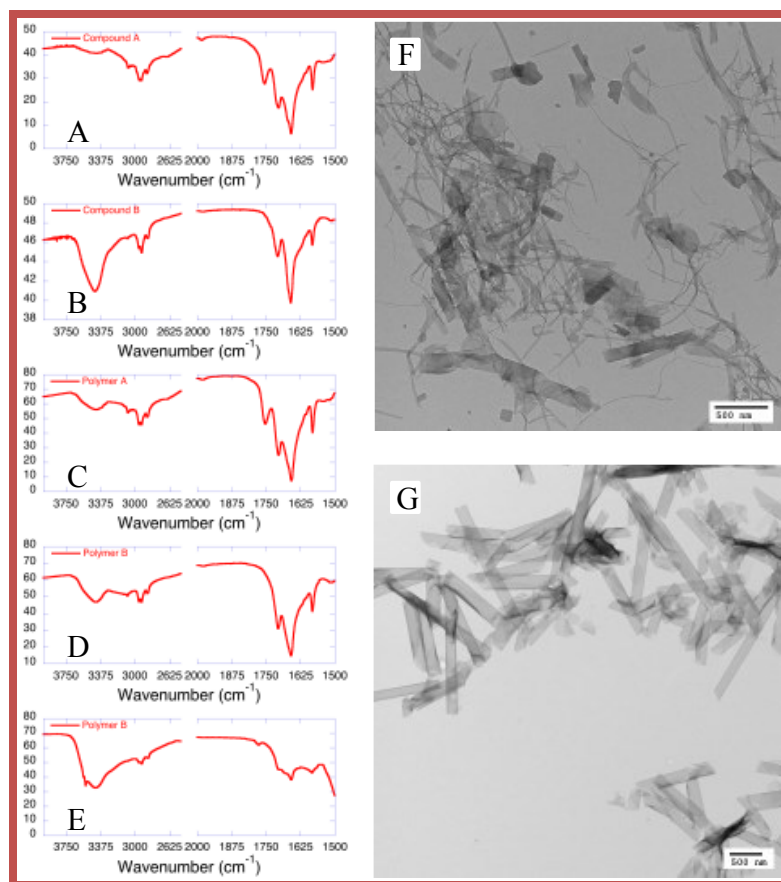


Figure 3.14: FT-IR of compound **A** (A), compound **B** (B), polymer **A** (C), polymer **A** after thermal hydrolysis at 130°C for 4h in water in a pressure tube (1 mM) (D), polymer **A** after chemical hydrolysis at pH=11 for 2 days (2 mM) (E). TEM of polymer **A** after thermal hydrolysis (F) and chemical hydrolysis (G).

the nanotubes were not stable under these conditions; sheets, helical coils, and fibers were observed (Figure 3.14 F and 3.15 A). In order to determine that polymer has

undergone hydrolysis, FT-IR spectroscopy was used to detect changes in the carbonyl region (1800 cm^{-1} to 1600 cm^{-1}). The IR for compound **A** and **B** differ at two wavelengths: the intensity at ca. 3550 cm^{-1} increased for zwitterion **B** due to the carboxylic acid and two carbonyl absorptions (NDI imines and carboxylic acid) at 1659 cm^{-1} and 1706 cm^{-1} . Compound **A** has a distinct methyl ester carbonyl absorption at 1754 cm^{-1} , which compound **B** lacks (Figure 3.14 A and B). The IR spectrum of polymer **A** was similar to that of compound **A**, where the absorption of 1754 cm^{-1} were observed for

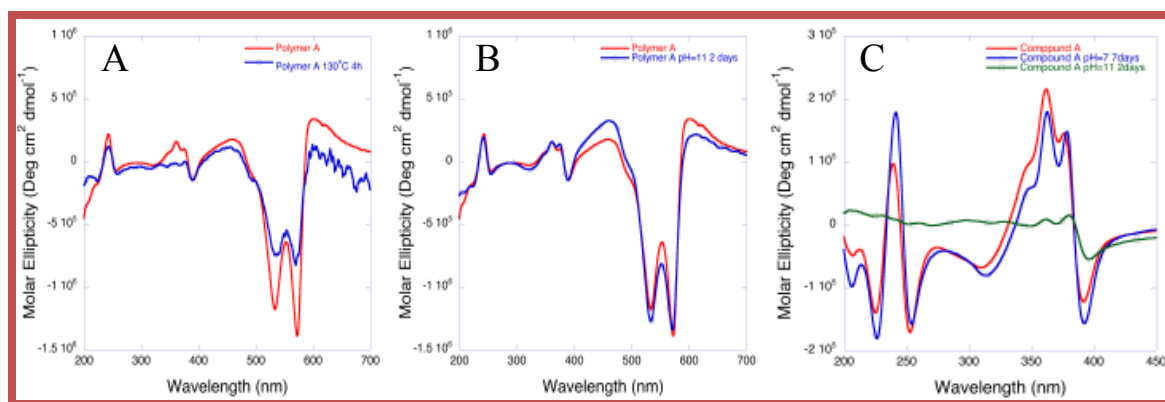


Figure 3.15: CD of polymer **A** heated at 130°C for 4 hours in water in a pressure tube at 1 mM (0.3 mM) (A). CD of polymer **A** at pH=11 for 2 days at 2 mM (0.3 mM) (B). CD of **A** (0.3 mM), **A** at pH=7 for 7 days at 2 mM (0.3 mM) (Blue) and pH=11 for 2 days at 2 mM (0.3 mM) (Green) (C).

both (Figure 3.14 C). When polymer **A** undergoes hydrolysis, similar IR absorption changes should be observed. The heat treated polymer **A** did show an increase at ca. 3550 cm^{-1} and lacked the 1754 cm^{-1} absorption indicating hydrolysis occurred similar to compound **A** (Figure 3.14 D). The pH was increased to 11 to retain the polymer's tube morphology due to less destructive conditions. Polymer **A** was subjected to a two day

aging period at pH=11 (2 mM, pH adjusted with 1 mM NaOH), the solution was lyophilized and IR once again showed an increase of the ca. 3550 cm⁻¹ absorption and the absence of the absorption at 1754 cm⁻¹ the same as the heat treated sample (Figure 3.14 E). TEM revealed the tubular structure was maintained (Figure 3.14 G). The CD of the chemically hydrolyzed polymer **A** displayed a similar spectrum as compound **A** (Figure 3.15 B). Also, the solubility of hydrolyzed polymer **A** was improved when compared to the zwitterion. The morphology of the nanostructure can affect solubility.

3.6 Conclusion

We have synthesized and examined the assembly properties of *n*-type amphiphiles that form organized nanostructures and polymerize readily under mild UV irradiation. The efficient polymerization suggests that the bilayer of the assembly was highly ordered with the diacetylene groups in a crystalline arrangement.^[157] The polymerization appears to not affect the nanostructure and was robust to degrading conditions such as temperature up to 100°C and to organic/water solutions, but the nanostructure did degrade at 130°C after prolonged periods of time (4h). When assembled, compound **A** undergoes hydrolysis rapidly even at pH of 7 over the course of seven days and stops at 80% conversion. Complete hydrolysis can be accomplished through thermal conditions (130°C 4h) or with an increase in pH to 11. Post-polymer modification has been accomplished by hydrolyzing the polymer **A** in basic conditions while maintaining the tubular morphology. We are aiming to expand this work by coupling varying molecules

to the polymerized tubes while retaining the nanostructure morphology and synthesize nanostructures with further complexity and functionality.

3.7 Methods and Experimentals

General Methods

Circular dichroism (CD) spectra were recorded using a Jasco CD spectrometer. All FT-IR spectra were collected on a PerkinElmer Spectrum 100 FT-IR spectrometer at ambient temperature. Transmission electron microscopy (TEM) was performed with Technai G2 Spirit instrument operating at 80 kV. All reactions were performed under argon or nitrogen atmosphere. Solution-state ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-250, DPX-400, or DPX-500 instrument as indicated. Dimethylformamide (DMF) was dried by distillation from MgSO_4 . Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents. HPLC was done with reverse-phased preparative Waters XBridge C8 column eluting with a linear gradient of $\text{CH}_3\text{CN}/\text{water}$ (20/80 to 100/0 over 40 minutes, 0.1 % TFA). Purity was assessed by analytical reverse-phase HPLC. The adjustment of pH was done with 0.2 M NaOH solution for all pH dependent studies. All water used for sample solutions was HPLC grade and passed through membrane filter (0.02 μm) before use. Polymerization of the

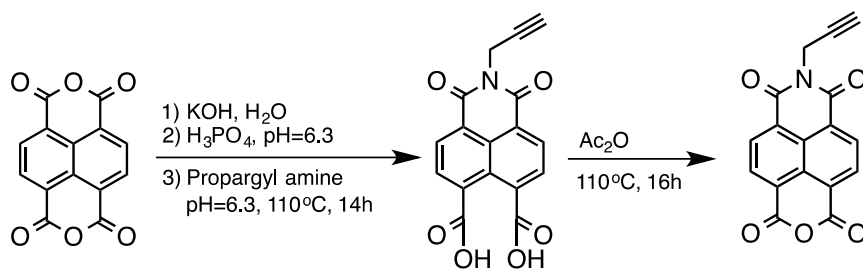
sample was done in a 1 mm cuvette with UV irradiation in a dark sealed container with a UV lamp (19 W) at a distance of 12 cm.

Circular Dichroism (CD) Spectroscopy

CD spectra were recorded on a Jasco CD spectrometer under a nitrogen atmosphere. Experiments were performed at 25°C in a quartz cell with a 1 mm or 1 cm path length over the range of 200-700 nm.

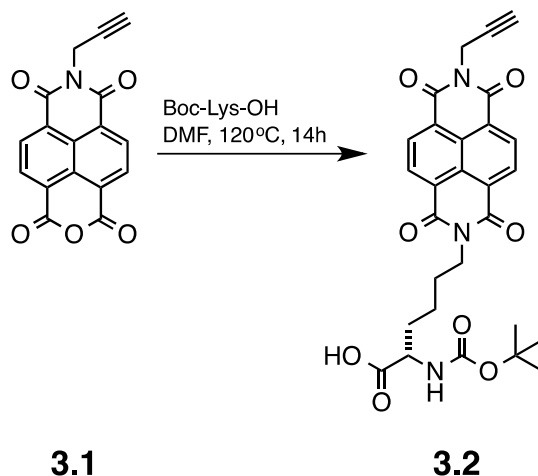
Transmission Electron Microscopy Measurements

10 μ L of sample solution was applied to a carbon-coated copper grid (Ted Pella, Inc.) for 2 min. After removal of excess solution with filter paper, the grid was negatively stained with 10 μ L of 2% (w/w) uranyl acetate solution for 1.5 min. the excess solution was removed by filter paper. The dried specimen was observed with Technai G2 Spirit TEM instrument operating at 80 keV, and data were analyzed with Image pro software.

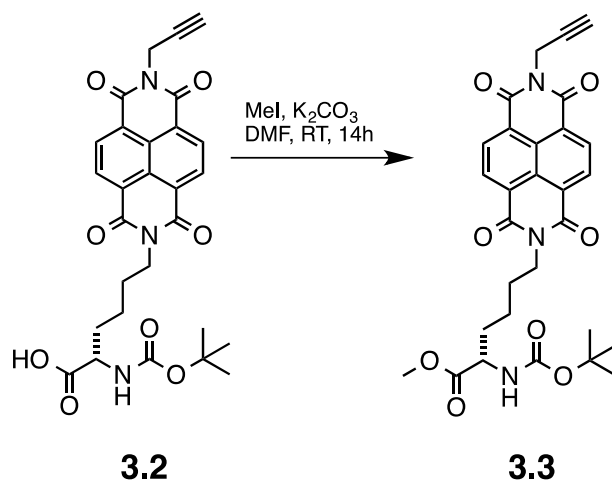


3.1

Propargyl-NMA (3.1):^[160] A round bottom flask was charged with 1,4,5,8-naphthalenetetracarboxylic dianhydride (5.00 g, 18.6 mmol), water (800 mL), and potassium hydroxide (88 mL, 1.0 M). The mixture was stirred until the solid dissolved and the pH was adjusted to 6.3 with phosphoric acid (1.0 M). To the solution, propargylamine (1.03 g, 18.7 mmol, 1.20 mL) was added and the pH was readjusted to 6.3 with phosphoric acid (1.0 M). The solution was heated to 110 °C and stirred for 14h. The reaction was cooled to room temperature and acidified with phosphoric acid (1.0 M) to a pH of ca. 2.0 to give a white precipitate. The precipitate was filtered, washed with water, and dried in a desiccator under vacuum. This solid was suspended into acetic anhydride (150 mL) and heated to 110 °C for 16 h. The acetic anhydride was removed via vacuum distillation to yield the monoanhydride **3.1** (4.40 g, 14.4 mmol, 77%). ¹H NMR (250 MHz; DMSO): δ 8.73 (s, 4H), 4.82 (d, *J* = 2.1, 2H), 3.20 (t, *J* = 2.1, 1H).

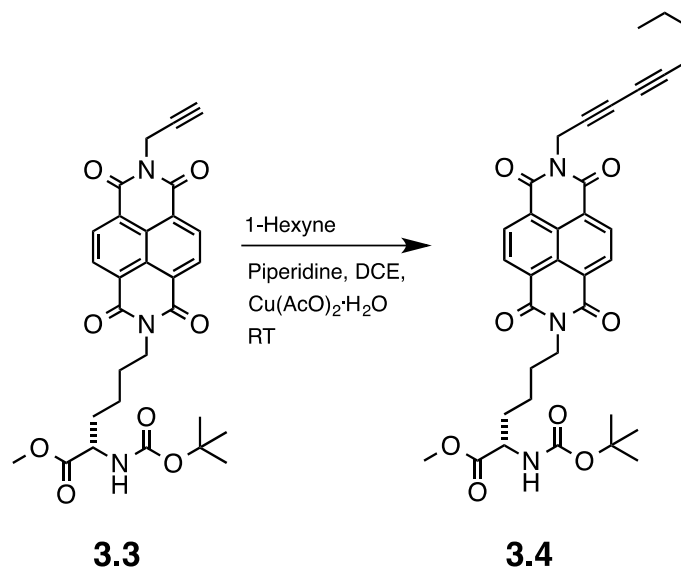


Boc-K(NDIMA)-OH (3.2): The monoanhydride **3.1** (4.40 g, 14.4 mmol) and Boc-Lys-OH (3.55 g, 14.4 mmol) was dissolved in DMF (350 mL) and stirred under nitrogen. The mixture was heated at 120 °C for 14h resulting in a dark brown solution. The DMF was removed by vacuum distillation to obtain a dark brown solid. The solid was passed through a silica column (CHCl₃ to 2% MeOH in CHCl₃) to yield a yellow amino acid **2** (6.38 g, 12.0 mmol, 83%). mp 109-111 °C; ¹H NMR (250 MHz; CDCl₃): δ 8.81-8.74 (m, 4H), 5.16 (dd, *J* = 6.6, 0.3, 1H), 4.97 (d, *J* = 2.4, 2H), 4.29 (s, 1H), 4.20 (t, *J* = 7.3, 2H), 2.23 (t, *J* = 2.5, 1H), 2.00-1.89 (m, 1H), 1.86-1.75 (m, 3H), 1.59-1.51 (m, 2H), 1.43 (s, 9H); IR (KBr) ν 3369, 3296, 2978, 2935, 2870, 2129, 1976, 1709, 1666, 1606, 1582, 1507, 1456, 1413, 1395, 1376, 1358 cm⁻¹; ESI-MS calcd. for C₂₈H₂₇N₃O₈ [M+Na]⁺ 556.1696, found 556.1688. (I need to plug in the carbon still)



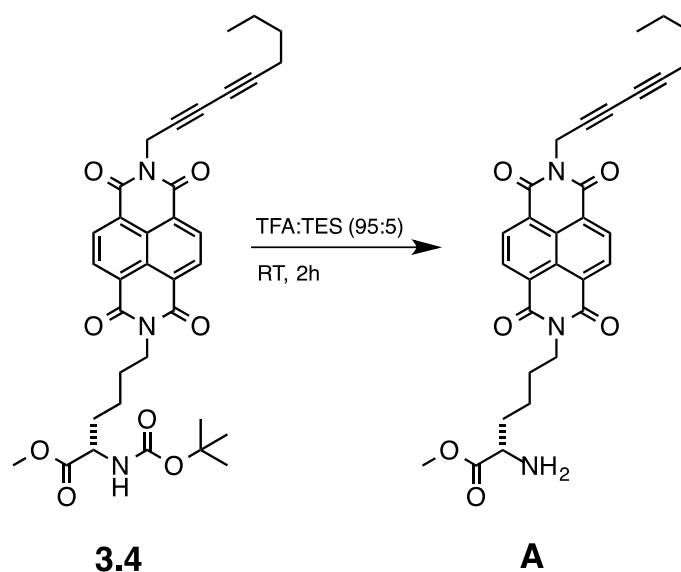
Boc-K(NDIMA)-OMe (3.3): Amino acid **3.2** (476 mg, 0.892 mmol) was dissolved in DMF (2 mL) under nitrogen. Potassium carbonate (370 mg, 2.68 mmol) was added followed by methyl iodide (380 mg, 2.68 mmol, 167 μ L) and stirred. The mixture turned brown with in 5 min. The reaction was stirred at room temperature for an additional 14h. The DMF was transferred by pipet and the solid was triturated with ethyl acetate (50 mL) and the ethyl acetate solution was washed with water (5x50 mL), saturated sodium thiosulfate (1x50 mL), and brine (1x50 mL). The organic layer was further dried over magnesium sulfate, filtered, and the solvent was removed. The crude product was purified by column chromatography (0.5% to 1% methanol in chloroform) to yield an off white solid **3** (468 mg, 0.855 mmol, 96%). mp 146-148 $^{\circ}$ C; ^1H NMR (500 MHz; CDCl_3): δ 8.79 (q, J = 8.6, 4H), 5.08 (d, J = 8.0, 1H), 4.98 (d, J = 2.4, 2H), 4.30-4.29 (m, 1H), 4.22-4.19 (m, 2H), 3.74 (s, 3H), 2.24-2.23 (m, 1H), 1.93-1.85 (m, 1H), 1.81-1.71 (m, 3H), 1.56-1.44 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz; CDCl_3): δ 173.4, 162.9, 162.2, 131.5, 131.2, 127.06, 126.92, 126.91, 126.4, 80.0, 78.0, 71.4, 53.4, 52.4, 40.6,

32.5, 30.0, 28.5, 27.7, 22.9; IR (KBr) ν 3569, 3365, 2966, 2955, 2932, 1977, 1740, 1709, 1665, 1582, 1521, 1456, 1413 cm^{-1} ; ESI-MS calcd. for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_8$ $[\text{M}+\text{Na}]^+$ 570.1852, found 570.1840.



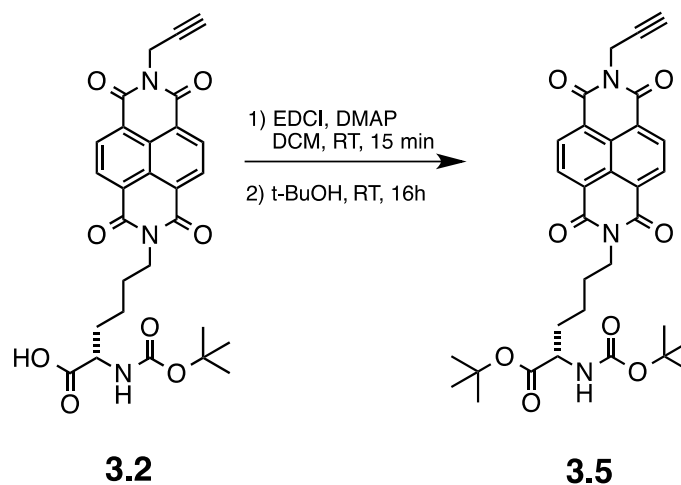
Boc-K(NDIDA)-OMe (3.4): A flask was charged with **3.3** (468 mg, 0.822 mmol), 1-hexyne (700 mg, 8.55 mmol, 980 μL), piperidine (220 mg, 2.57 mmol, 250 μL), and dichloroethane (2 mL). **3** was stirred to dissolve. To the brown solution, copper acetate monohydrate (17 mg, 0.085 mmol, 10 mol%) was added. The solution was allowed to stir in the open air for 10h. The remaining solvent was removed and the resulting solid was re-dissolved in chloroform (20 mL). This purple material was purified via column chromatography ($\text{CHCl}_3/\text{MeOH}$ 99.5%/0.5%) to yield **3.4** (214 mg, 660 μmol , 77%). mp 128-130 $^{\circ}\text{C}$; ^1H NMR (250 MHz; CDCl_3): δ 8.78 (d, $J = 16.8$, 4H), 5.09 (q, $J = 10.2$, 1H), 5.02 (s, 2H), 4.30 (q, $J = 7.0$, 1H), 4.20 (t, $J = 6.8$, 2H), 3.74 (s, 3H), 2.22 (t, $J = 6.8$,

2H), 1.89-1.68 (m, 5H), 1.60-1.58 (m, 2H), 1.49-1.45 (m, 3H), 1.43 (s, 9H), 0.86 (t, J = 7.2, 3H); ^{13}C NMR (126 MHz; CDCl_3): δ 173.4, 162.9, 162.1, 155.5, 131.5, 131.2, 127.0, 126.9, 126.9, 126.5, 80.7, 80.0, 77.4, 69.7, 68.3, 64.7, 53.5, 52.4, 40.6, 32.5, 30.7, 30.2, 29.8, 28.5, 27.7, 22.9, 22.0, 19.0, 13.6; IR (KBr) ν 3368, 3340, 2934, 2866, 1979, 1746, 1709, 1662, 1582, 1521, 1455, 1412, 1393, cm^{-1} ; ESI-MS calcd. for $\text{C}_{35}\text{H}_{37}\text{N}_3\text{O}_8$ $[\text{M}+\text{Na}]^+$ 650.2478, found 650.2480.



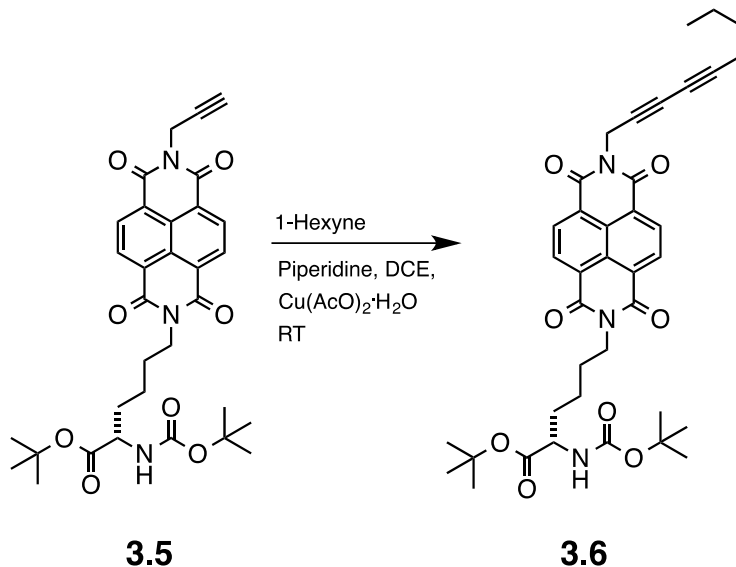
NH_2 -K(NDIDA)-OMe (A): Compound **3.4** (70 mg, 0.11 mmol) was dissolved in trifluoroacetic acid:triethylsilane (95:5, 1.0 mL). The solution was allowed to stir for 2h. The solvent was removed by passing nitrogen over the surface of the liquid. The material was taken up in water and TFE (Added until dissolved. At this point, exposure to light must be minimized, a color will appear (polymerization) with in 5 min in water) and purified by reverse phase HPLC. The collected solution was lyophilized to yield a white-

pink powder **A** (43 mg, 0.082 mmol, 73%). mp 186-188 °C; ¹H NMR (500 MHz; DMSO): δ 8.62 (q, J = 9.4, 4H), 4.97-4.89 (m, 1H), 4.89 (s, 1H), 4.03 (q, J = 7.0, 2H), 3.74 (s, 3H), 2.28 (t, J = 6.9, 2H), 1.87-1.85 (m, 2H), 1.74-1.64 (m, 2H), 1.52-1.47 (m, 1H), 1.45-1.35 (m, 3H), 1.32-1.29 (m, 2H), 0.82 (t, J = 7.3, 3H); ¹³C NMR (126 MHz; DMSO): δ 170.1, 162.6, 162.0, 158.5, 130.9, 130.5, 126.6, 126.21, 126.18, 126.17, 126.0, 81.0, 71.7, 67.1, 64.6, 53.0, 52.0, 30.2, 29.9, 29.6, 27.0, 21.9, 21.4, 18.0, 13.4; IR (KBr) ν 3437, 3042, 1756, 1705, 1660, 1582, 1456, 1412 cm⁻¹; ESI-MS calcd. for C₃₀H₃₀N₃O₆ [M+H]⁺ 528.2129, found 528.2062.



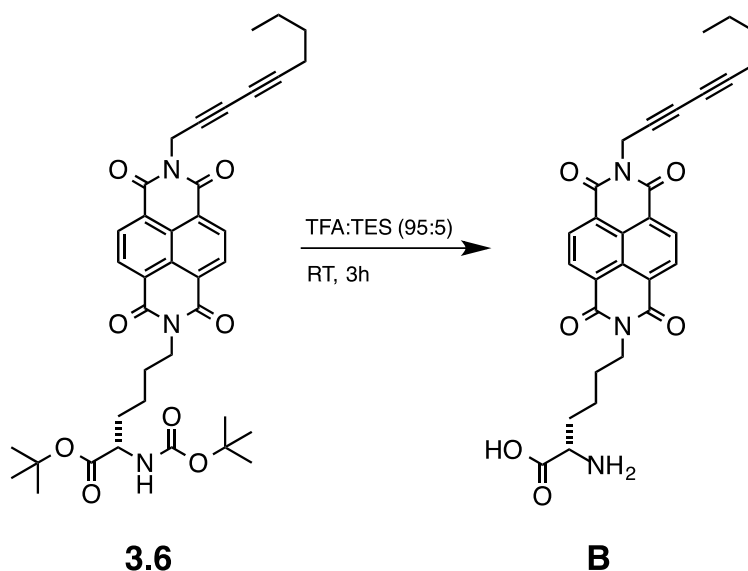
Boc-K(NDIMA)-OtBu (3.5): Amino acid **3.2** (1.20 g, 2.25 mmol) was dissolved in dry DCM (11 mL) under nitrogen. EDCI (474 mg, 2.47 mmol) was added followed by DMAP (136 mg, 1.125 mmol) and stirred. The reaction was left for 15 min, then anhydrous *tert*-butanol (183 mg, 2.47 mmol, 237 μL) was injected to the reaction vessel and left at RT for an additional 16 h. The solvent was removed and the crude product was purified by column chromatography (1% methanol in DCM) to yield an off white solid

3.5 (1.00 g, 1.70 mmol, 75%). mp 163-165 °C; ^1H NMR (400 MHz; CDCl_3): δ 8.78 (q, $J = 7.5$, 4H), 8.78 (q, $J = 7.5$, 4H), 5.05 (d, $J = 7.9$, 1H), 5.05 (d, $J = 7.9$, 1H), 4.98 (d, $J = 2.4$, 2H), 4.98 (d, $J = 2.4$, 2H), 4.20 (t, $J = 7.3$, 2H), 4.22-4.15 (m, 3H), 4.18-4.12 (m, 1H), 2.23 (t, $J = 2.4$, 1H), 2.23 (t, $J = 2.4$, 1H), 1.81 (ddt, $J = 27.7$, 14.0, 7.0, 4H), 1.81 (ddt, $J = 27.7$, 14.0, 7.0, 4H), 1.71-1.68 (m, 1H), 1.71-1.68 (m, 1H), 1.58-1.52 (m, 2H), 1.56 (d, $J = 6.7$, 2H), 1.45 (s, 9H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz; CDCl_3): δ 171.9, 162.7, 162.0, 131.3, 131.0, 127.0, 126.8, 126.8, 126.3, 81.8, 79.6, 77.8, 77.2, 71.2, 53.8, 40.5, 32.6, 29.9, 28.3, 28.0, 27.7, 22.7; IR (KBr) ν 3547, 2979, 2934, 2869, 1710, 1664, 1605, 1583, 1511, 1507, 1457, 1415 cm^{-1} ; ESI-MS calcd. for $\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_8$ $[\text{M}+\text{Na}]^+$ 612.2322, found 612.2326.



Boc-K(NDIDA)-OtBu (3.6): A flask was charged with **3.5** (264 mg, 0.448 mmol), 1-hexyne (368 mg, 6.29 mmol, 515 μL), piperidine (114 mg, 1.34 mmol, 132 μL), and dichloroethane (1.1 mL). **3.5** was stirred to dissolve. To the brown solution, copper

acetate monohydrate (8 mg, 0.04 mmol, 10 mol%) was added. The solution was allowed to stir in the open air for 16h. The remaining solvent was removed by evaporation in vacuo and the resulting solid was re-dissolved in chloroform (10 mL). This purple material was purified via column chromatography (CHCl₃/MeOH 99.5%/0.5%) to yield **3.6** (214 mg, 0.660 mmol, 77%); mp 71-73 °C; ¹H NMR (400 MHz; CDCl₃): δ 8.77 (q, J = 5.9, 4H), 5.06 (dd, J = 8.4, 0.5, 1H), 5.02 (s, 2H), 4.20 (t, J = 7.4, 2H), 4.19-4.13 (m, 1H), 2.22 (t, J = 6.9, 2H), 1.89-1.76 (m, 3H), 1.73-1.65 (m, 1H), 1.52-1.47 (m, 2H), 1.45 (s, 9H), 1.42 (s, 9H), 0.86 (t, J = 7.2, 3H); ¹³C NMR (100 MHz; CDCl₃): δ 172.0, 162.8, 162.1, 155.5, 131.5, 131.2, 127.1, 126.9, 126.9, 126.4, 81.9, 80.7, 79.7, 77.4, 69.8, 68.3, 64.7, 54.0, 40.7, 32.8, 30.7, 30.2, 28.5, 28.2, 27.9, 22.9, 22.0, 19.0, 13.6; IR (KBr) ν 3430, 3044, 1709, 1669, 1583, 1506, 1456, 1412 cm⁻¹; ESI-MS calcd. for C₃₈H₄₃N₃O₈ [M+Na]⁺ 692.2948, found 692.2963.



NH₂-K(NDIDA)-OH (B): Compound **3.6** (34 mg, 0.050 mmol) was dissolved in trifluoroacetic acid: triethylsilane (95:5, 0.5 mL). The solution was allowed to stir for 3h. The solvent was removed by passing nitrogen over the surface of the liquid. The material was taken up in TFE:TFA (1.0% TFA, Added till dissolved. At this point, exposure to light must be minimized, a color will appear (polymerization) with in 20 min in water) and purified by reverse phase HPLC. The collected solution was lyophilized to yield a white-pink powder **B** (17 mg, 0.033 mmol, 67%). dec pt 199-201 (Purple in color); ¹H NMR (500 MHz; DMSO-*d*₆): δ 8.71 (q, *J* = 8.6, 4H), 8.31 (s, 1H), 8.14 (s, 2H), 4.93 (s, 2H), 4.07 (t, *J* = 6.9, 2H), 3.88 (s, 1H), 2.30 (t, *J* = 6.9, 2H), 1.89-1.75 (m, 2H), 1.73-1.67 (m, 2H), 1.57-1.48 (m, 1H), 1.45-1.39 (m, 3H), 1.36-1.29 (m, 2H), 0.84 (t, *J* = 7.3, 3H); IR (KBr) ν 3547, 2959, 1977, 1709, 1661, 1582, 1456, 1413 cm⁻¹; ESI-MS calcd. for C₂₉H₂₈N₃O₆ [M+H]⁺ 514.1978, found 514.2070.

Polymerization of Compound A: A 0.1 cm UV quartz cell was charged with compound **A** in water (2 mM, pH = 7.0). The cell was irradiated in a dark sealed container with a UV lamp (19 W) at a distance of 12 cm from the cell for 30 min. The colorless solution turned purple. The solvent was freeze dried to yield a red-purple polymer in quantitative yield. IR (KBr) ν 3427, 3079, 2956, 1981, 1752, 1704, 1658, 1581, 1454 cm^{-1} .

Thermal hydrolysis of polymer A: A 0.1 cm UV quartz cell was charged with compound **A** in water (2 mM, pH = 7.0). The cell was irradiated in a dark sealed container with a UV lamp (19 W) at a distance of 12 cm from the cell for 30 min. The colorless solution turned purple. The solution was placed in a pressure tube, diluted with water to 1 mM, and heated in an oil bath at 130°C for 4 h. The resulting mixture was allowed to cool and then freeze dried to yield polymer **B** in quantitative yield. IR (KBr) ν 3432, 3084, 1978, 1706, 1659, 1581, 1512, 1455, 1411 cm^{-1} .

Chemohydrolysis of polymer A: A vial was charged with compound **A** in water (2 mM, pH = 11.0, adjusted with 1 mM NaOH). The vial was left in the dark for 2 days. The resulting mixture was freeze dried to yield polymer **B** in quantitative yield. IR (KBr) ν 3538, 3433, 3081, 1777, 1702, 1680, 1658, 1583, 1448 cm^{-1} .

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Chapter 4

Self-Assembled Nanotube Templates for Gold Nanoparticles

4.1 Introduction

Gold nanoparticles have gained interest during the past decades due to their optical, electronic, and chemical properties.^[161] These properties show application potential in optics,^[162] sensing,^[163] nanoelectronics,^[164] catalysis,^[165] biotechnology,^[166] and medicine.^[167] The properties of gold nanoparticles are heavily dependent on the size and shape of the particle.^[168] For example, gold nanoparticle catalysts are more reactive when the surface area is increased, therefore a smaller diameter particle will yield higher reactivity.^[169] Also, the absorbance of the gold nanoparticle increases in wavelength as the size increases, resulting in near IR absorbance useful for biomedical imaging.^[170] During the reduction of gold salt, the gold nanoparticle growth can be hard to control because of the lack of a stabilizing agent that will prevent agglomeration and reduce surface area. Synthesis occurs through a reduction of gold(III) to gold(0) using chemical reducing agents such as citrate, sonochemical, and photochemical.^[171] Usually a

stabilizing agent (thio- ligand) is added that will surround the nanoparticle and prevent agglomeration or growth of the nanoparticle.^[172]

The growth mechanism for the Turkevich method (reduction via citrate) was thought to be a fast gold(III) to gold(0) reduction, which yielded larger particles.^[173] The reduction mechanism has recently been determined to be a quick reduction from gold(III) to gold(I), then the gold nanoparticle formation occurs through a slower reduction of gold(I) to gold(0).^[172] The slower reduction of gold(I) to gold(0) allows for an organized crystal of gold atoms that first form nanoclusters (<2 nm) by nucleation. The nanoclusters will self aggregate and with the remaining gold(I) will grow to gold nanoparticles with a diameter of 7-8 nm.

Besides using small molecular stabilizing agents to control shape and size, templates made from polymers,^[174] inorganic particles,^[175] or assembled 1-D nanostructures can be used.^[176] Templates with amine and thio- attractive functionalities have had success for gold nanoparticle formation on the template surfaces.^[177] Amphiphilic lysine-NDI molecules have an amine in the polar head that has a positive charge that can attract anionic gold tetrachloride salts and gold nanoparticles stabilize by negatively charged citrate. This chapter will go into detail on the exploration of robust nanotube assemblies comprised of lysine-NDI-diacetylene amphiphiles used as a template for gold nanoparticles.

4.2 Research Design

The most common way to synthesize gold nanoparticles would be to reduce the strong acid tetrachloroauric acid (HAuCl_4) with sodium citrate in water at 75°C (Figure 4.1).^[178] The auric acid will dissociate into water as a gold(III)tetrachloride anion, which can electrostatically be attracted to a cationic species.^[179] During the reduction reaction, agglomeration can be hindered by the citrate coating the gold particle, acting as a stabilizing agent. The citrate coating is also anionic and is attracted to cations (Figure 4.1 B and 4.2 D).^[177] Therefore the gold was attracted to a cationic surface in both ionic and colloidal forms.

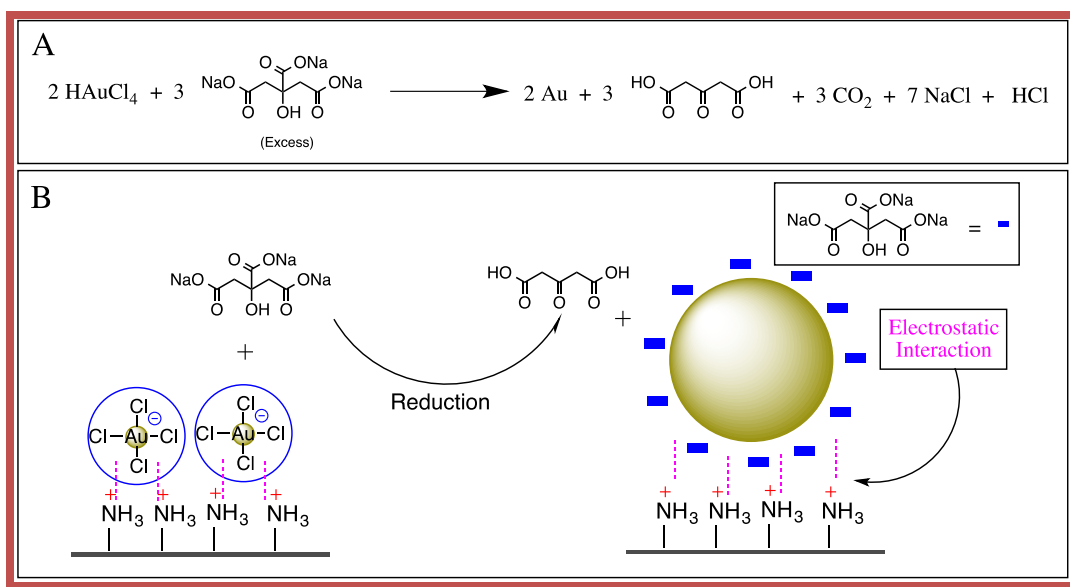


Figure 4.1: Turkevich method to reduce gold(III) to gold(0) (A). Two different ways gold can electrostatically interact with cations; gold(III)tetrachloride anion or citrate coated colloidal gold can interact with the positively charged surface (B).

Templates with cationic functionality such as ammonium groups can provide a surface for gold nanoparticles-template interaction. Using a silica surface coated with poly(methyl methacrylate) (PMMA) followed by etching and exposing the silica surface,

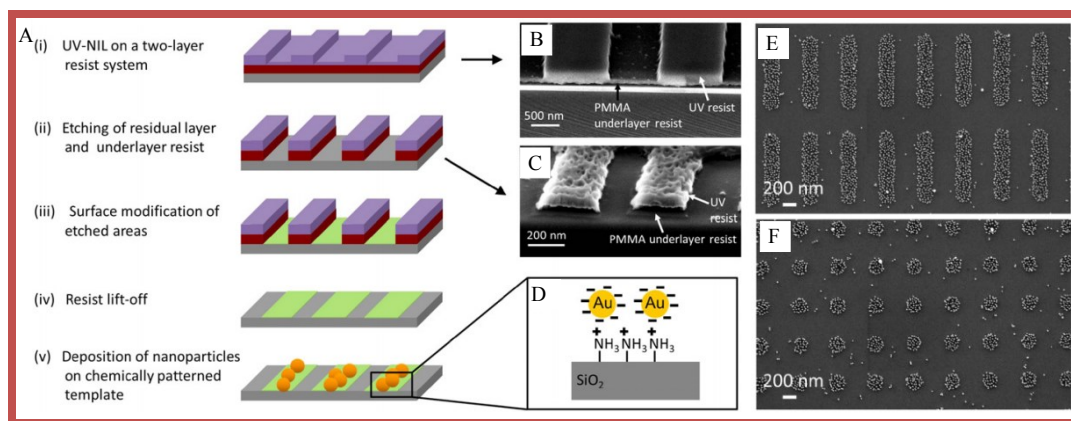


Figure 4.2: Preparation procedure of the silica-amine template (A). SEM of the template before and after etching and exposing the silica surface (B and C). Depiction of the citrate coated gold nanoparticle interacting with the silica surface charged with ammonium cations (D). SEM images of the gold nanoparticles on the prepared template (E and F).

provided locations that allowed the silica to be coated with 3-aminopropyltriethoxysilane through a silane ether linkage.^[172] The 3-aminopropyltriethoxysilane gives the surface an amine rich template that when protonated will form positively charged ammonium and interact with premade gold nanoparticles with a sodium citrate coating. This strategy can be demonstrated by etching different shapes therefore, creating a variety of surfaces made of gold nanoparticles (Figure 4.2).

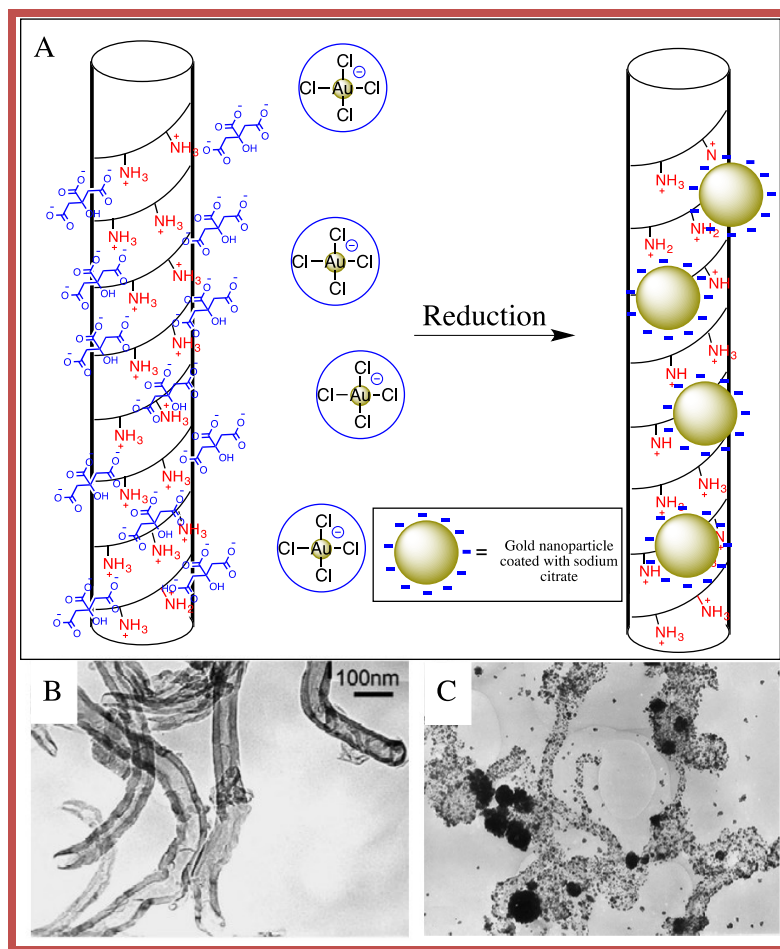


Figure 4.3: Anionic gold salt will interact with the cationic template surface and will be reduced by the coating citrate decorating the surface of the carbon nanotube (A). The carbon nanotubes before and after addition of tetrachloroauric acid (B and C).

Multi-walled carbon nanotubes can be modified with polyethyleneamine (PEI) wrapping around the tube and functionalizing the surface with amine groups. In a solution of citric acid, the amines are protonated and an electrostatic interaction between

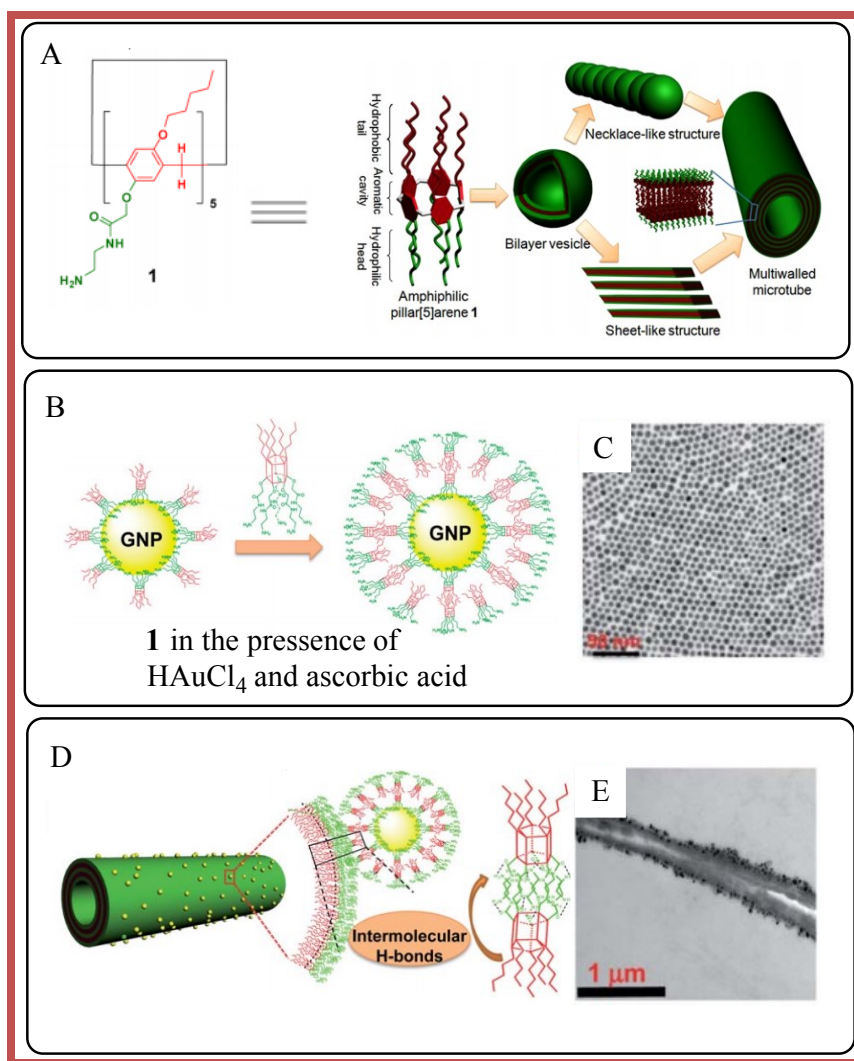


Figure 4.4: The structure of pillar[5]arene and the self-assembly into vesicles and microtubes (A). The bilayer formation around the gold nanoparticle with pillar[5]arenes (B). TEM of the gold nanoparticle stabilized with pillar[5]arene (C). A depiction of premade microtubes decorated with gold nanoparticle stabilized with pillar[5]arene (D). TEM image of a premade microtube decorated with gold nanoparticle stabilized with pillar[5]arene (E).

the amine and the citric acid arises.^[179] With the reducing agent on the surface of the tube, gold(III) can be reduced to gold(0) to yield carbon nanotubes decorated with gold particles (Figure 4.3). The same can be done by modifying the nanotube through a heat treatment with ammonia and trapping the amine on the inside of the tube. This gave

ammonium groups on the interior of the tube wall. After the addition of citric acid followed by gold(III), gold nanoparticles only formed on the inside of the tube.

Pillar[5]arene initially formed vesicles in water,^[180] but the presences of H₂AuCl₄ and the reducing agent ascorbic acid disrupts the vesicle assembly (Figure 4.4 A and B).^[181] Instead, the ammonium rich amphiphile acts as a stabilizing agent where the polar end interacts with the gold surface and the hydrophobic tail promotes a bilayer to be formed around the nanoparticle. A solution containing the pillar[5]arene vesicles were aged for 2 weeks and they merge to form a more stable microtubule. When the microtube interacts with the pillar[5]arene stabilized gold nanoparticles, the assembly

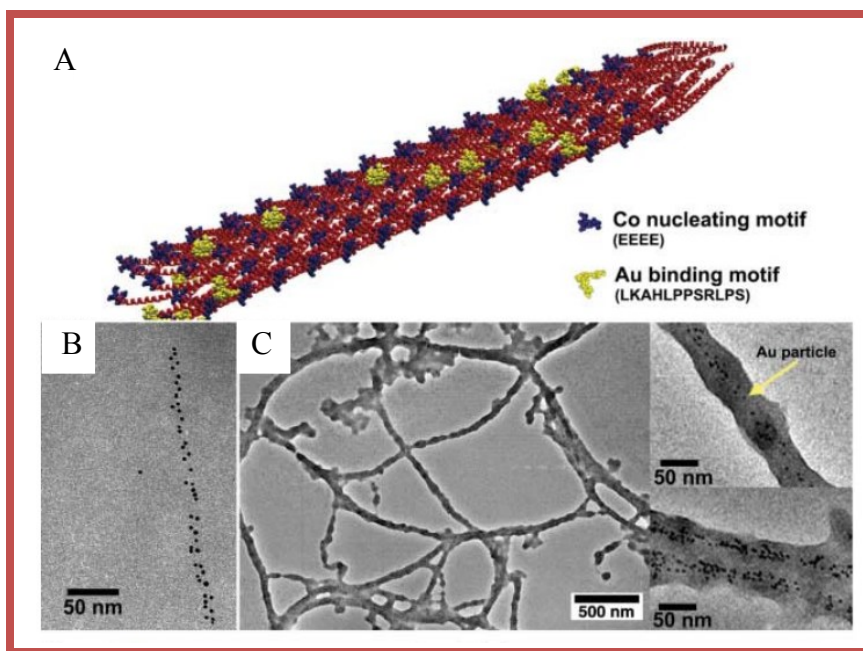


Figure 4.5: Depiction of the virus assembly with the modified proteins EEEE (blue) and LKAHLPPSRLPS (yellow) (A). Gold-virus assembly control without cobalt (B). Virus assembly template with both gold nanoparticles and cobalt oxide (C).

was not disrupted but the particles decorated the surface through hydrogen bonding (Figure 4.4 D). Interestingly, the gold incorporated microtubes did form from pillar[5]arene stabilized gold nanoparticles, but it took 2 months verse 2 weeks in a sample of pillar[5]arene and water.

The M13 virus has a cylinder structure made of mostly one type of protein with complimentary trace proteins wrapped around a strand of DNA.^[182] The virus can assemble to various lengths and proved to be a good template for colloidal nanoparticles. One set of proteins were modified with chelating a peptide that has an affinity to a cobalt chloride (EEEE) or premade gold nanoparticles (LKAHLPPSRLPS).^[183] The modified virus assembly was put into a solution of cobalt chloride to allow coordination to the EEEE peptide. The cobalt chloride was reduced with sodium boron hydride, followed by a spontaneous oxidation (due to water) and yielded cobalt oxide nanoparticles on the virus surface. The gold nanoparticles were then incorporated into the cobalt-virus assembly because of the selective peptide modification. The assembly survived the decoration of both nanoparticles and allowed for virus-virus interaction yielding lined up metal template nanorods, when formed into a monolayer during battery construction. The formed metal template nanorods behaved as an efficient anode in a Li/nanorod battery cell that reached 94% of the theoretical capacity.

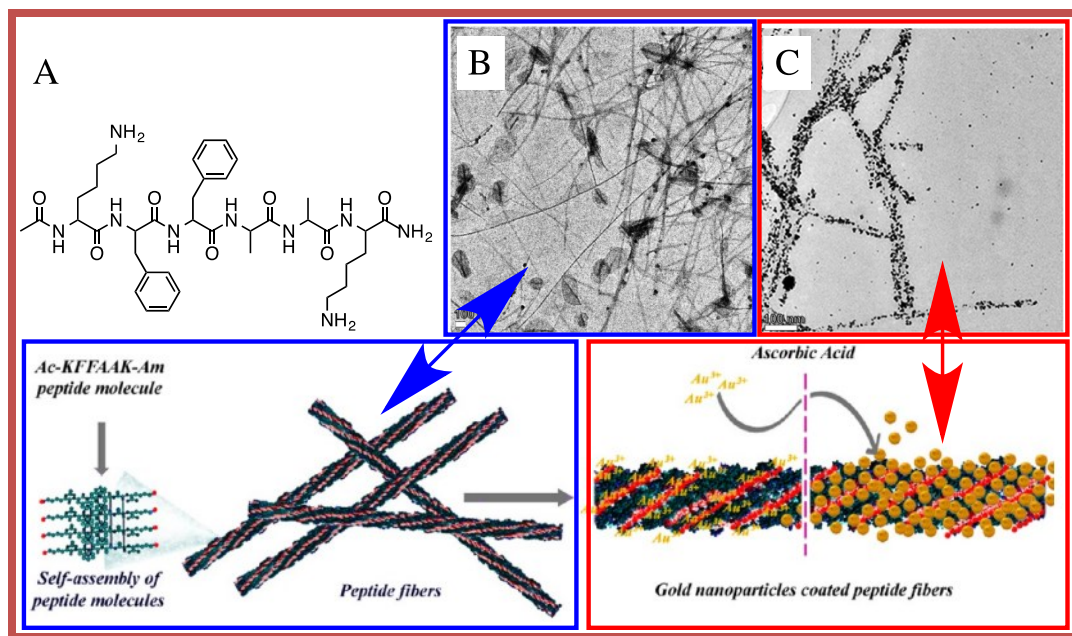


Figure 4.6: Hexapeptide molecular structure (A). TEM of the fiber assembly before and after addition of gold(III) tetrachloride anion (B and C). Self-assembly of the hexapeptide and the reduction of gold(III) onto the fiber (Bottom).

Peptides that form fibers through intermolecular β -sheet hydrogen bonding also proved to be suitable as a gold nanoparticle template (Figure 4.6).^[184] The sequence Ac-KFFAAK-NH₂ has adjacent phenylalanine amino acids and the presence of these two amino acids in a polypeptide promotes self-assembly into amyloid fibers and tubes due to π - π stacking and hydrophobicity.^[185] When the assembly forms, lysine provides the ammonium cation that attracts the tetrachloroauric anion. The ascorbic acid was used as the reducing agent, which reduced gold(III) in gold nanoparticles on the surface of the fiber assembly. These gold decorated fibers were drop casted between two conducting gold surfaces and the fiber exhibited tunnel-dominated conductance.

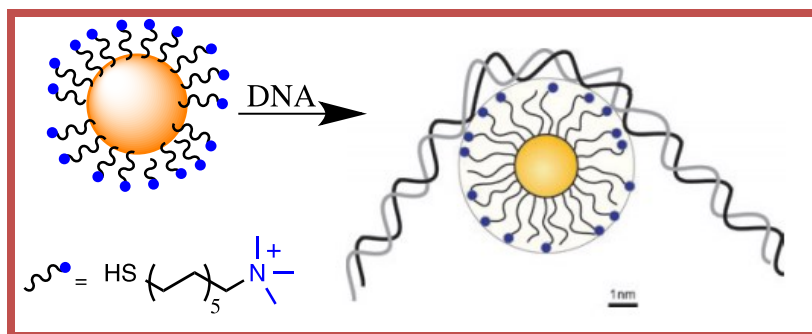


Figure 4.7: Depiction of the gold nanoparticle with a stabilizer the yields cationic surface interacting with a DNA strand.

Gold nanoparticles with a trimethyl ammonium cationic stabilizer have been used to bind to DNA and to protect the DNA from enzymatic degradation (Figure 4.7).^[186] The system is attractive for gene therapy where DNA can be delivered to the cell. Bending around the positively charged gold particle protected the initial linear anionic DNA from the enzyme DNase, which needs a linear system to cleave the DNA. Gold nanoparticles modified to have DNA binding peptides, CALNN-Linker-FQCGII (Linker is 1-aminohexanoic acid), attached to the surface will also decorate DNA (Figure 4.8 A).^[187] Initial gold nanoparticles were coated with CALNN peptides and these did not interact with the DNA. Upon further functionalization of the gold nanoparticle surface with the DNA binding peptide, the interaction between the gold nanoparticle and DNA became stronger as the amount of binding peptide increased. Two types of DNA assemblies were created: DNA created from two sequences that resulted in long DNA strands (Template 1), and a self-complementary short sequence that formed small DNA strands (Template 2) (Figure 4.8 B). The gold nanoparticles interacted with template 1

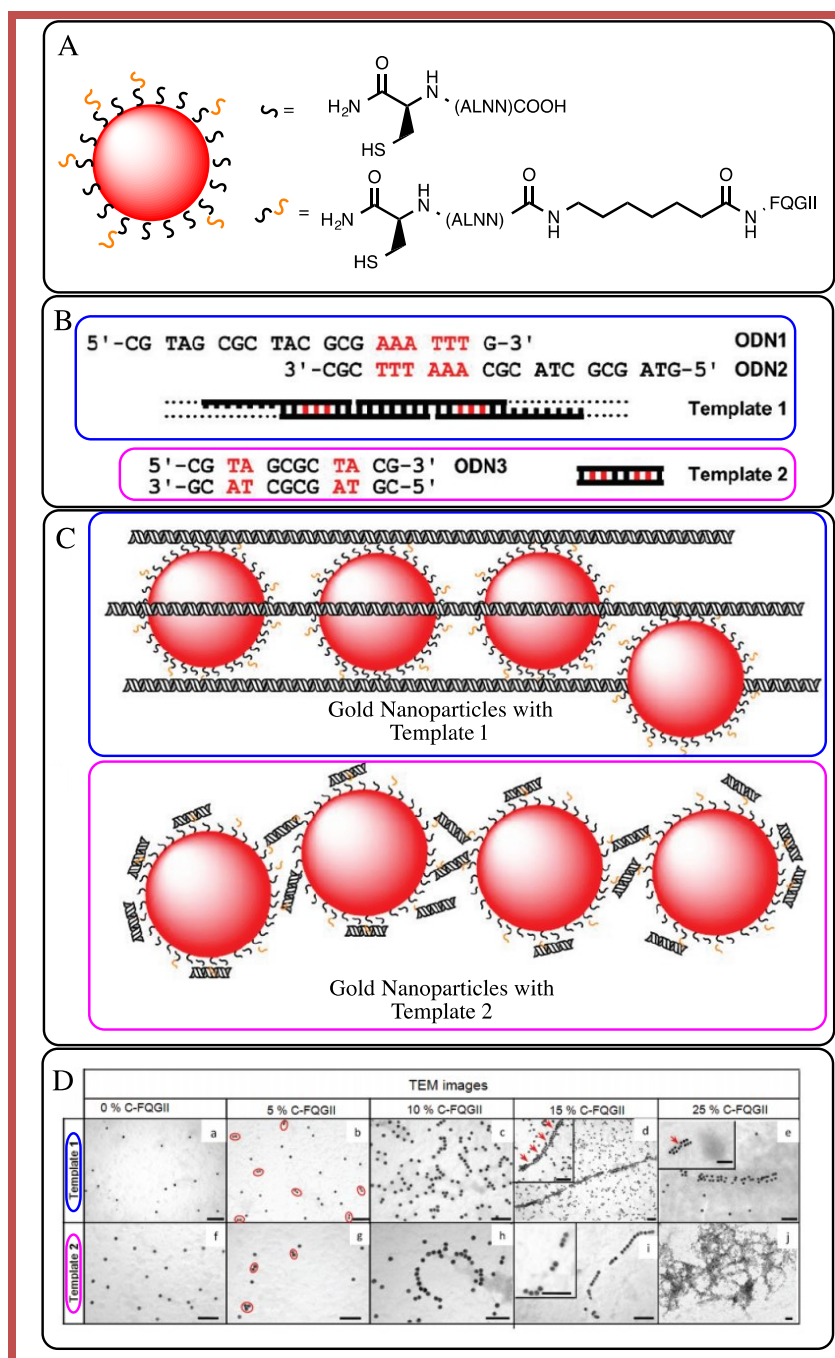


Figure 4.8: Peptide coated gold nanoparticle (A). Template 1 was made from two different sequences that yield long DNA strands and Template 2 was made from self-complementary sequences and yielded short DNA strands (B). Depiction of the modified gold nanoparticles interacting with Template 1 (Blue) and Template 2 (Purple) (C). TEM images of gold nanoparticles with increasing percentages of DNA binding peptides interacting with both DNA templates. The gold nanoparticles with 5% binding peptide start to interact with the DNA (red circles) (D).

and would use multiple long DNA strands, where the gold nanoparticles would act as the step in a ladder and form somewhat straight assemblies when at least 15% of the gold nanoparticle was covered with the DNA binding peptide (Figure 4.8 blue boxes). As for template 2, assembly was less linear and formed aggregates of gold nanoparticles when 25% of the gold nanoparticle was covered with the binding peptide. Here, the short DNA strands acted as linkers that connected the gold nanoparticles together (Figure 4.8 purple boxes).

Hydrogel forming fiber assemblies with strong π - π stacking has been used as gold nanoparticle templates (Figure 4.9).^[176a] The authors developed a molecular achiral gelator, a benzene core with three terpyridine branches, that had an affinity for gold(I). The gelator formed nanofibers and was not affected by the addition of gold. Interestingly, the fiber with gold(I) coordinated to the terpyridine branches, develops a

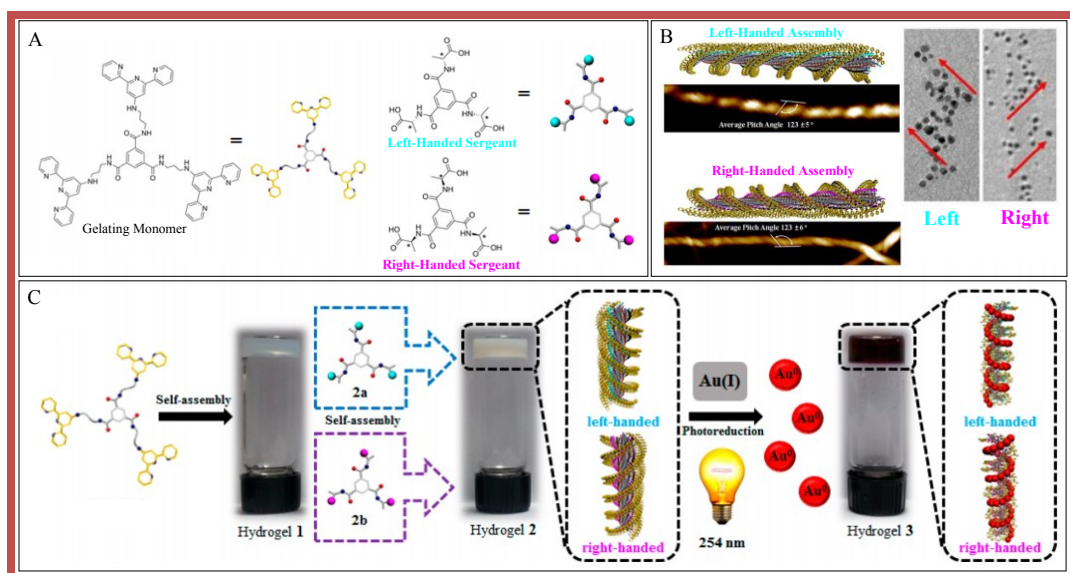


Figure 4.9: Molecular structures of the gelator and the chiral additives (A). The AFM of the left-handed and right-handed helical fibers, and TEM images of gold deposited on the right and left-handed helical fibers (B). Images of the gels formed of the achiral, chiral, and gold decorated fibers (C).

helical bias controlled by the sergeant-and-soldier effect. The sergeant was a chiral gelator and when a small amount was added to the achiral gelator, the soldier, a chiral nanofiber was formed. The sergeant gelator favors an *M* or *P*-helical nanofiber depending on the gelator's chirality and an unbalanced ratio (not 1:1) or a majority of *M* and *P* promoting subunits are present in solution. The soldier gelators will conform to the sergeant's chirality due to steric interactions, and form a helical fiber. The chelating gold(I) can be reduced with UV irradiation to yield colloidal gold in a helical configuration.

4.3 Research

Lysine-NDI amphiphilic molecules exhibit an ammonium cation in the polar head group.^[144] The NDI amphiphiles with diacetylene functionality displayed some robust characteristics toward conditional changes especially after polymerization, where the nanotube morphology was stable to elevated temperature and pH change. The directional assembling interaction was π - π stacking of the NDI core and the diacetylene tail, which enforces the robustness of the nanotube assembly. Small simple amphiphilic molecules that undergo self-assembly and lack intermolecular interactions, such as hydrogen-bonding and π - π stacking, are sensitive to conditional changes.^[188] Many surfactants are known to cover the surface of the colloidal nanoparticle, so the assembly will most likely fall apart and coat the gold nanoparticle due to stronger gold-ligand interaction.^[181] Amphiphilic assemblies used as gold nanoparticle templates are more rare and most templates designed for gold nanoparticle decoration involved a fixed surface such as carbon nanotubes, silica oxide, titanium oxide, and other inorganic surfaces.^[175b, 189] Larger molecules that undergo self-assembly with very strong intermolecular interactions such as peptides and larger proteins have shown to be stable enough to provide a compatible surface for in situ gold nanoparticle synthesis.^[184] The lysine-NDI-diacetylene (compound **A**) nanotube assembly would be stable to citrate addition and the gold(III) tetrachloride reduction because of the intermolecular π - π stacking between the NDIs and diacetylene. The ammonium on the lysine will attract citric acid/citrate coating the tube in reducing agent, followed by the addition of tetrachloroauric anion and reduce

the gold(III) on the tube surface decorating the tube with gold nanoparticles coat (Figure 4.10).

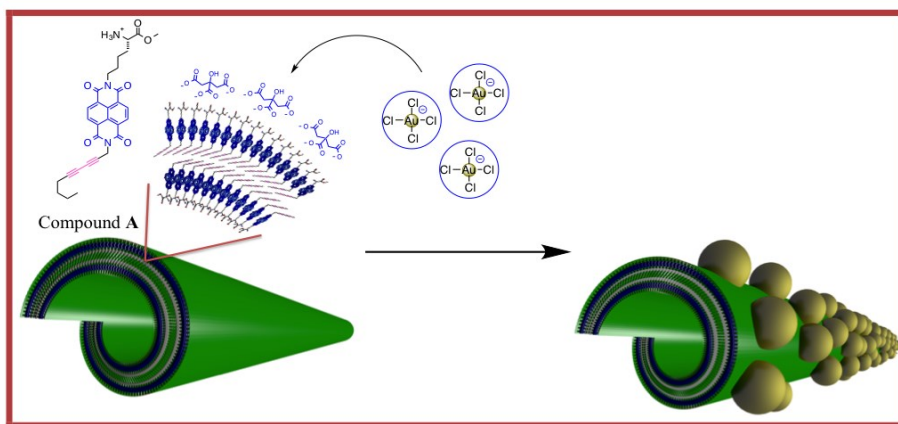


Figure 4.10: Depiction of the **A** amphiphilic assemblies being decorated with gold nanoparticles.

4.4 Results and Discussion

Compound **A** was soluble in neutral water and formed nanotube assemblies at a concentration of 2 mM. When citric acid (2 mM, 1 eq, pH = 3.4) was added to the solution, the pH decreased, and the nanotube morphology was similar to that found at pH = 7.0. When tetrachloroauric acid (0.67 mM, 0.67 eq) was added, the pH dropped slightly to 3.0. Examining the sample by TEM, spherical gold nanoparticles were observed on the surface of the nanotube (Figure 4.11 B). When these gold nanoparticles

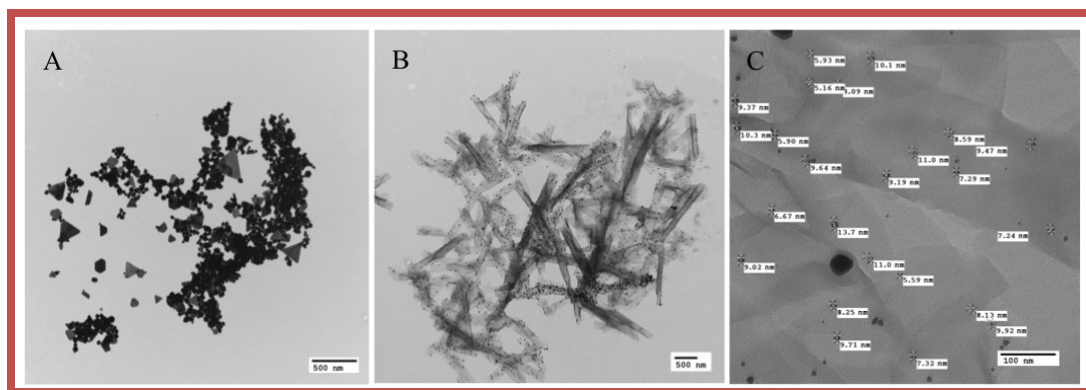


Figure 4.11: Control: TEM (carbon-coated grid and not stained) of citric acid and tetrachloroauric acid (3:2, 500 μ M citric acid) in water, aged for 1 d at pH = 3.3 (A). TEM of 1 equiv. of citric acid in a solution of compound **A** (500 μ M), followed by an addition tetrachloroauric acid (0.67 equiv.) and aged for 1 day at pH = 3.0 (B). Sizes of observed gold nanoparticles (C).

were compared to the same conditions in the absence of compound **A**, non-spherical particles were also observed (triangles and hexagons) (Figure 4.11 A). The nanotube template controls the growth of the nanoparticles similar to a stabilizing agent.^[172] The gold nanoparticles were measured to have a diameter of an average 7.6 nm for these conditions (Figure 4.11 C).

The order of addition, citric acid to the nanotube solution followed by the addition of tetrachloroauric acid, was critical in order to obtain spherical gold nanoparticles. The

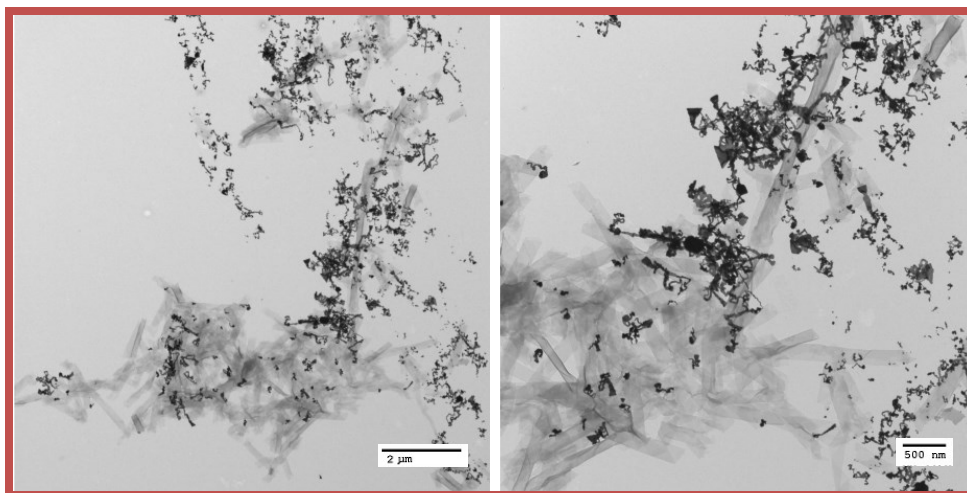


Figure 4.12: TEM of **A** (500 μM) and tetrachloroauric acid (333 μM) after the addition of citric acid (500 μM).

hypothesis was that the tetrachloroauric anion would interact with the ammonium cation and coat the tube surface where the citric acid would reduce the gold(III) giving an evenly decorated nanotube. When the citric acid (1 equiv., 1 mM) was added to the gold(III) (667 μM) and compound **A** solution (1 mM), irregular gold nanoparticles formed (Figure 4.12). As seen in previous reports, citric acid coordinates to the ammonium cations and allows controlled growth of the gold nanoparticle because the tube surface provides stability.^[179] Citric acid also acts as a stabilizing agent, so if the citric acid was added to the gold(III) coated nanotube the citric acid would be diluted and not concentrated on the tube. Therefore, as the nanoclusters of colloidal gold form, the lack of citric acid allows for agglomeration to occur. Another possibility for the behavior could be due to hydrolysis of the tetrachloroauric anion to trichloroauric hydroxide. The tetrachloroauric anion exists in water/NaCl solutions because of an increase in chloride

ion and ligand exchange was slowed.^[190] Perhaps the trichloroauric hydroxide was protonated in the acid pH forming a neutral species and had less affinity to the ammonium surface.

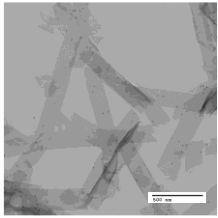
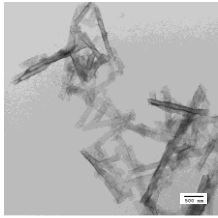
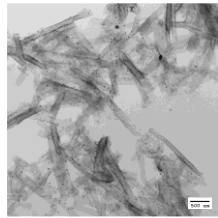
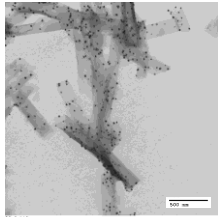
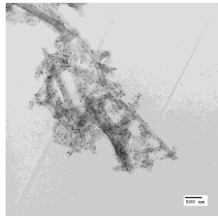
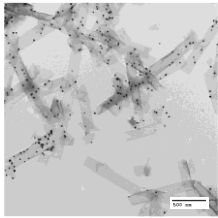
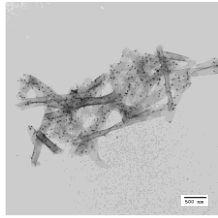
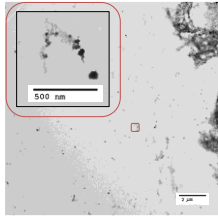
				
Ratio of Gold to Citric Acid	0.2	0.4	0.6	0.8
Concentration of Compound A and Citric Acid (μM)	417	357	308	268
Average Gold Nanoparticle Diameter (nm)	8.4	9.5	16.9	21.2
				
Ratio of Gold to Citric Acid	1.0	1.2	1.6	3.2
Concentration of Compound A and Citric Acid (μM)	233	204	158	60
Average Gold Nanoparticle Diameter (nm)	22.5	22.8	23.9	29.5

Table 4.1: Titration of A (500 μM) and citric acid (500 μM) with tetrachloroauric acid (1 mM).

A titration of a solution of compound A and citric acid (500 μM) with tetrachloroauric acid (1.0 mM) was performed to show the growth of the gold nanoparticles. Initially, the gold nanoparticles quickly grew as the ratio of gold(III): compound A reached a ratio of 0.8, where the diameter of the gold nanoparticles went from 8.4 nm at a ratio of 0.2 to 21.2 nm at a ratio of 0.8 (Table 4.1). Upon further increase of the gold(III): compound A ratio, the size growth stagnated due to the lack of

available reducing agent and reached a diameter of 23.9 nm when a ratio of 1.6 was reached. At a ratio of 3.2, gold(III): compound **A**, the concentration of compound **A** had been diluted (60 μM) enough, that the critical micellar concentration has been reached and the tubes started to break apart. The gold nanoparticle diameter in this sample increased significantly to 29.5 nm. The zoomed in image of the gold nanoparticles showed the amphiphile coating the particles. The gold nanoparticle diameter increase that occurred between a ratio of 1.0 and 1.6 was small (1.4 nm). To determine if the gold nanoparticle did have a surfactant coating, tetrachloroauric acid (5 mM, 10 equiv.) was added to compound **A**: citric acid (1:1, 500 μM) (1:1 v:v) resulting in a 250 μM

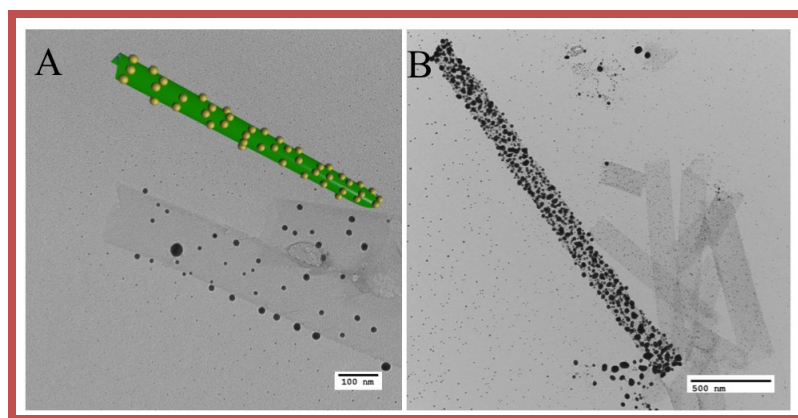


Figure 4.13: TEM images of gold decorated compound **A** in water (250 μM , 10 equiv. HAuCl_4 , and 250 μM citric acid) (A and B).

concentration of compound **A**. This will yield a concentration where the nanotubes do not deteriorate. Most nanotubes did show an even coating of gold nanoparticles between 6 nm to 25 nm in diameter (Figure 4.13). Close examination of the gold nanoparticles revealed that the particles had clean curved edges without a noticeable surfactant coating.

Gold nanoparticles have been shown to have an affinity to acetylene functionalities and acetylene groups are known to coordinate to metal.^[191] With cationic surfactants, gold nanoparticles with a citrate coating interact through electrostatic charge. To rule out acetylene coordination and demonstrate that the decoration process was electrostatic, auric acid was reduced in the presence of assembled NH₂-Lys(NDI-*n*Bu)-OMe (**4.4**) nanotubes and citric acid. Unfortunately, the nanotube morphology was not stable under these conditions (500 μ M **4.4**, 500 μ M citric acid, and 333 μ M) and irregular

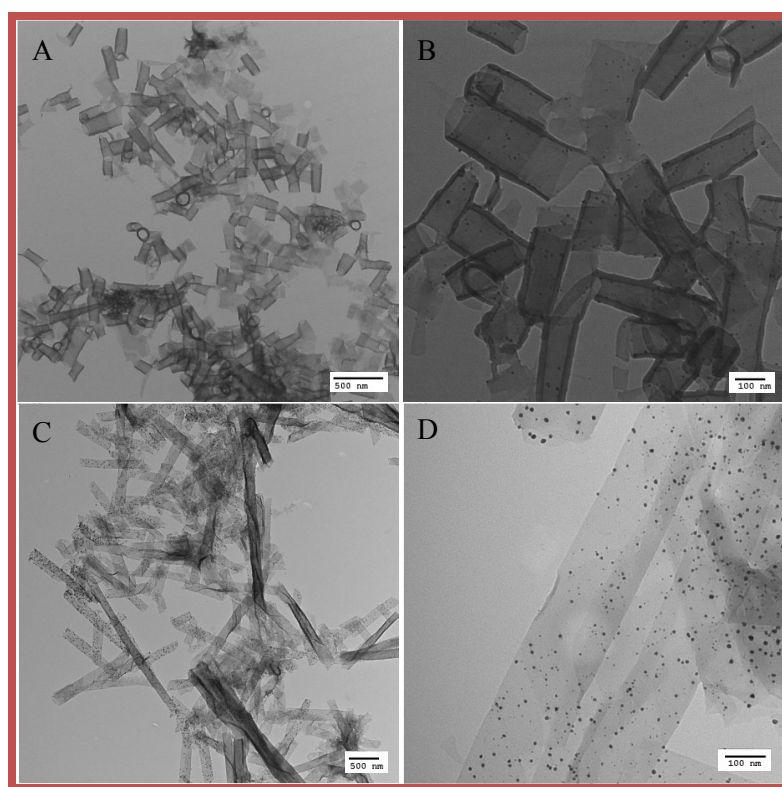


Figure 4.14: TEM of NH₂-Lys(NDI-*n*Bu)-OMe (**4.4**) in water (500 μ M, 1 eq sodium citrate, 0.67 eq HAuCl₄) at pH = 5.2 (A and B). TEM of compound **A** in water (500 μ M, 1 eq sodium citrate, 0.67 eq HAuCl₄) at pH = 5.2 (C and D).

aggregates were observed. To see if the lower pH was the cause, the citric acid was replaced with sodium citrate to increase the pH to 5.2. Even though the original long

narrow nanotube morphology was not observed when the assembly was at neutral pH, shorter and wider nanotubes formed (Figure 4.14 A and B).^[144] In a solution of **4.4** (1 mM) and sodium citrate (1 mM) was added gold(III) (0.67 mM) and gold nanoparticles once again formed on the surface of the nanotubes, which suggested strong electrostatic interactions do occur between the gold nanoparticles and the nanotube surface. The gold nanoparticles were very uniform in size ranging 9.0 to 13 nm in diameter and evenly dispersed.

Under the same condition but with compound **A** (1:1 sodium citrate, 0.67 equiv. tetrachloroauric acid), the nanotube morphology was retained and the gold nanoparticles were dispersed evenly, more so than the samples using citric acid (Figure 4.9 C and D). The sizes of the gold nanoparticles were once again in the range of 9.0 to 13 nm in diameter. As seen with other research involving the gold decorating of templates, the pH was an important factor.^[177] The sodium citrate will be attracted to the positive nanotube surface more so than more neutral citric acid. The pKa of the mono- and disodium citrate was 4.77 and 5.19 respectively and the pKa of citric acid was 3.15. The more basic the solution, sodium citrate formation would be more favorable, therefore having an increased negative formal charge. The increase in formal negative charge increases the

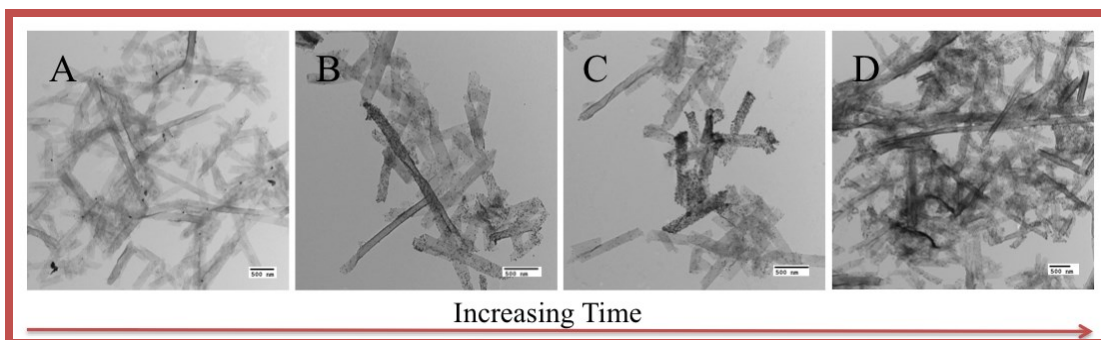


Figure 4.15: TEM of **A** (500 μM) and sodium citrate (500 μM) with tetrachloroauric acid (333 μM) aged for 1 day: gold nanoparticle diameter average – 13.4 nm (A), 2 day – 12.9nm (B), 3 day – 12.0 nm (C), 4 day – 14.4 nm (D).

electrostatic interaction with ammonium tube surface. Having more reducing agent on the surface of the nanotube will result in more colloidal gold nanocluster nodes, which will further grow into evenly dispersed nanoparticles.

The main purpose of a template for gold nanoparticles was to increase the stability of a gold nanoparticle and prevent agglomeration. A solution of tetrachloroauric acid (0.67 mM, 0.67 equiv.) was added to a solution of **A** (1 mM) and sodium citrate (1 mM) and aged for up to 4 days (Figure 4.15). After 4 days of aging, the gold

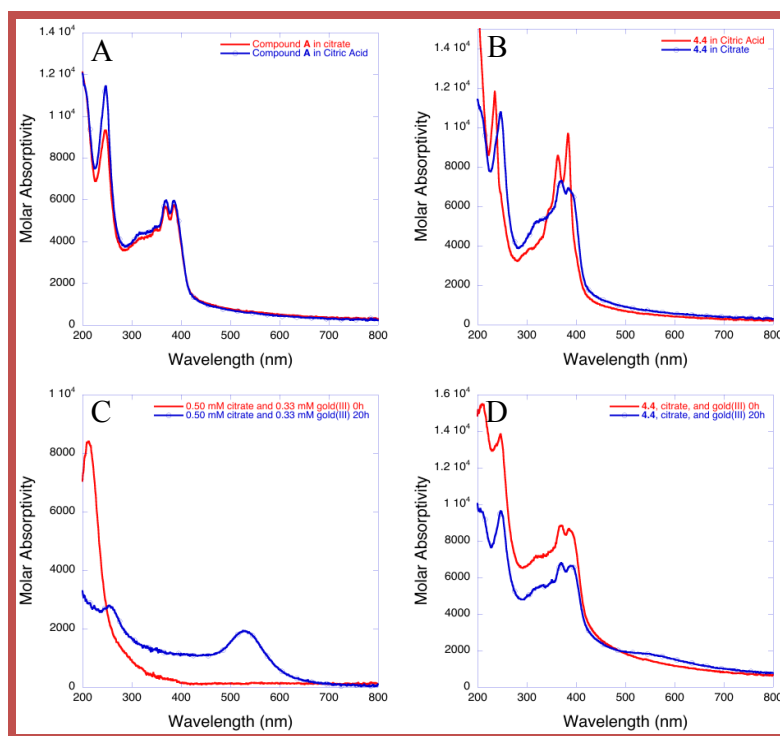


Figure 4.16: UV-Vis of **A** in sodium citrate (red) or citric acid (blue) (A), and **4.4** in sodium citrate (red) or citric acid (blue) (B). Time dependent UV-Vis of the reduction of tetrachloroauric acid (333 μ M) with sodium citrate (500 μ M): 0h (red) and 20h (blue) (C). Time dependent UV-Vis of the reduction of tetrachloroauric acid (333 μ M) with sodium citrate (500 μ M) in the presence of **4.4**: 0h (red) and 20h (blue) (C).

nanoparticles did not agglomerate according to the measured average gold nanoparticle diameter. The average diameter of the gold nanoparticles in each sample ranged from 12.0 nm to 14.4 nm. The nanotubes showed to stabilize the gold nanoparticles and prevented agglomeration for up to 4 days.

Nano-sized gold nanoparticles can absorb UV light due to surface plasma oscillations.^[184] The size of the particle was determined to be directly related to the absorption wavelength.^[192] The absorption of **4.4** showed the NDI band I (330 nm to 390 nm) and II (240 nm to 270 nm) absorptions, but lacks any absorption higher than 400 nm

(Figure 4.16 B). When gold(III) (333 μM) was reduced without amphiphile **A** or **4.4** in sodium citrate (500 μM) in 20h at room temperature, an absorption of 525 nm appeared, indicating gold nanoparticle formation. In the presence of amphiphile **4.4**, a similar absorption appeared in the same region, but slightly red shifted (550 nm). Therefore, the gold nanoparticles on the surface of the tube clearly were different than without amphiphilic templates and the red shift (an increase in absorbance wavelength) indicates a larger spherical particle.^[192]

4.5 Conclusion

Initially, citric acid was used as the reducing agent, but when the pH was increased using sodium citrate, gold nanoparticles formed much more evenly with a diameter of 9 to 13 nm. The reducing agent, sodium citrate, also allowed more dispersed gold coverage on the surface of the nanotubes that absorbed at 550 nm. The absorption indicates that the nanoparticles are spherical as seen in TEM. Between the two nanostructures formed from lysine-NDI amphiphile, the amphiphile with the diacetylene functionality, compound **A**, appears to be most stable in the gold decorating conditions before polymerization. This stability could be due to the π - π stacking between the diacetylenes, which amphiphile **4.4** lacks. Nanotubes produced from compound **A** has potential to be an interesting platform for gold heterogeneous catalysis because of the ability to lock the structure through polymerization. The polymerized nanotubes are stable to elevated temperatures and to pH conditions, therefore varying conditions can be

achieved to optimize the reactions. Also, the polymer can be used to examine the conducting properties of this material.

4.6 Methods and Experimentals

General Methods

All FT-IR spectra were collected on a PerkinElmer Spectrum 100 FT-IR spectrometer at ambient temperature. Transmission electron microscopy (TEM) was performed with Technai G2 Spirit instrument operating at 80 kV. All reactions were performed under argon or nitrogen atmosphere. Solution-state ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-250, DPX-400, or DPX-500 instrument as indicated. Dimethylformamide (DMF) was dried by distillation from MgSO_4 . Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents. HPLC was done with reverse-phased preparative Waters XBridge C8 column eluting with a linear gradient of CH_3CN /water (20/80 to 100/0 over 40 minutes, 0.1 % TFA). Purity was assessed by analytical reverse-phase HPLC. All water used for sample solutions was HPLC grade and passed through membrane filter (0.02 μm) before use.

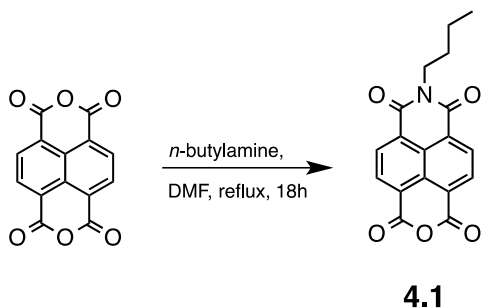
Transmission Electron Microscopy Measurements

10 μL of sample solution was applied to a carbon-coated copper grid (Ted Pella, Inc.) for 2 min without uranyl acetate negative stain. The dried specimen was observed with

Technai G2 Spirit TEM instrument operating at 80 keV, and data were analyzed with Image pro software.

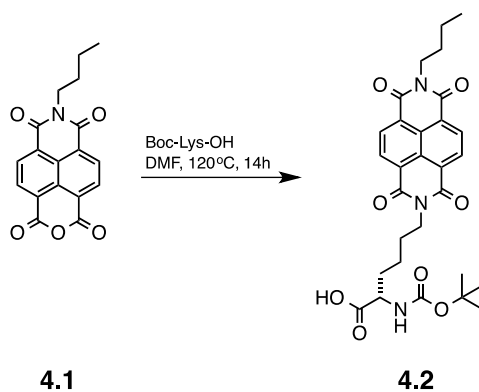
General Gold Decoration Procedure

The amphiphile was dissolved in water (2 mM, pH=7) and aged for 12h. Sodium citrate or citric acid was added to the solution (2 mM, 1:1 amphiphile: citrate) to give a 1 mM solution of nanotubes coated in citrate. Tetrachloroauric acid (0.667 mM) was added to the solution to give a amphiphile: citrate:gold ratio of 1:1:0.67 (500 μ M: 500 μ M: 333 μ M) and aged for an additional 12 h at room temperature.

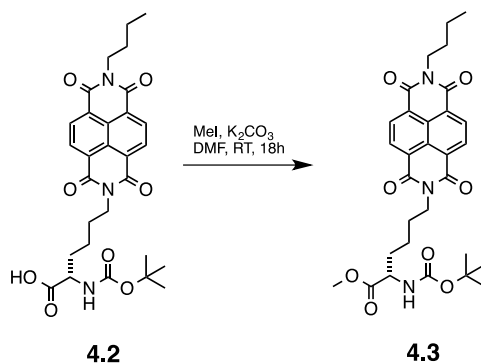


***n*-Bu-NMA 4.1:**^[25b] 1,4,5,8-Naphthalenetetracarboxylic dianhydride (9.65 g, 35.9 mmol) was dissolved in DMF (300 mL) and degassed with nitrogen. The mixture was heated to 140 °C and a solution of *n*-butylamine (2.59 g, 35.3 mmol, 3.50 mL) in DMF (50 mL) was added dropwise to the dianhydride solution via addition funnel over 2h. The solution was heated to reflux and was left and stirred for 18h. The reaction was allowed to cool

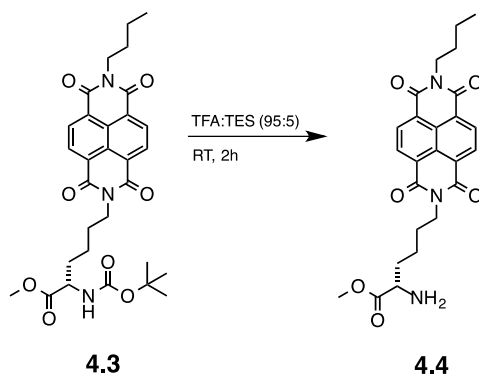
and was then placed in the freezer for 1h. A brown precipitate formed and was filtered. The filtrate condensed via vacuum short-path distillation. The remaining residue was purified with flash column chromatography (CHCl_3) to yield a yellow solid n-butyl-naphthalene monoanhydride **4.1** (1.51 g, 4.48 mmol, 13%). ^1H NMR (250 MHz, CDCl_3) δ 1.00 (t, $J = 3.6$ Hz, 3H), 1.46 (m, 2H), 1.73 (m, 2H), 4.21 (t, $J = 3.9$ Hz, 2H), 8.82 (s, 4H).



Boc-Lys-(NDI-*n*Bu)-OH 4.2: Compound **4.1** (1.51 g, 4.48 mmol) was combined with Boc-Lys-OH (1.08 g, 4.37 mmol) in DMF (110 mL). The solution was heated to 120 °C and was left to stir for 14h under inert atmosphere. DMF was removed via short-path vacuum distillation. The remaining residue was purified with column chromatography (CHCl_3 , 1% MeOH/ CHCl_3 , up to 10 % MeOH/ CHCl_3) to yield a yellow solid Boc-Lys-(NDI-*n*Bu)-OH **4.2** (1.21 g, 2.19 mmol, 53%). ^1H NMR (250 MHz, CDCl_3) 0.99 (t, $J = 3.7$ Hz, 3H), 1.35-1.55 (m, 13H), 1.68-1.79 (m, 5H), 1.97 (m, 1H), 4.20 (t, $J = 3.8$ Hz, 4H), 4.30 (m, 1H), 8.74 (s, 4H).



Boc-Lys-(NDI-*n*Bu)-OMe 4.3: Compound **4.2** (0.30 g, 0.55 mmol) was dissolved in DMF (1.2 mL) and potassium carbonate (0.23 g, 1.6 mmol) was added. Methyl iodide (0.23 g, 1.6 mmol, 0.10 mL) was then added via syringe. The reaction stirred for 18 h. The remaining solid was dissolved in ethyl acetate and washed with water (3 x 75 mL). The organic layer was dried with Na₂SO₄. The crude residue was purified via flash column chromatography (0.5% MeOH/CHCl₃) to give a yellow solid Boc-Lys-(NDI-*n*Bu)-OMe **4.3** (0.14 g, 0.24 mmol, 44%). ¹H NMR (400 MHz; CDCl₃): δ 8.74 (s, 4H), 5.09 (d, *J* = 7.0, 1H), 4.34-4.25 (m, 1H), 4.19 (t, *J* = 7.2, 4H), 3.74 (s, 3H), 1.93-1.84 (m, 1H), 1.82-1.69 (m, 6H), 1.68-1.00 (m, 1H), 1.53-1.44 (m, 5H), 1.42 (s, 9H), 0.98 (t, *J* = 7.2, 3H); ¹³C NMR (100 MHz; CDCl₃): δ 173.4, 163.0, 162.9, 155.5, 131.4, 131.0, 126.9, 126.8, 126.6, 80.0, 77.4, 53.5, 52.4, 40.9, 40.5, 32.4, 30.3, 28.5, 27.7, 22.9, 20.5, 13.9.



NH₂-Lys-(NDI-*n*Bu)-OMe 4.4:^[25b] Compound **4.3** (0.78 g, 1.4 mmol) was dissolved in 95:5 TFA:TES (1 mL). The solution was left for 2h in a capped vial. The solvent was removed via blowing nitrogen over the surface of the solution. The remaining solid was dissolved in water and acetonitrile and purified via reverse phase HPLC to yield NH₂-Lys-(NDI-*n*Bu)-OMe **4.4** (0.38 g, 0.82 mmol, 58 %). ¹H NMR (500 MHz, DMSO-*d*₆) 0.94 (t, *J* = 7.0 Hz, 3H), 1.35-1.41 (m, 4H), 1.62-1.71 (m, 4H), 1.82-1.86 (m, 2H), 3.76 (s, 3H), 4.07 (m, 5H), 8.30 (s, 3H), 8.68 (s, 4H).

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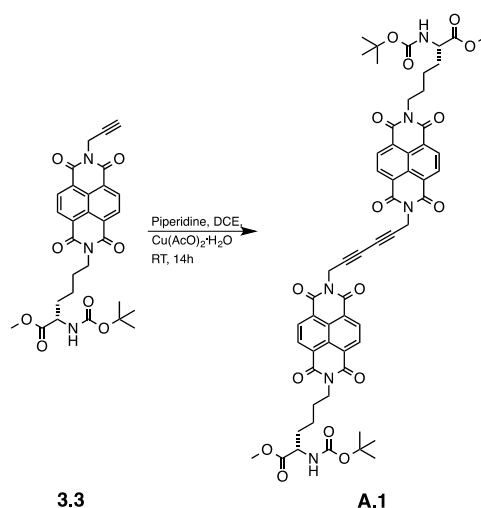
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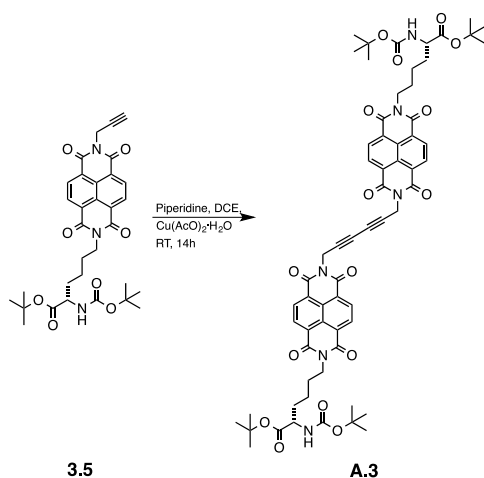
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Appendix A: Procedures of Diacetylene Derivatives



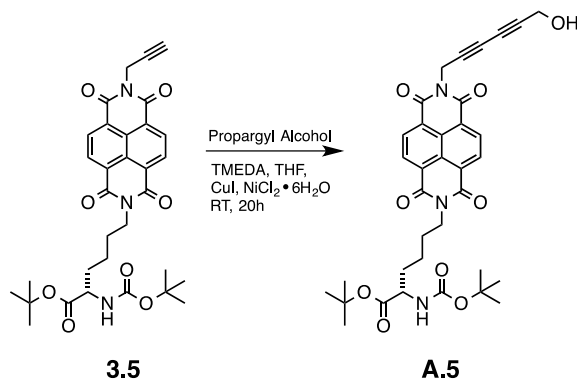
Boc-K(DiNDIDA)-OMe (A.1): A flask was charged with **3.3** (200 mg, 0.365 mmol), piperidine (95 mg, 1.11 mmol, 108 μL), and dichloroethane (0.860 mL). **3.3** was allowed to dissolve and the solution was stirred. To the brown solution, copper acetate monohydrate (8 mg, 0.04 mmol, 10 mol%) was added. The solution was allowed to stir in the open air for 14h. The remaining solvent was removed and the resulting solid was re-dissolved in chloroform (20 mL). This pink material was purified via column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97%/3.0%) to yield **A.1** (187 mg, 0.171 mmol, 94%). dec pt 179-183 $^\circ\text{C}$; ^1H NMR (400 MHz; CDCl_3): δ 8.76 (s, 8H), 5.09 (d, $J = 8.1$, 2H), 5.00 (s, 4H), 4.30 (q, $J = 6.2$, 2H), 4.23-4.16 (m, 4H), 3.75 (s, 6H), 1.91-1.85 (m, 3H),

1.81-1.70 (m, 12H), 1.49-1.47 (m, 4H), 1.43 (s, 18H); ^{13}C NMR (100 MHz; CDCl_3): δ 173.4, 162.8, 162.0, 155.5, 131.5, 131.2, 127.1, 126.9, 126.9, 126.3, 80.0, 77.4, 72.8, 67.4, 53.4, 52.4, 40.6, 32.5, 30.6, 29.0, 28.5, 27.7, 22.9; IR (KBr) ν 3377, 3082, 3041, 2957, 2929, 2866, 1976, 1742, 1708, 1662, 1581, 1518, 1454, 1410, 1392, 1374, 1355, 1338, 1299, 1244, 1222, 1178, 1120, 1073, 1014, 985, 893, 807, 770, 734, 714, 653, 616, 565 cm^{-1} ; ESI-MS calcd. for $\text{C}_{35}\text{H}_{37}\text{N}_3\text{O}_8$ $[\text{M}+\text{Na}]^+$, found .



Boc-K(DiNDIDA)-OtBu (A.3): A flask was charged with **3.5** (100 mg, 0.170 mmol), piperidine (44 mg, 0.51 mmol, 50 μL), and dichloroethane (0.40 mL). **3.5** was allowed to dissolve and the solution was stirred. To the brown solution, copper acetate monohydrate (3 mg, 0.02 mmol, 10 mol%) was added. The solution was allowed to stir in the open air for 14h. The remaining solvent was removed and the resulting solid was re-dissolved in chloroform (20 mL). This pink material was purified via column chromatography

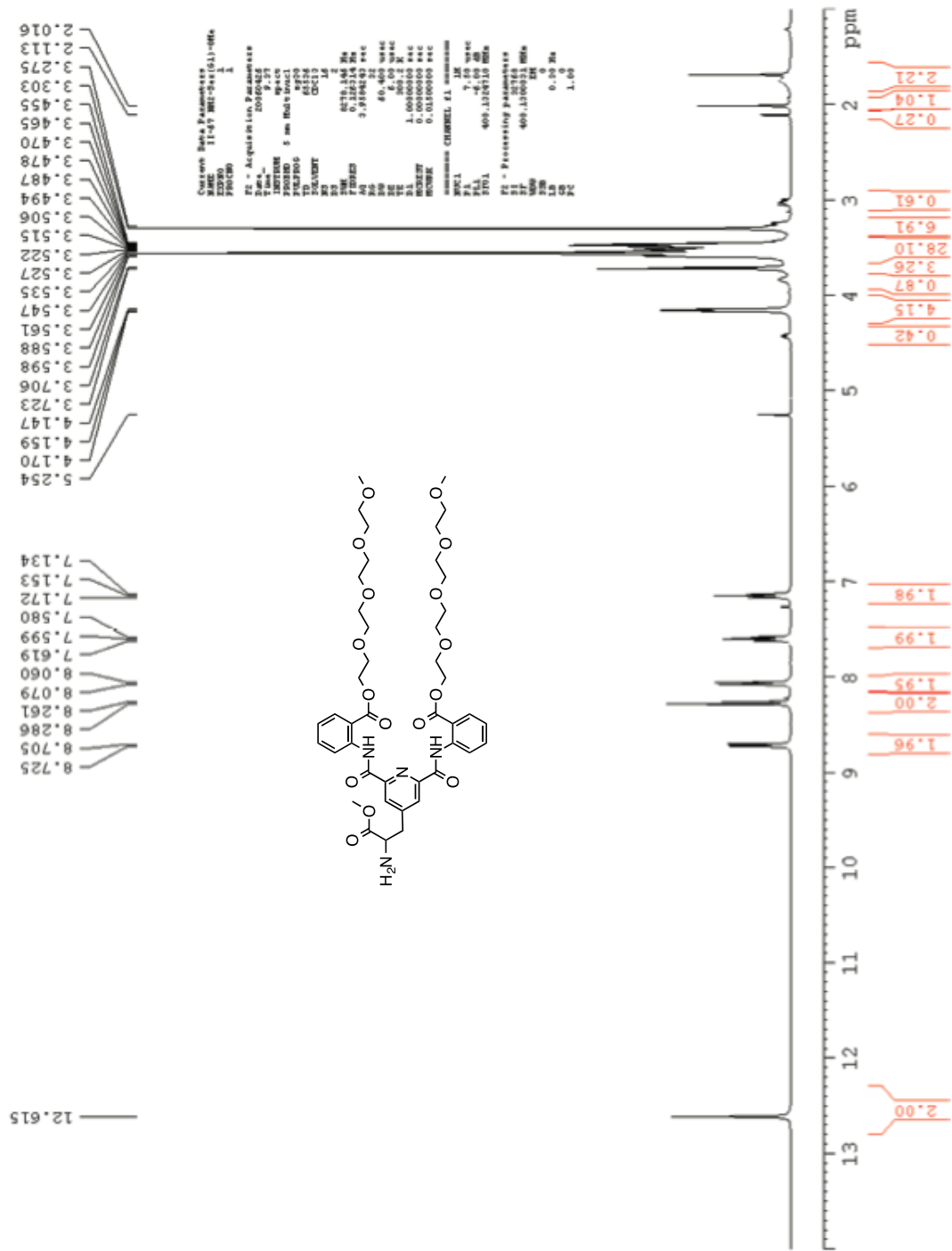
(88 μ L) and then added to the reaction and stirred in the open air for 20 h. The solvent was removed in vacuo and dissolved in minimal amount of chloroform. The material was purified via silica chromatography (CHCl_3) to yield a pink solid (115 mg, 0.191 mmol, 87%). ^1H NMR (500 MHz; CDCl_3): δ 8.77 (dd, $J = 11.0, 7.5$, 4H), 5.11 (d, $J = 7.8$, 1H), 5.02 (s, 2H), 4.29-4.28 (m, 1H), 4.25 (s, 2H), 4.21-4.17 (m, 2H), 3.74 (s, 3H), 2.13 (s, 1H), 1.92-1.84 (m, 1H), 1.83-1.73 (m, 4H), 1.54-1.46 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz; CDCl_3): 173.4, 162.9, 162.1, 155.5, 131.5, 131.2, 127.1, 126.9, 126.9, 126.3, 80.0, 76.8, 73.9, 69.8, 67.2, 53.4, 52.4, 51.4, 40.6, 32.4, 30.6, 28.4, 27.7, 22.9 δ ; IR (KBr) ν 3483, 3354, 3083, 3045, 2952, 2937, 2858, 2258, 1982, 1747, 1705, 1685, 1659, 1582, 1521, 1456, 1411, 1392, 1374, 1357, 1335, 1246, 1218, 1179, 1165, 1122, 1066, 1029, 992, 967, 920, 894, 863, 806, 771, 729, 717, 634, 606, 595, 561, 530 cm^{-1} ; ESI-MS calcd. for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_9$ $[\text{M}+\text{Na}]^+$ 624.2185, found 624.1958.

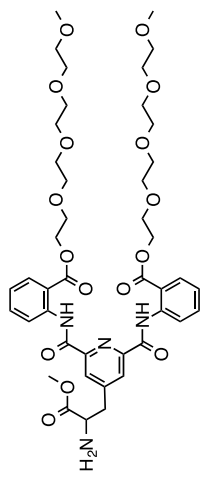


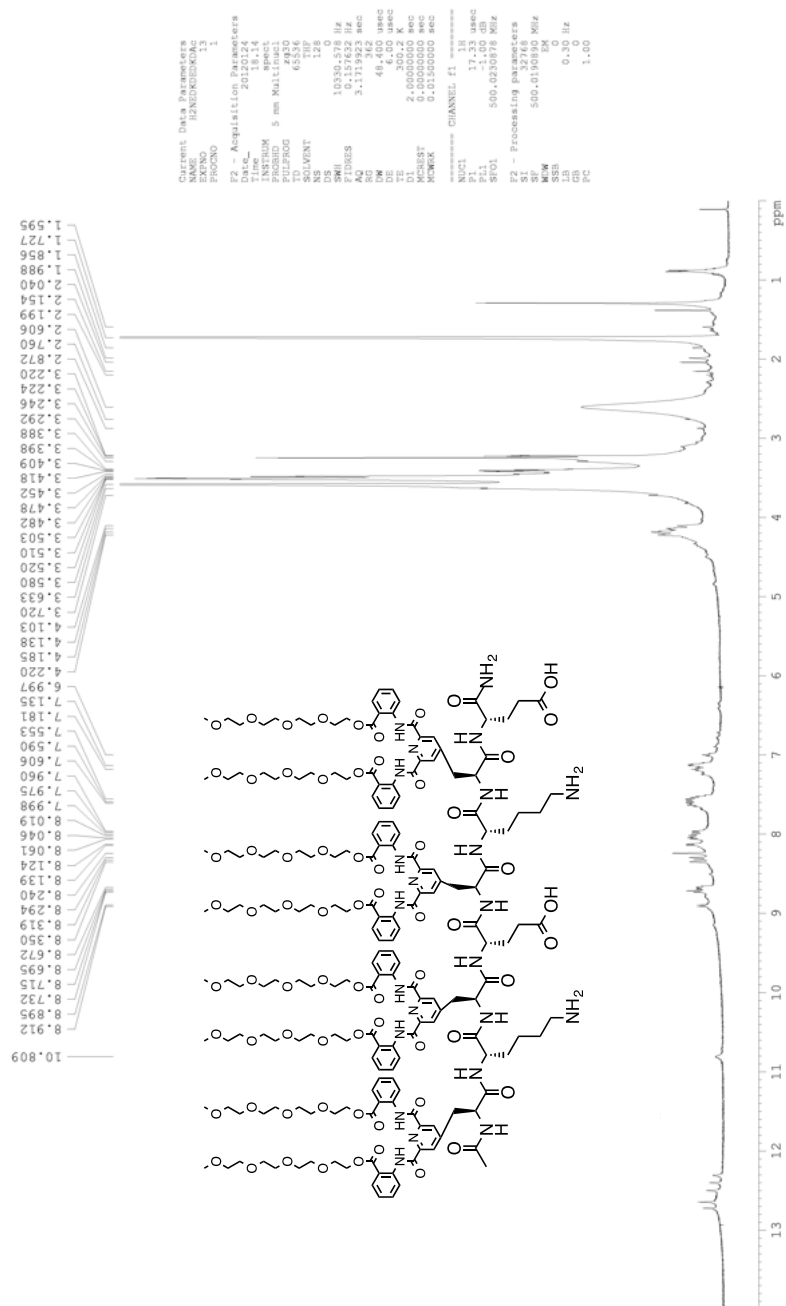
Boc-Lys(NDIDA-OH)-OtBu (A.5): A flask was charged with $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (3.0 mg, 1.1 μmol , 5 mol%) and THF (100 μL). Copper (I) Iodide (2.5 mg, 11 μmol , 5 mol%) followed by TMEDA (5.9 mg, 44 μmol , 8.0 μL , 20 mol%) were added to the reaction

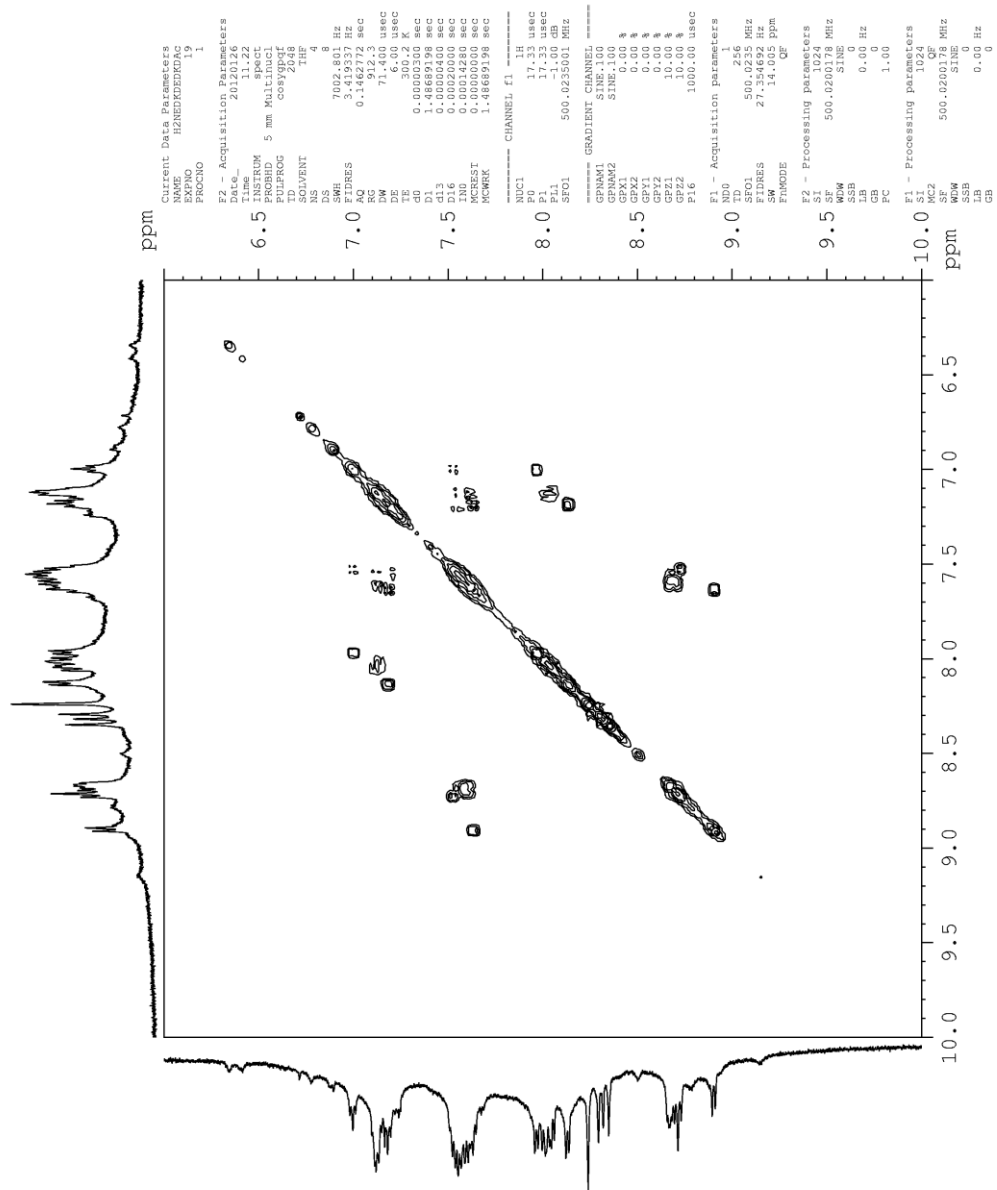
vessel and stirred to dissolve. Propargyl alcohol (16 mg, 1.3 mmol, 74 μ L) was added and stirred for 5 min. Boc-Lys(NDIMA)-OMe (**3.5**) (150 mg, 0.255 μ mol) was dissolved in THF (100 μ L) and then added to the reaction and stirred in the open air for 20 h. The solvent was removed in vacuo and dissolved in minimal amount of chloroform. The material was purified via silica chromatography (CHCl_3) to yield a pink solid (98 mg, 0.15 mmol, 59%). ^1H NMR (500 MHz; CDCl_3): δ 8.81 (q, $J = 6.5$, 4H), 5.07 (s, 2H), 4.30 (s, 2H), 4.23 (t, $J = 7.5$, 2H), 4.19-4.17 (m, 1H), 1.85-1.79 (m, 3H), 1.73-1.69 (m, 3H), 1.54-1.50 (m, 1H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (126 MHz; CDCl_3): ; IR (KBr) ν 3492, 3380, 3082, 3044, 2978, 2932, 2864, 2258, 1979, 1707, 1667, 1582, 1507, 1455, 1411, 1392, 1370, 1357, 1333, 1246, 1179, 1155, 1121, 1068, 1028, 992, 965, 920, 891, 847, 808, 770, 729, 716, 605, 578, 562 cm^{-1} ; ESI-MS calcd. for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_9$ $[\text{M}+\text{H}]^+$ 644.2603, found 644.2180.

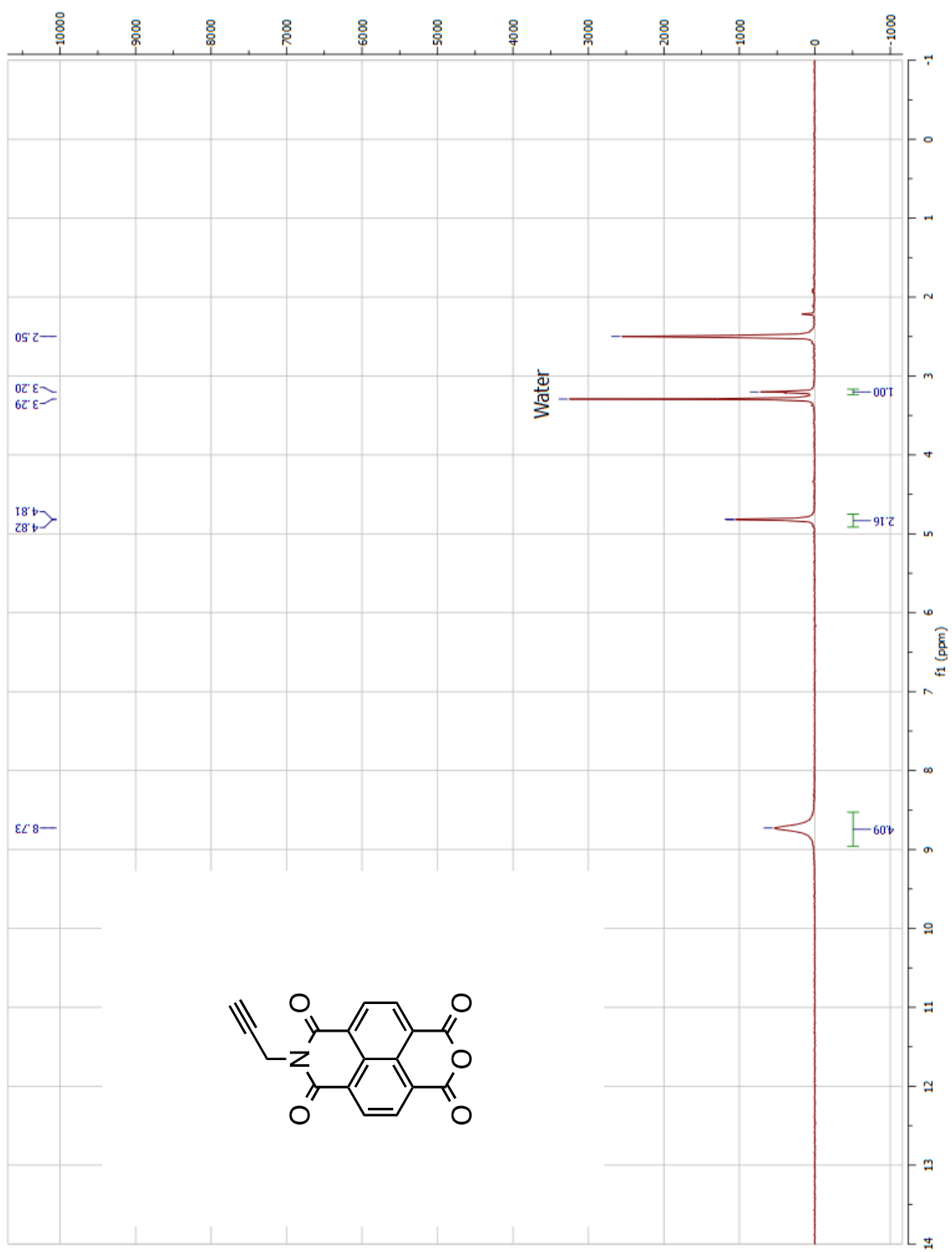
Appendix B: NMR Spectrum

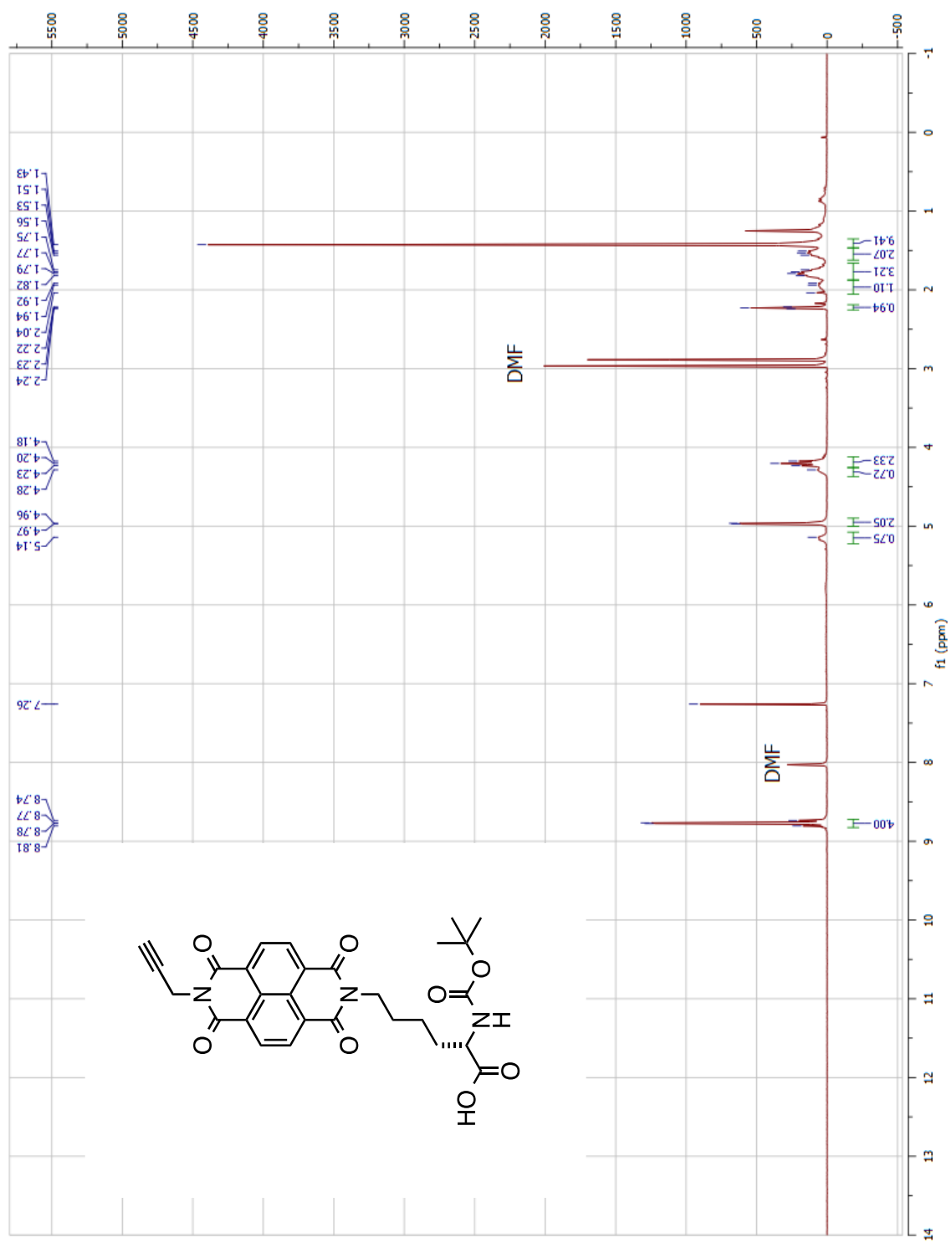


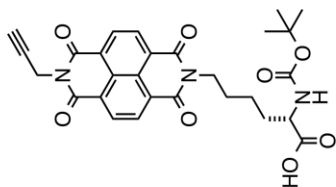
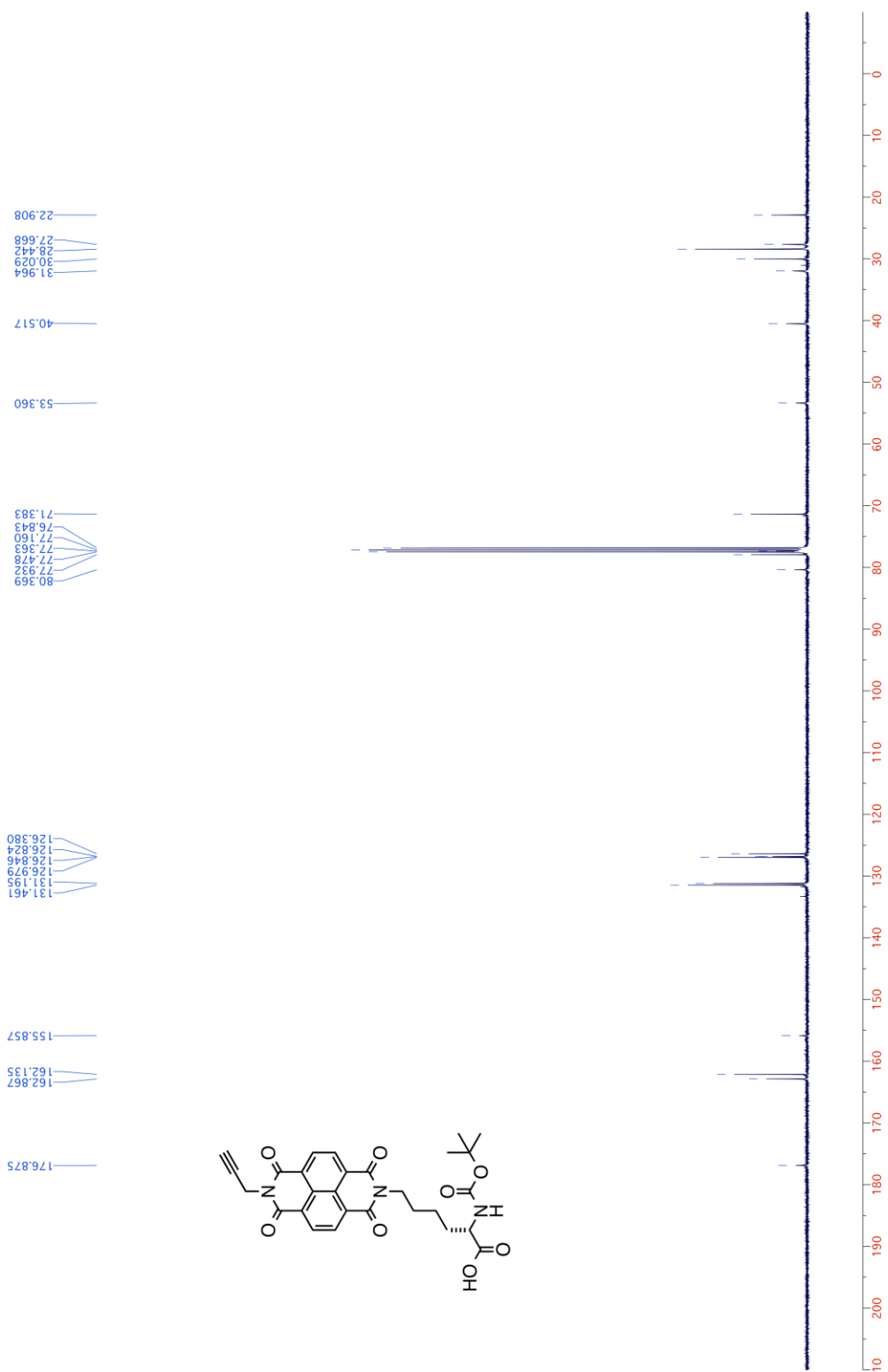


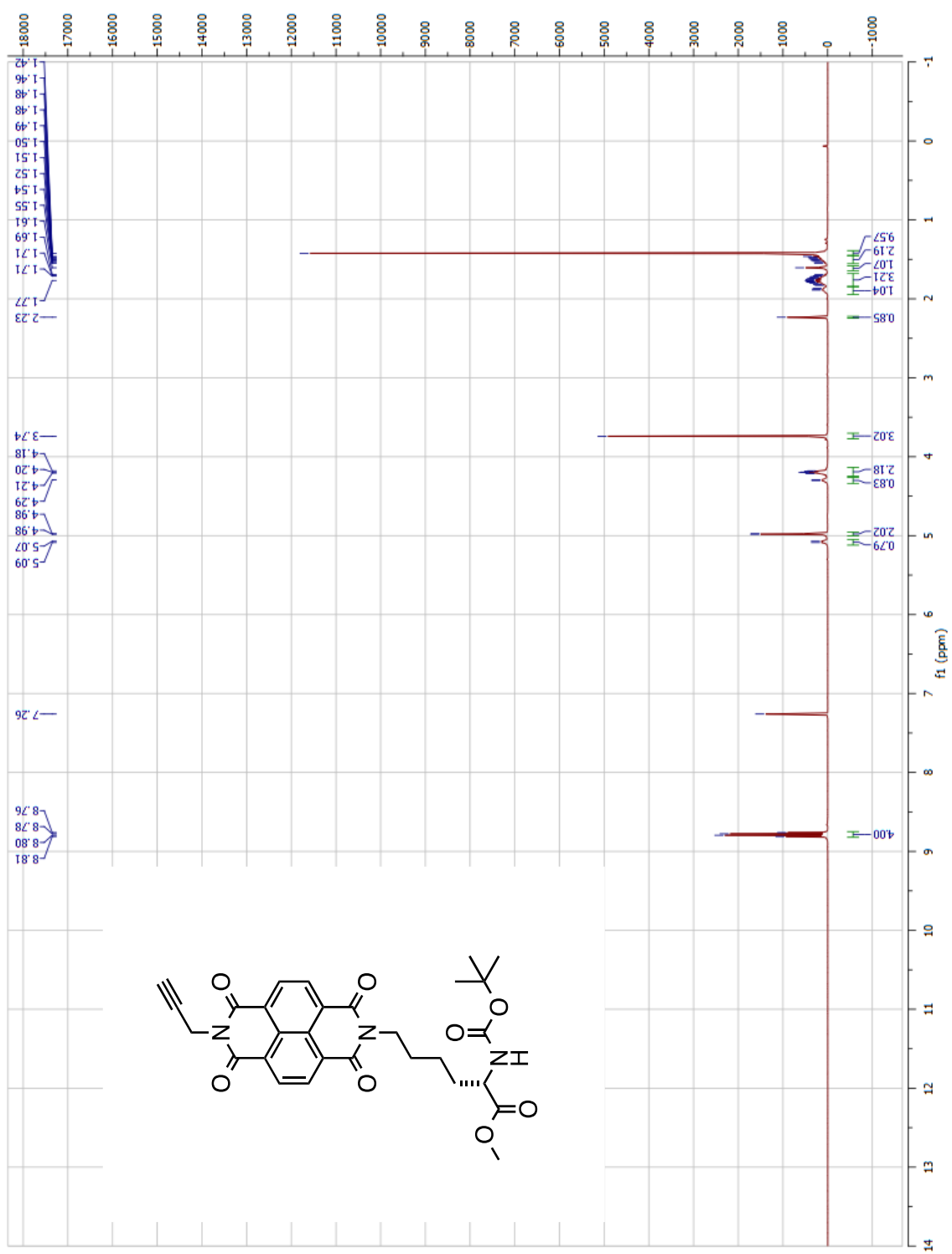


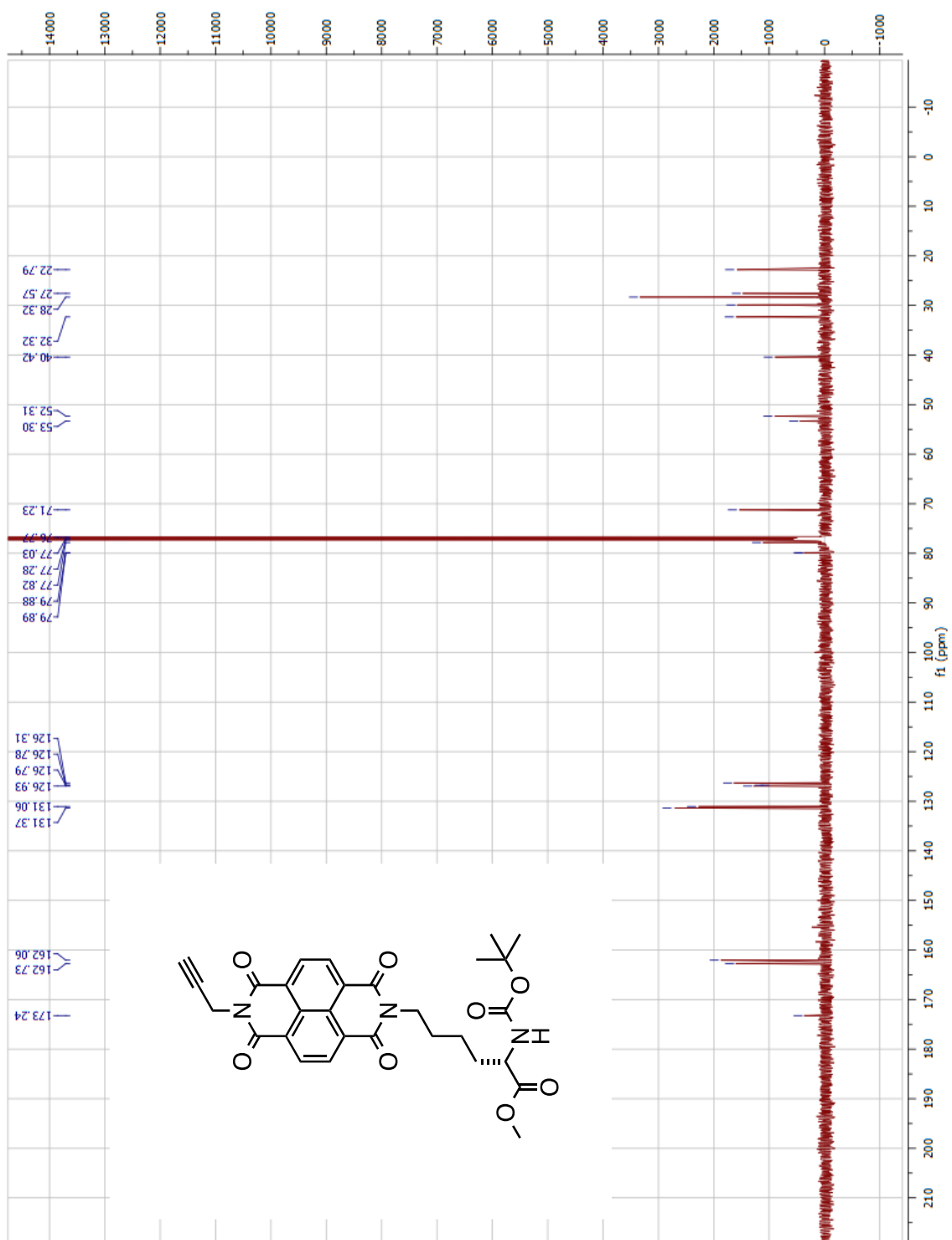


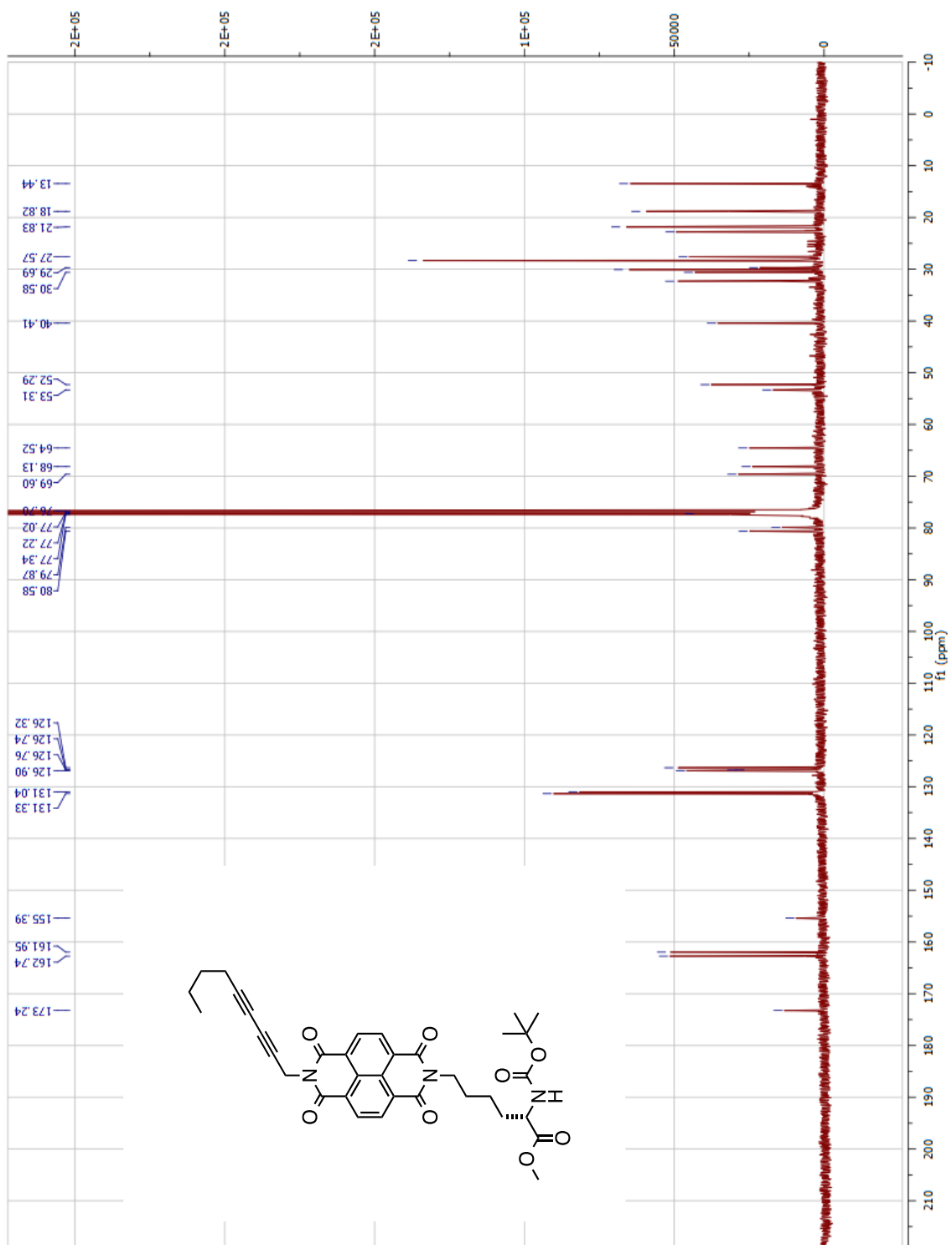


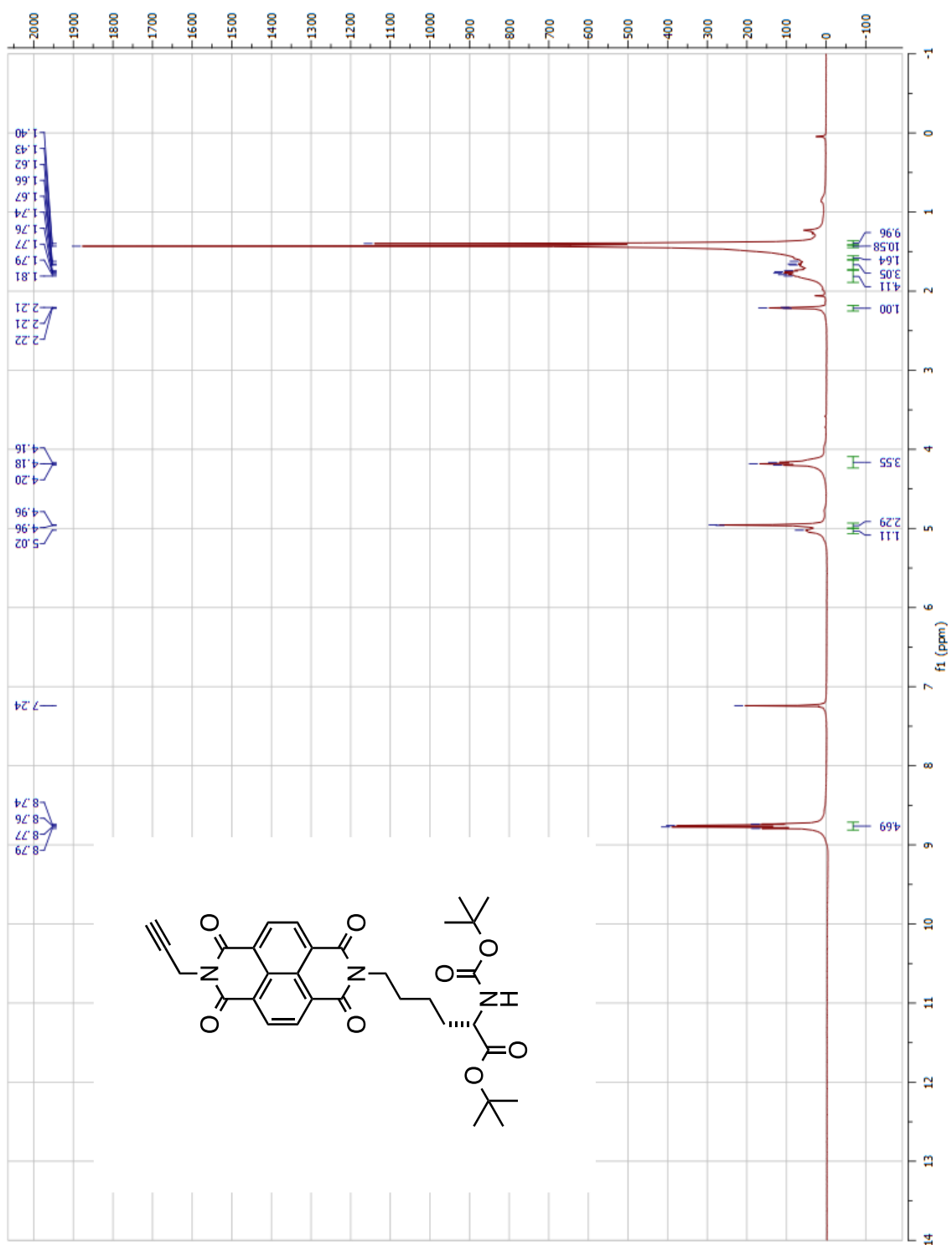


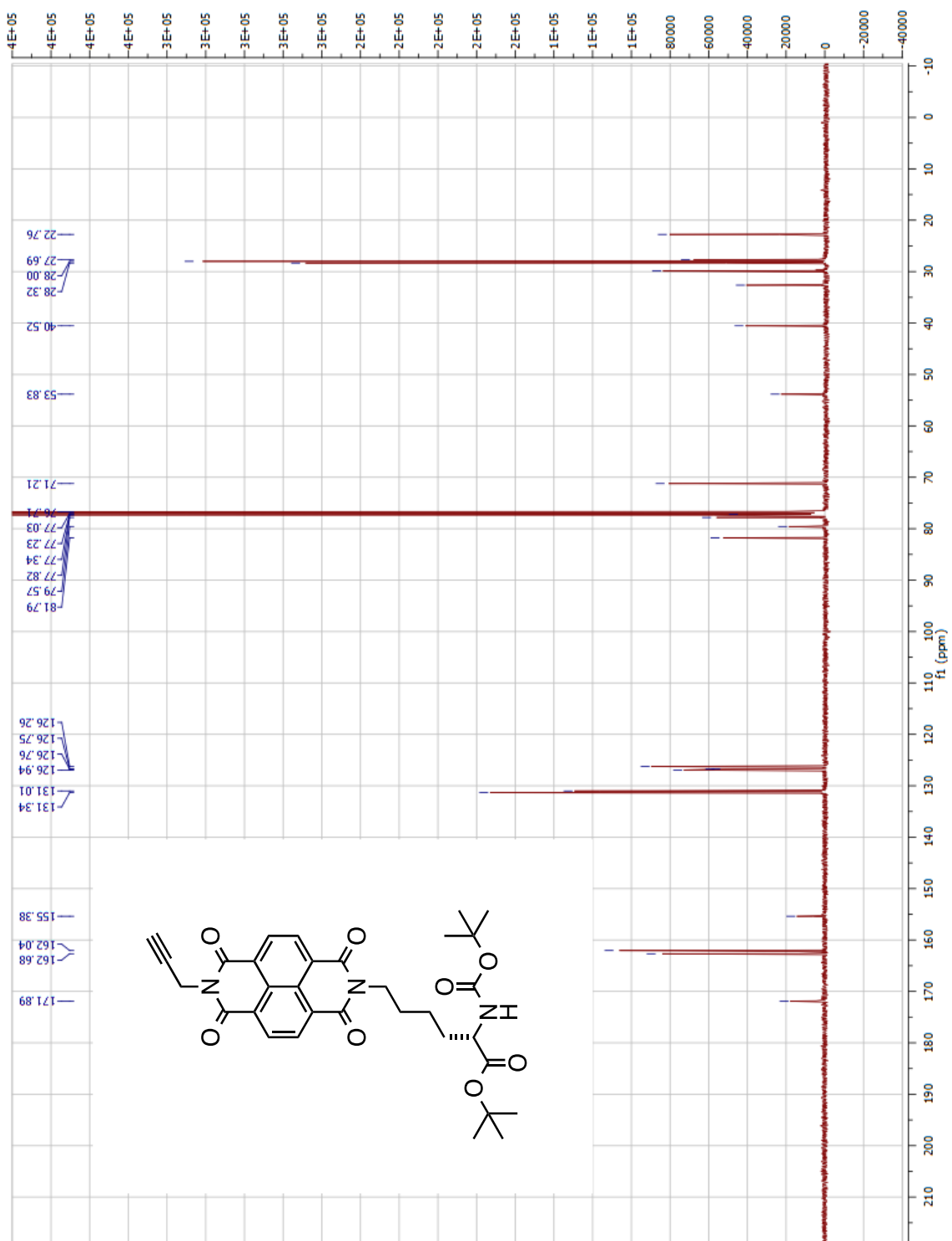


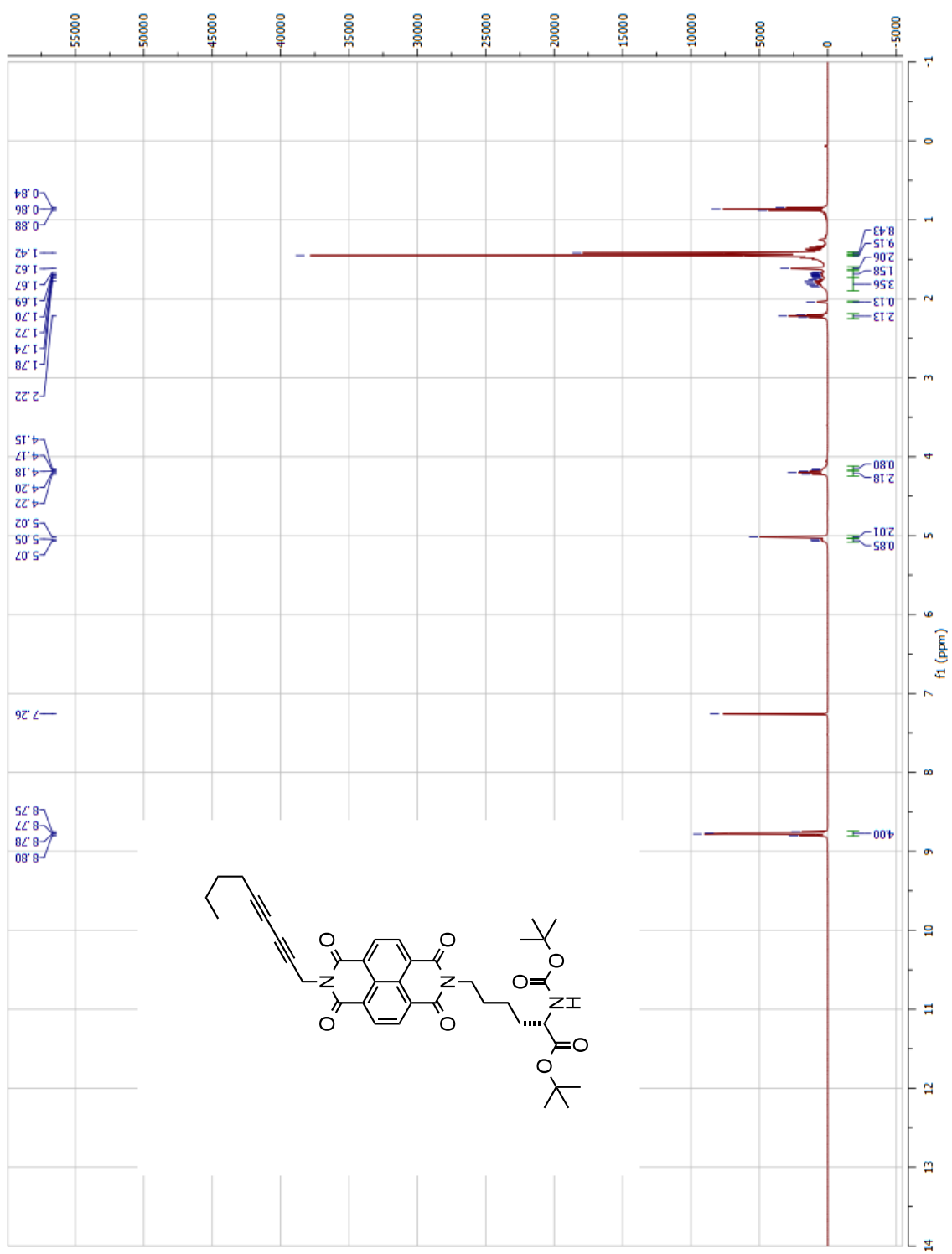


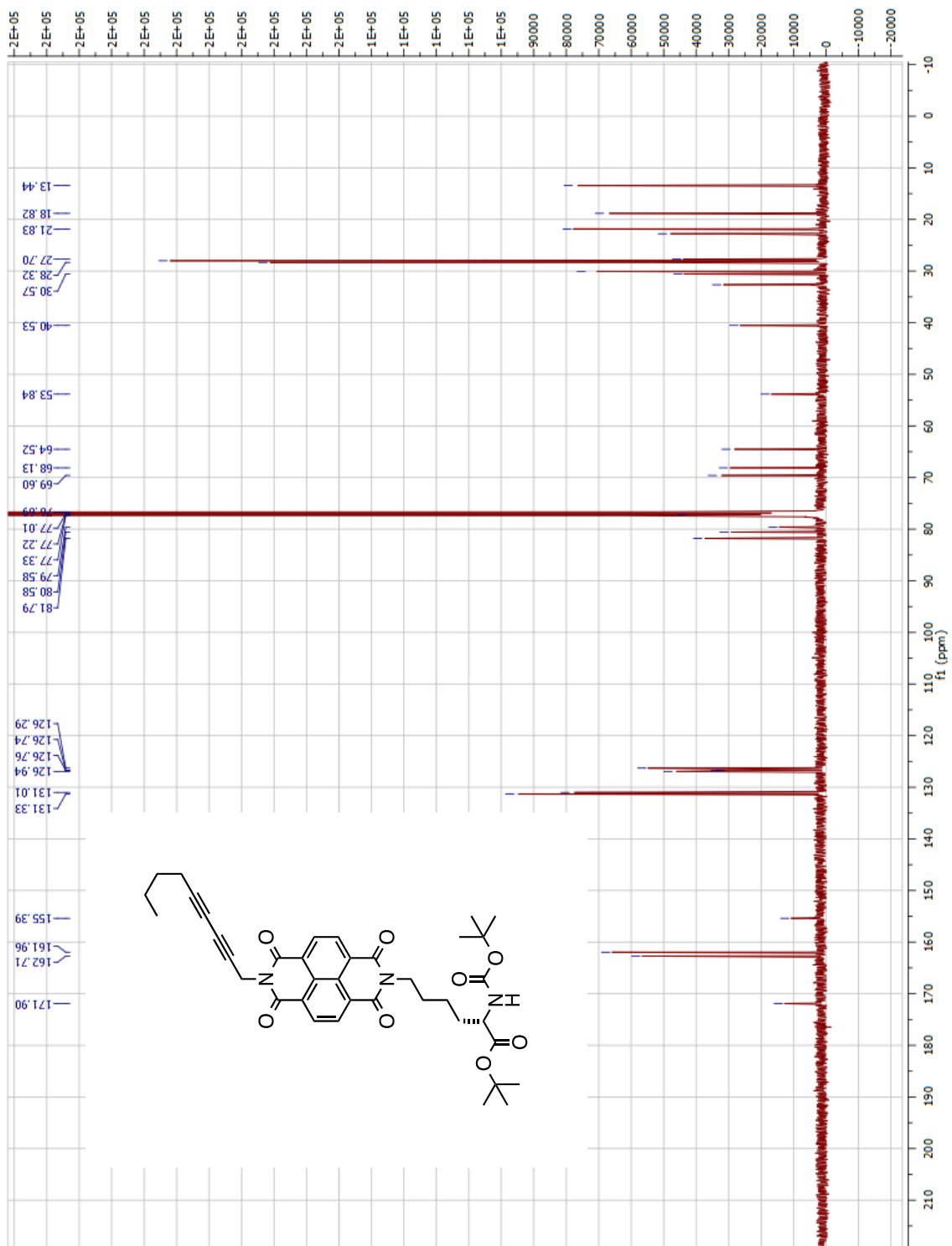


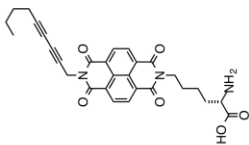


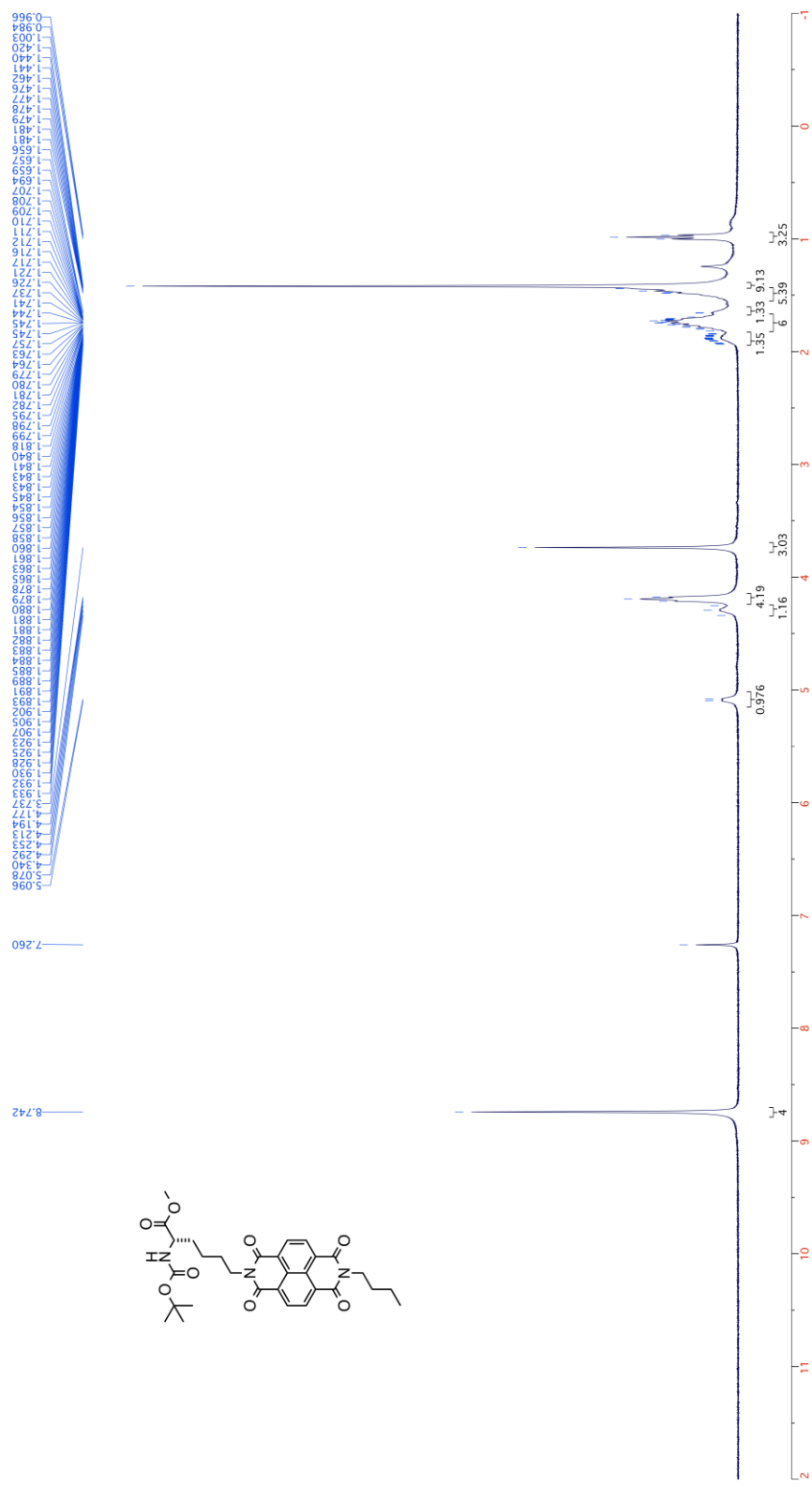


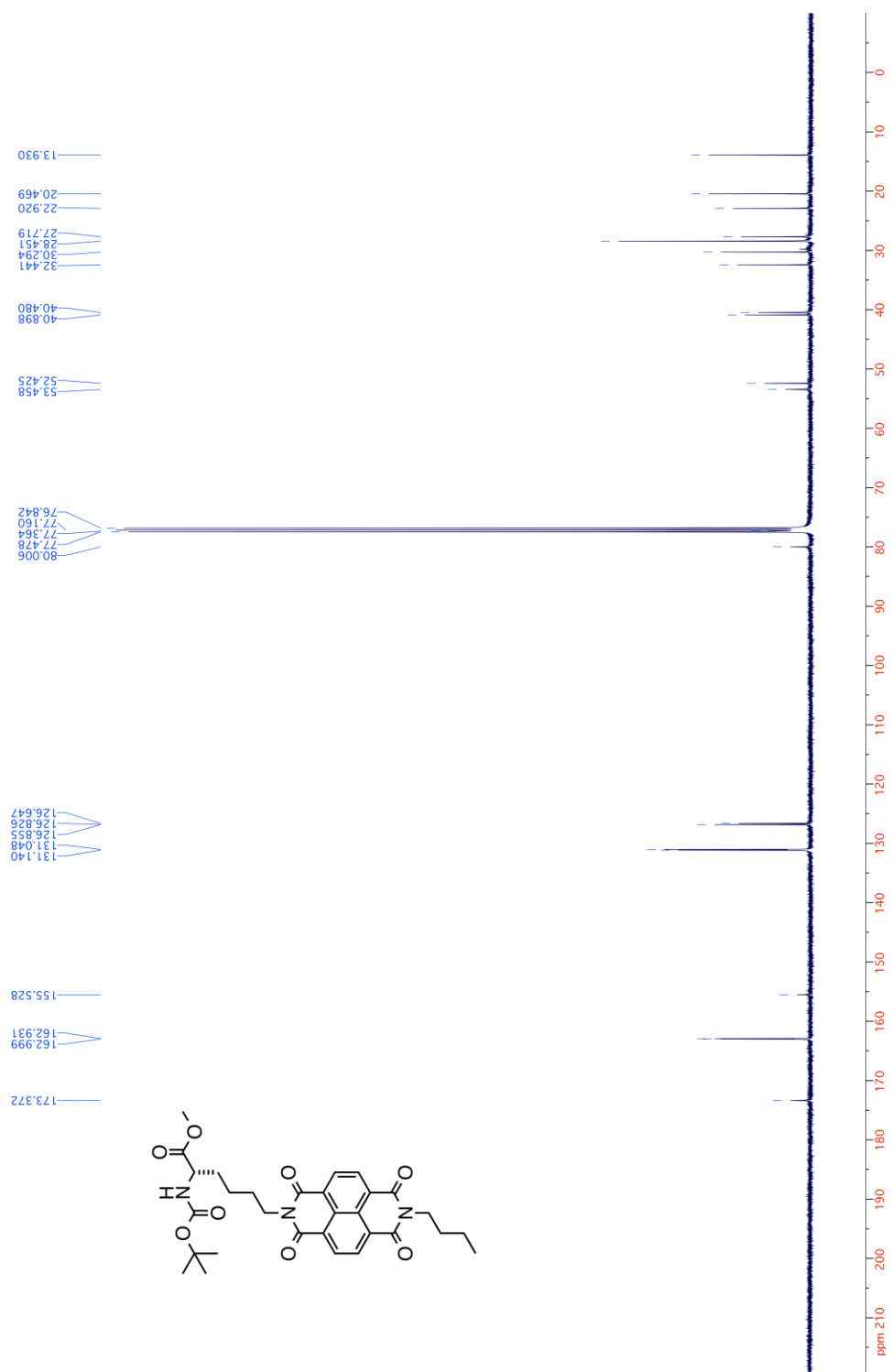


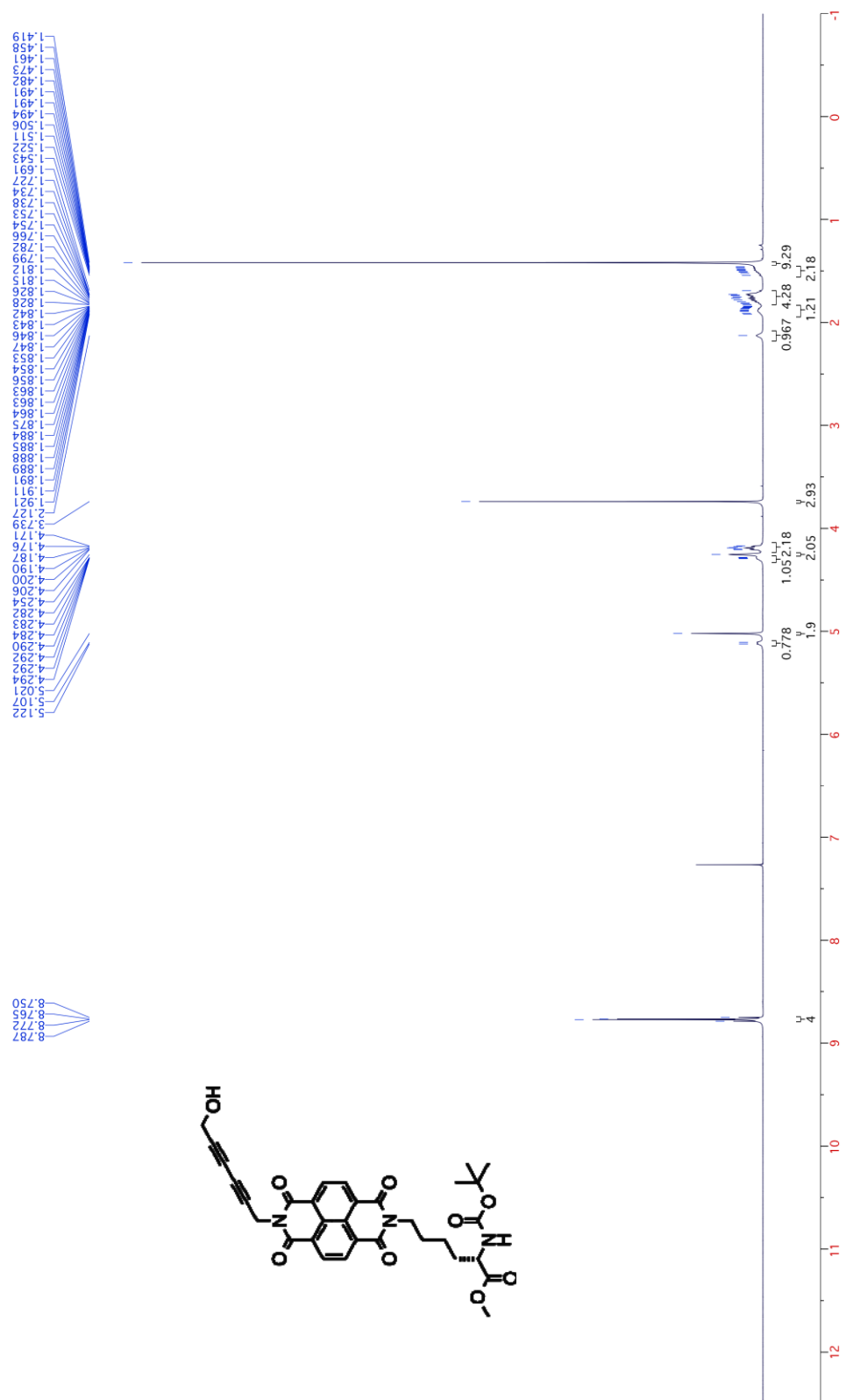


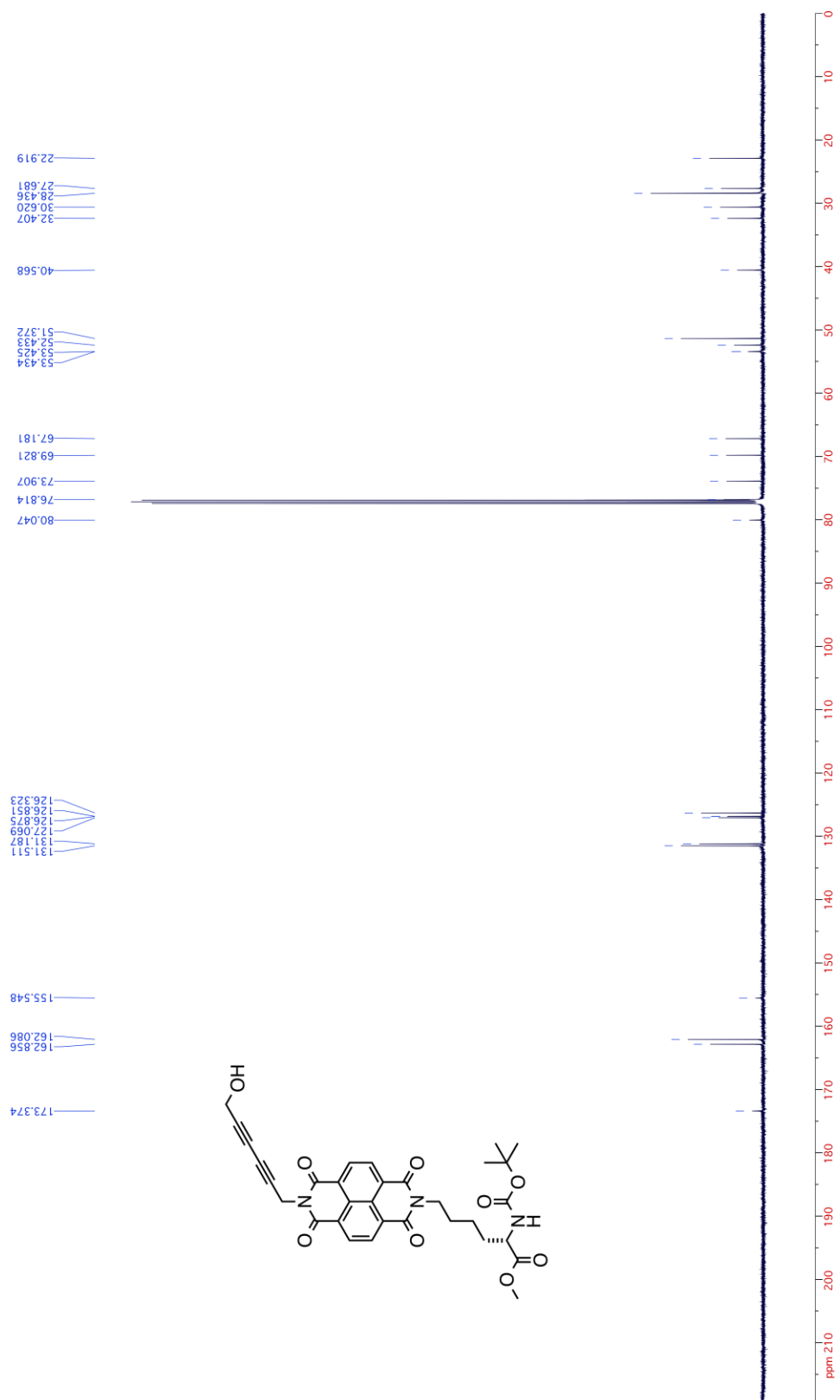


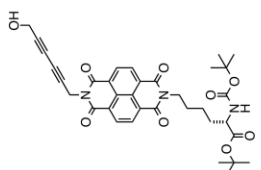


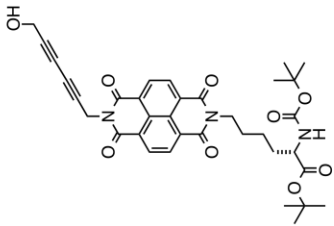












Appendix C: HPLC Traces, Mass Spectrums, FT-IR Spectrums

