RECOGNITION MEDIATED FABRICATION AND TAILORING OF POLYMERIC AND COLLOIDAL MICROSTRUCTURES

by

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To my mother and my family

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Finally, I dedicate this thesis to my family who has always believed, trusted and supported me.

ABSTRACT

RECOGNITION MEDIATED FABRICATION AND TAILORING OF POLYMERIC AND COLLOIDAL MICROSTRUCTURES

Molecular self-assembly is the spontaneous and reversible organization of molecular units into ordered structures by non-covalent interactions. Due to specific non-covalent interactions, the building blocks such as molecules, macromolecules or colloidal particles with appropriate ligand shells recognize each other and result in formation of different structures such as micelles, vesicles, microspheres, colloidal microcapsules. In this thesis hydrogen bonding and hydrophobic interactions were employed to obtain self-assembled systems. Depending on the purpose, to supply more stable systems, some covalent crosslinking methods were applied to arrest dynamic systems.

Study outlined in the thesis consists of three parts: (a) Using dendritic scaffolds to encapsulate polymeric chains via three point hydrogen bonding, (b)fabrication of robust polymersomes via molecular recognition and arresting these self-assembled structures, and (c) construction of colloidal microcapsules by the help of host-guest chemistry between appropriately functionalized gold and iron oxide nanoparticles.

For the first study, monomeric flavin and polymeric flavin (a styrene based polymer appended with flavin units) were synthesized. Three generations of polyaryl ether dendrons containing diaminopyridine (DAP) unit at their core were utilized to investigate the supramolecular encapsulation of monomeric and polymeric flavin units. Through the specific three point hydrogen bonding between the DAP moiety and flavin, the dendrons binds to monomeric and polymeric flavins to produce supramolecular structures. Monomeric flavins upon mixing with DAP containing dendrons, exhibit reversible, redox-modulated behavior consistent with previous flavin model systems. Polymeric flavins, however, show diffusion limited redox behavior and site isolation when bound to increasing DAP dendrimer generations.

For the second study, chloromethyl styrene/styrene copolymer was synthesized as a parent polymer. The parent polymer was functionalized with azide units and DAP units respectively to result in polymer I (PS-DAP-Az). After converting some chlorine units onparent poylmer into alkyne and thymine functionalities, polymer II (PS-THY-Alk) was obtained. Polymer I and polymer II selfassemble upon mixing in chloroform via three point hydrogen bonding held between DAP and Thy units. These microspheres are only stable in non-protic solvents such as chloroform and toluene. They disassemble upon addition of THF or methanol. To overcome the stability problem arising from the dynamic nature of these kind of systems, Cu(I) catalyzed Huisgen reaction occurring between azide and alkyne groups was utilized to arrest these selfassembled structures and build up stable polymersomes. Thus obtained stable polymersomes were converted to water dispersible systems by attaching PEG chains onto their surfaces. Amenability to further functionalization was demonstrated by attachment of fluorescent dye (BODIPY) and immobilization of an enzyme, streptavidin.

In the last part, dynamic colloidal microcapsules or colloidosomes were fabricated by assembly of appropriately functionalized gold and ironoxide nanoparticles at the oil-water interface. For this purpose, β-cyclodextrin coated gold nanoparticles and adamantly coated ironoxide nanoparticles were prepared. Due to the host guest interaction between β-cyclodextrin and adamantane, fabrication of stimuli-responsive colloidal microcapsules at the oil-water interface was successfully accomplished.

ÖZET

POLİMERİK VE KOLLOİDİMSİ MİKRO YAPILARIN TANIMA YOLUYLA FABRİKASYONU VE İŞLEVSELLEŞTİRİLMESİ

Moleküllerin kendi kendine bir araya gelmesi moleküler birimlerin kovalent olmayan etkileşimler sayesinde kendiliğinden olan ve tersine çevrilebilir düzenli yapılar oluştumalarıdır. Kovalent olmayan belirli etkileşimler sayesinde, moleküller, makromoleküller, uygun ligandla donatılmış koloidimsi parçacıklar gibi yapı taşları bibirlerini tanır ve bu tanıma misel, vesikül, mikrosfer ya da kolloidal kapsüller gibi farklı yapıların ortaya çıkmasıyla sonuçlanır. Bu tezde kendi kendine bir araya gelen sistemler kurmak için hidrojen bağı ve hidrofobik kuvvetler kullanılmıştır. Amaca göre, daha sağlam sistemler sağlamak için, bazı kovalent çapraz bağlama yöntemleri dinamik sistemleri sabitlemek için uygulanabilinir.

Çalışma üç kısım içermektedir: (a) üç noktada gerçekleşen hidrojen bağı yoluyla flavin türevlerinin dentritik yapılar ile kapsüle edilmesi, (b) polimer yapılı topların moleküler tanıma yolu ile fabrikasyonu ve bu kendi kendine bir araya gelmiş yapıların hapsolması ve (c) uygun şekilde fonksiyonelleştirilmiş altın ve demir nano parçaçıkları arasında olan misafir komşu ilişkisi ile mikrokapsüllerin yapımı.

İlk çalışma için monomerik flavin ve polimerik flavin (yan zincirlerinde flavin birimleri içeren stiren yapılı polymer) sentezlendi. Odağında diaminopiridin (DAP) birimi bulunan üç jenerasyon poliaril eter dendronları kullanılarak monomerik ve polimerik flavin birimlerinin molekülüstü kapsüllenmesi incelendi. DAP ve flavin arasında üç noktada gerçekleşen hidrojen bağları sayesinde, dendronlar molekülüstü yapılar oluşturmak için monomerik ve polimerik flavinlere bağlanırlar. Monomerik flavinler DAP taşıyan dendronlarla karıştırıldığında önceki flavin model sistemleriyle tutarlı tersine çevrilebilir, redoks-modüle edilmiş davranışlar sergilediler. Bununla birlikte polimerik flavinler artan DAP dendrimer jenerasyonuna bağlandıkça diffüzyonu sınırlanmış redoks davranışı ve bölge izalasyonu gösterdiler.

İkinci çalışma için, metilklorin stiren/stiren kopolimer ana polimer olarak sentezlendi. Ana polimer sırasıyla azido ve DAP birimleriyle polimer I (PS-DAP-Az) elde etmek için işlevsel hale getirildi. Polimer II (PS-THY-Alk) parent polimerdeki bazı klorin birimlerinin alkin ve Thy birimlerine dönüştürülmesi sonucunda elde edildi. Polimer I ve polimer II kloroform içinde DAP ve Thy arasında üç noktada gerçekleşen hidrojen bağı sayesinde kendi kendine biraraya gelir. Bu mikrosferler sadece kloroform ve tolüen gibi aprotik çözücülerde bozulmadan kalabilirler. THF ve metanol eklenmesiyle bozulurlar. Bu gibi sistemlerin dinamik yapısından kaynaklanan dayanıklılık probleminin üstesinden gelmek için, alkin ve azido grupları arasında gerçekleşen bakır katalistli Huisgen reaksiyonu kendiliğinden biraraya gelen yapıları hapsetmek ve dayanıklı polimer yapılı toplar inşa etmek için kullanıldı. Elde edilen dayanıklı mikrosferler yüzeylerine PEG zincirleri eklenerek suda dağılabilir sistemlere çevrildiler. Mikrosferlere flüoresans boya (BODIPY) bağlanması ve enzimin, streptavidin hareketsiz hale getirilmesi ile mikrosferlerin fonksiyonelleştirilmeye uygun olduğu gösterildi.

Son kısımda, dinamik yapılı koloidimsi mikrokapsüller uygun olarak işlevsel hale getirilmiş β-siklodekstrin ve altın nanoparçacıklarının yağ-su ara yüzeyinde bir araya gelmesiyle imal edildi. Bu amaç için β-siklodekstrin ile fonksiyonelleştirilmiş altın nanoparçacıkları ve adamantane ile fonksiyonelleştirilmiş demir nanoparçacıkları hazırlandı. β-siklodekstrin ve adamantin arasındaki komşu misafir ilişkisinden dolayı yağ-su ara yüzeyinde uyarıcıya duyarlı kolloidal mikrokapsüllerin fabrikasyonu başarıyla gerçekleştirildi.

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LIST OF ABBREVIATIONS

ADA	Adamantane
AIBN	2,2-azobisisobutironitrile
CD	Cyclodextrin
$CDCl_3$	Deutorated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CV	Cyclic Voltammetry
DAD	Donor-Acceptor-Donor
DAP	Diamidopyridine
DMF	N,N-dimethylformamide
DMSO	N,N-Dimethyl sulfoxide
ESEM	Enviromental Scanning Electron Microscopy
FMN	Flavin mononucleotide
FAD	Flavin adenine dinucleotide
FTIR	Fourier Transform Infrared
GPC	Gel Permeation Chromatography
G1	Generation 1
MC	Microcapsule
NP	Nanoparticle
PDI	Polydispersity index
PEG	Poly(ethylene glycol)
PMDETA	N,N,N-pentamethyldiethylenetriamine
PS	Polystyrene
SAM	Self assembled monolayer
TBAP	Tetrabutylammonium perchlorate
TEM	Transmission Electron Microscopy
THF	Tetrahydrofuran
Thy	Thymine

1. INTRODUCTION

1.1. Supramolecular Chemistry

Molecular self-assembly is a powerful tool to bring molecules together via non-covalent interactions to construct structurally well-defined association of molecules which are stable and thermodynamically controllable. Use of reversible non-covalent interactions provides an opportunity for self-correction during the assembly process, thus resulting in formation of uniform, well defined structures.

Nature is the main source of inspiration for utilizing in synthetic systems. Many biological systems utilize self-assembly to obtain highly ordered structures in living organisms. Some of the well known examples of self assembling systems in nature are the formation of the DNA double helix, the folding of polypeptides into their tertiary structures, and tobacco mosaic virus composed of 2000 coat-protein subunits arranged into a right-handed helix conformation (Figure 1.1).

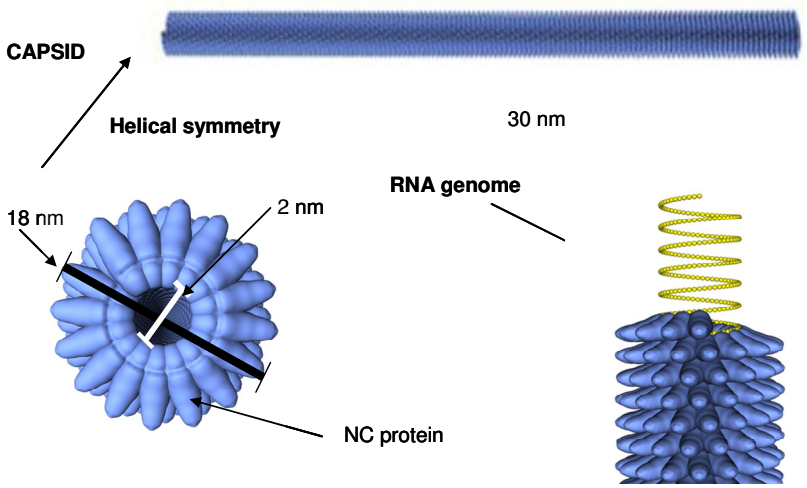

Figure 1.1. RNA genome of tobacco mosaic virus

The study of self-assembling molecular systems has evolved into a new area of chemistry called “supramolecular chemistry” [1]; that is the chemistry beyond the

molecules that held molecules non-covalently. While traditional chemistry deals with covalent interactions, supramolecular chemistry mainly bases on inter molecular interactions to obtain highly integrated architectures.

The complementarity between the pairs, namely “host” and “guest” building blocks lies at the core of design and formation of various architectures. As a result of selective binding, receptor and substrate recognize each other with specificity (Figure 1.2).

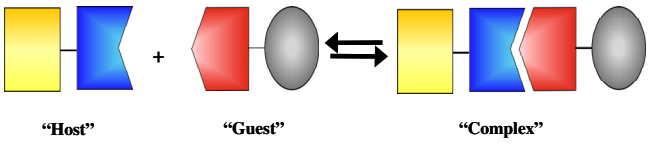

Figure 1.2. Host-guest interaction to form self-assembled complex

Molecular recognition is an important concept that has been demonstrated by supramolecular chemistry. This molecular recognition can be held through forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi stacking, electrostatic effects etc. Strength of these forces can vary from a few kJ to hundreds of kJ (Table 1.1) [1].

Table 1.1. Strengths of Intermolecular Forces

Type of Interaction	Strength (kJ mol^{-1})
ion-ion	100-350
ion-dipole	50-200
Dipole-dipole	5-50
hydrogen bonding	4-120
Cation-Π	5-80
Π-Π	0-50
van der Waals forces	<5
metal ligand	0-400
covalent bondind	100-400
Hydrophobic effects	difficult to assess

1.1.1. Dendrons and Dendrimers in Supramolecular Chemistry

1.1.1.1. Dendrons and Dendrimers. Dendrimers are one of the most interesting nanoscale molecular architectures developed over the past 20 years [2]. Dendrons and dendrimers are comprised of repeating branched building blocks and their structures are monodisperse. Dendrons can be considered as individual dendritic branches, while dendrimers are structures in which a number of dendrons are attached to a single core unit.

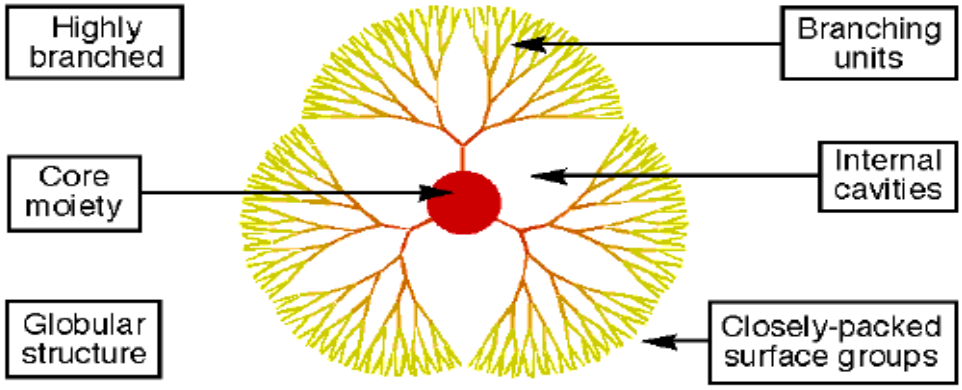

Figure 1.3. General structure of dendrimers

Dendrimers and dendrons are attracting an increasing attention because of their unique structures and properties. Core, branching units and surface groups are the three important parts of dendrimers (Figure 1.3). During the synthesis, each repetition cycle leads to the addition of one more layer of branches which is called generation. Playing around these units and generation numbers can result in different chemical and physical properties.

They are globular, hyperbranched monodisperse macromolecules; they can be synthesized via either divergent or convergent iterative methods. Divergent method was pioneered by Newkome [3] and Tomalia [4] and in this method; dendrimers are built from the central core out to the periphery. In each repeat cycle reactive groups on the dendrimer periphery react with the same number of monomer units to add a new layer or generation to the dendrimer. Number of coupling reactions increases with each successive generation.

First examples of convergent approach to dendrimers synthesis belong to Fréchet and Hawker [5], Miller [6], and Moore [7]. In this approach contrast to divergent one, building process starts from periphery and goes towards the core. The initial reaction sites ultimately reside on the periphery of dendrimer, while the reactions take place at the reactive core (called the *focal point*). The important difference in this strategy is that the number of coupling reaction needed to increase the generation is constant throughout the synthesis so the construction of defective products is prevented. However, as the generation number increases, the core becomes so overcrowded that reaction yields drops dramatically. Dendrimers due to their unique properties can be used for a wide range of applications. However, in this thesis it is focused on the use of dendrons in supramolecular chemistry; particularly in molecular recognition and self-assembling systems [8].

1.1.1.2. Dendrimers in Molecular Recognition. Dendrimers can be used in molecular recognition. Linear polymers usually adopt random-coil structures, hovewer the three dimensional structure of dendrimers is more or less radiate out to a peripheral surface. Especially, as the successive layers are added, dendrimer adopts a spherical three-dimensional structure. This gross structural similarity suggests that dendrimers might function in many of the same ways as their natural counterparts. Indeed, host-guest chemistry can take place either in the interior or on the periphery of the dendrimer, just as the molecular recognition exhibited by proteins may occur deep within the biopolymer or at its surface. Binding groups on the interior of the dendrimer have been called endo-receptors, whereas peripheral, or end groups involved in complexation chemistry are called exo-receptors [9].

1.1.1.3. Molecular Recognition of Dendrimers via Hydrogen Bonding. Hydrogen-bonding interactions are spread everywhere in the biological systems and during the last decade has occured a significant interest in synthetic hosts that complex guests via hydrogen bonding. When intermolecular forces are considered, hydrogen bonding is both a directional and strong binding force, at least in apolar media. Newkome and co-workers [10] described a series of dendritic hosts (Figure 1.4) containing (diacylamino) pyridine hydrogen-bonding units. These hydrogen-bonding units contain a donor-acceptordonor (DAD) hydrogen-bonding motif that has been widely used to bind complementary guests such as imides or

barbituric acids. Two such units may cooperate to bind the two ADA sites on barbituric acid.

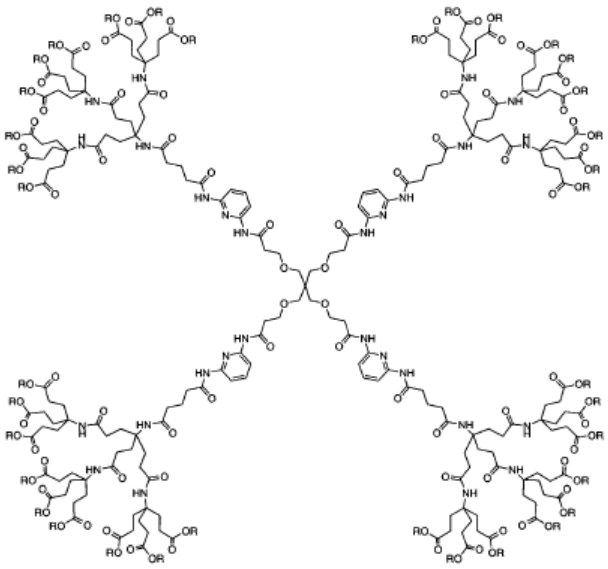

Figure 1.4. Newkome's dendritic host with multiple hydrogen-bonding sites

1.1.2. Dendronized Polymers

Dendronized polymers are subclass of comb polymers where dendrons represent the comb's teeth [11, 12]. Appended large dendrons to the backbone transform random coil conformation of backbone to extended conformation (Figure 1.5).

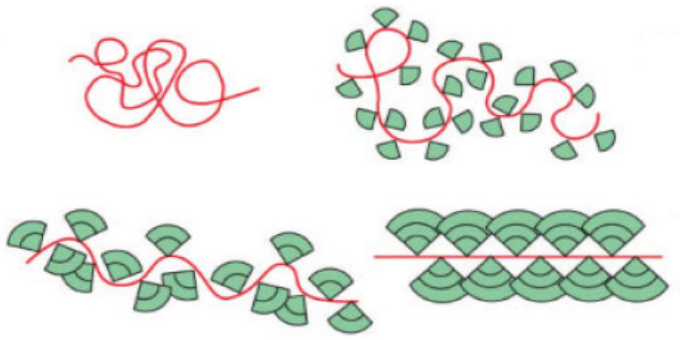

Figure 1.5. Different conformations of dendronized polymers

Dendronized polymers can be obtained by covalent approaches or non-covalent interactions that are established between dendrons and polymers. In covalent approaches of dendronized polymers, three main routes are common which are ‘macromonomer method’, ‘graft-to’ method, and the ‘graft from’ method [11]. Non-covalent approaches generally involve utilization of the ‘graft-to’ method. The section below highlights the formation of supramolecular dendronized polymers.

1.1.2.1. Supramolecular Self-Assembly of Dendronized Polymers. Percec et al. [13, 14] has recently reported covalently dendronized polymer that, the shape of a polymer can be controlled by the covalent attachment of different dendritic side groups bearing extended alkyl chains. In addition, supramolecular self-assembly using molecular recognition processes, such as hydrogen bonding and metal-ligand interaction, has become a versatile tool for dendrimer construction [15, 16, 17, 18, 19].

The self-assembling functionalization on polymers usually requires high-affinity binding recognition motifs between small molecular components and polymers. Stoddart et al reported a class of acid-base switchable supramolecular dendronized polymers (Figure 1.6) based on a conducting polymer polyacetylene and a nonconducting polymer-polystyrene as backbones [20].

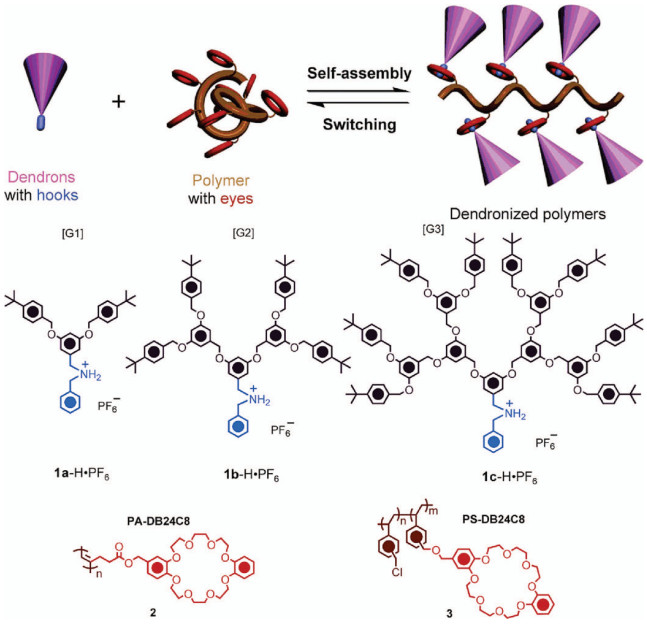

Figure 1.6. Acid-base switchable dendronized polymers composed of polyacetylene or PS backbones bearing dibenzo[24]crown-8 "eyes" and Fréchet dendrons bearing dialkylammonium "hooks"

Lin reported the synthesis of H-bond acceptor polymers and copolymers noncovalently jacketed with hydrogen bond donor dendrons (Figure 1.7) [21].

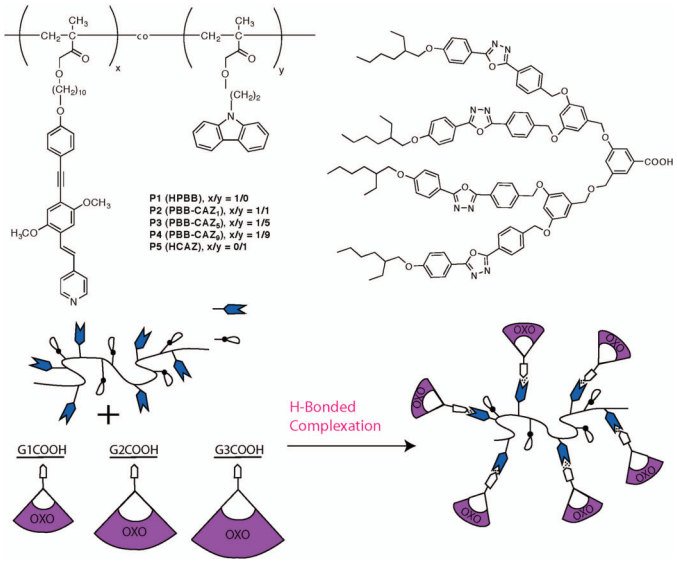

Figure 1.7. Noncovalent dendronization of light-emitting polymers hydrogen-bond acceptor polymers with hydrogen-bond donor 1,3,4-oxadiazole-containing dendrons

1.1.3. Site Isolation and Encapsulation of Redox Active Group Bearing Polymers via Dendrons

Site isolation and encapsulation of redox-active cofactors control the electron transfer process within many enzymatic systems [22, 23], protecting the redox center from unwanted interactions with water and other interfering species. Various methods have been used to mimic this effective biological insulation of redox-active core moieties for use in artificial enzymes and fiber optics [24, 25], catalysts [26], light harvesting systems [27], construction of insulated molecular wires, light-emitting diodes [28]. Additional efforts have focused on synthetic systems, such as inclusion complexes and dendrimer cages [29] for applications as data storage units, sensors, catalysts, and magnets [30, 31]. Dendritic scaffolds have gained considerable interest due to their unique molecular architecture. These dendritic scaffolds have been used for the spatial arrangement of functionalities and tuning the properties of redox-active moieties through the interplay of structural subunits. However, these synthetic systems differ from biological systems because they primarily focus on covalent attachment of dendritic scaffolds to control the encapsulation. Therefore, model systems where modulation of electron transfer properties occurs via noncovalent interactions would be more representative of typical enzyme–cofactor systems and would also lead to supramolecular strategies for materials and device applications.

Among various enzyme–cofactor systems, flavoenzymes make attractive model systems because they catalyze a wide variety of biological processes such as redox transformations, signal transduction, and electron transfer. They use cofactors (FMN or FAD) that bind to the active site of the apoenzyme through a series of non-covalent interactions. The interactions are responsible for fine-tuning the $FADH_2$–FAD redox cycle and isolating the cofactor within a hydrophobic pocket. Hence, flavin model systems serve as a useful tool to modulate the effective site isolation and encapsulation of flavin through non-covalent interactions with dendritic scaffolds.

1.2. Crosslinked Polymersomes via Arresting Molecular Recognition Mediated Self-Assembled Structures

Synthetic world improves by the guidance from nature. While biological systems are the source of inspiration for many applications, supramolecular chemisty [32, 33] emerges as an instrument to construct many useful scaffolds like vesicles [34], micelles [35], liposomes and microspheres. Polymers used as building blocks of such architectures can be called as polymersomes [36]. These highly ordered supramolecular polymeric structures [37, 38, 39] can be utilized in many areas ranging from targeting agents [40], encapsulation of active agents [41, 42], microreactors [43, 44] to drug delivery [33, 34]. Self-assembling [45] in polymers can be built up through non-covalent interactions along the polymer backbone or among the polymer chains. Synthesis of side-chain-functionalized polymers [46] that carry units which can participate in non-covalent interactions can lead to formation of functionalizable polymers. A key factor in molecular recognition [47] is complementarity that complementary units [48] on the polymers recognize each other very well like in lock and key model [49, 50].

Non-covalent interactions can be established via specific three point hydrogen bonding [51, 52]. Presence of multiple hydrogen bonding units rather than a single one make the assemblies stable. Molecular recognition between polymers can be achieved via three point hydrogen bonding between complementary diamidopyridine (DAP) and thymine (Thy) moieties that are appended to polymeric backbone. Self-assembly at molecular levels [53, 54] can be carried to higher ordered structures via the bottom-up method [55, 56]. Mixing of polymers functionalized with complementary recognition units results in formation of spherical microspheres or vesicles.

1.2.1. Dynamic Nature of Self-assembled Systems

Self-assembly, thermal reversibility, self-healing are some valuable features of molecular level recognition based on specific hydrogen bonding [57]. These kind of advantageous properties provide a good control in fabrication processes. But, on the other hand these systems are dynamic in nature and this limits the construction of long-term

stable scaffolds. To overcome such stability problems, covalent cross-linking approaches can be applied [58, 59].

1.2.2. Crosslinking of Self-assembles Structures

Non-covalent interactions between recognition sites of building blocks fabricate self-assembled structures. This fabrication may generate different shapes such as microspheric shape. If the building blocks are decorated with appropriate reactive units, crosslinking can serve as a method to preserve the shape. As a result covalent crosslinking may arrest polymeric assemblies while keeping the shape gained through recognition unchanged. In a recent study, Rotello and coworkers showed the covalent crosslinking of self-assembled polymersomes via [2πs+2πs] cycloaddition between thymine units upon exposure to UV (200–300 nm) light (Figure 1.8) [59].

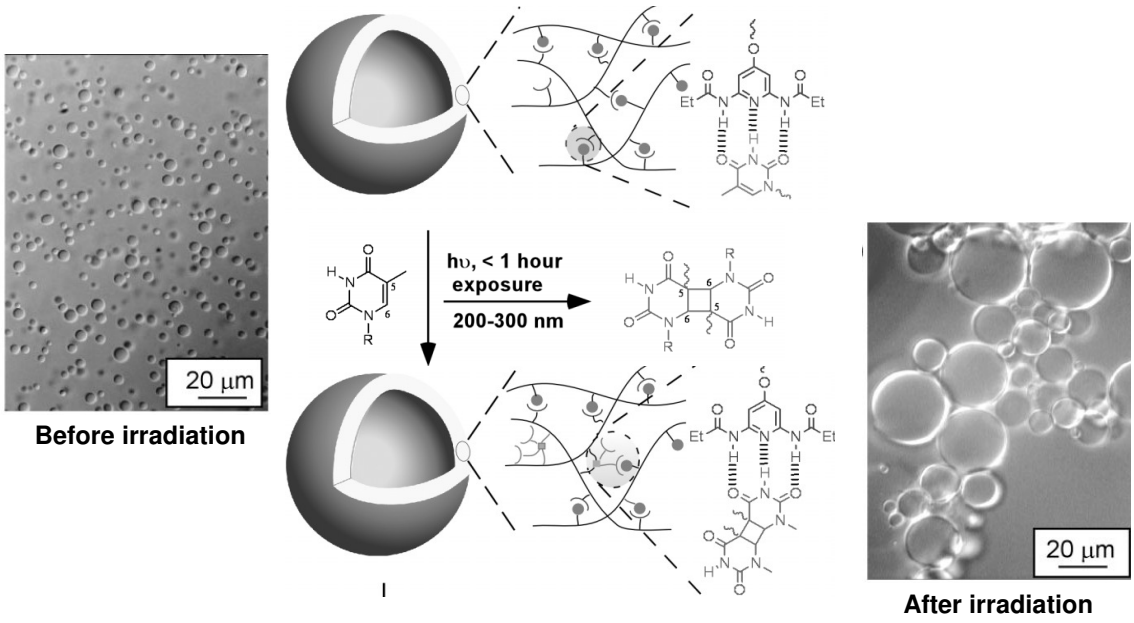

Figure 1.8. Crosslinked polymersomes under UV

1.2.3. Copper Catalyzed Huisgen [3+2] Cycloaddition

The Huisgen [3+2] cycloaddition reaction is a widely used click reaction. The cycloadditon reaction takes place between an azide and alkyne functional group to give a mixture of 1,4 and 1,5-disubstituted triazoles. In 2002 Sharpless and Fokin [60] introduced a new method for the Huisgen reaction. In the presence Cu (I) catalyst, the reaction resulted in only 1,4-disubstituted triazole (Figure 1.9).

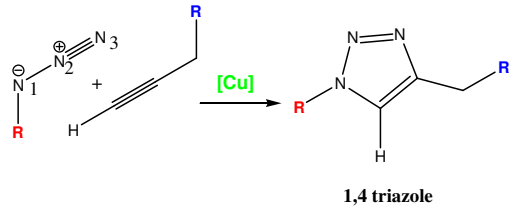

Figure 1.9. Copper catalyzed Huisgen reaction

The addition of copper catalyst results in an increase in the yield of the reaction and room temperature is suitable for the efficient reaction. Commonly used Cu-systems are $CuSO_4$/ NaAsc and CuBr/PMDETA because they provide regiospecificity leading to only 1,4-disubstituted triazole, mild reaction conditions, easy purification, high reaction yield and wide functional group tolerance.

1.2.3.1. The Huisgen [3+2] Cycloaddition to Fabricate Stable Microspheres. [3+2] Huisgen Cycloaddition is an effective crosslinking method [61].‘‘Click’’ chemistry has been utilized in polymer [62] and dendrimer [63, 64] synthesis, in the formation of colloidosomes [65] and in the functionalization of micelles and nanoparticles [66, 67]. The copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition can be applied as a new method to arrest self-assembled structures to fabricate stable microspheres and decorate them with different functionalities to prove further functionality.

1.3. Microcapsules or Colloidosomes

Colloidal microcapusules, often referred to as colloidosomes, are an emerging class of microcapsules where colloidal particles such as gold and iron nanoparticls are used as one of the building blocks.

1.3.1. Microcapsules

Microcapsules (MCs) are attractive materials because to their small size, high surface area, large inner volume and stable membrane. Due to these properties, they have potential applications as drug delivery vehicles, micro reactors, and catalyst supports and encapsulants [68]. Recently, several types of nano- and microcapsules, such as liposomes [69], polymerosomes [70, 71] and polyelectrolyte capsules [72, 73] have been developed. These microcapsules have been clinically used for drug delivery, gene delivery and cancer therapy and other medical applications [74]. Numerous approaches, relying mainly on self-assembly and the use of templates have been developed to create microcapsules with diverse functionalities both on the outer surface and in the interior. Usually the self-assembly of lipids and/or polymers is used to engineer stable and well defined multifunctional microcapsules through tailoring of the composition and structure of the building blocks.

Colloidal MCs stabilized by micro/nanoparticles provide a useful alternative to polymer and lipid-based systems [75, 76]. These are fabricated by stabilizing emulsions via self-assembly of colloidal micro/nanoparticles at liquid-liquid interface. In these systems, colloidal particles serve as modular building blocks, allowing incorporation of the particle properties into the functional capabilities of the MCs. As an example, nanoparticles (NPs) can serve as appropriate antennae to induce response by external triggers (e.g. magnetic fields or laser) for controlled release of encapsulated materials [77]. Additionally, the dynamic nature of the colloidal assembly at liquid-liquid interfaces result defects free organized nanostructures [78] with unique electronic, magnetic and optical properties which can be tuned by their dimension and cooperative interactions. The physical properties of colloidal microcapsules such as permeability, mechanical strength, and

biocompatibility can be precisely controlled through the proper choice of colloids and preparation conditions for their assembly.

Over the last decade, research on nano/micro particle stabilized emulsions has evolved significantly due to advancements in the understanding of the interfacial assembly at both the macro- and nanoscopic level [79, 80]. A variety of interesting strategies have been developed to stabilize NPs at the oil-water interface and provide long term stability to these colloidal assemblies.

1.3.2. Stability of the emulsion based template

Colloidal particles tend to localize at the liquid-liquid interface to minimize the interfacial energy between immiscible liquids, e.g. oil-water (o/w) emulsions. This phenomenon of stabilization of emulsions via colloidal particles was observed almost a century ago and termed as "Pickering emulsions", named after its discoverer S. U. Pickering. Later pioneering work by Pieranski showed that the decrease in interfacial energy is related to the effective radius (r) of particle and surface tension of the particle with respect to oil (O) and water (W) [81]. The simplified equation is $\Delta E = -\frac{\pi r^2}{\gamma_{o/w}}\left[\gamma_{o/w} - \left(\gamma_{p/w} - \gamma_{p/o}\right)\right]^2$ where $\gamma_{p/o}$ = interfacial energy of particle-oil, $\gamma_{p/w}$ = interfacial energy of particle-water and $\gamma_{0/w}$ = interfacial energy of oil-water systems. The subsequent sections illustrate the role played by the size and wettability of the colloidal particles in the governing the dynamic behavior of the colloidosomes as predicted by the "Pirenski equation".

1.3.2.1. Effective radius of the particle (r). Particle stabilization of the liquid-liquid interface is strongly size-dependent. ΔE is proportional to r^2, this means that the energy gain is smaller and the assembly is less stable for smaller NPs when compared to larger ones. While larger micron sized particles can irreversibly adsorb at the interface and form stable emulsions, smaller NPs (<20 nm) adsorb much more weakly at the interface. As a result, thermal fluctuation can result in the displacement of the NPs from the interface, setting particle exchange equilibrium at the interface which results in size selective particle assembly (Figure 1.10.a). Russell et al used CdSe quantum dots to demonstrate the size

selective adsorption of NPs at the oil-water interface by using fluorescent [82]. Initially smaller size CdSe NPs (~2.8 nm, green fluorescence) were used to stabilize water-in-oil type emulsion. Later, they introduced larger size CdSe NPs (~4.6 nm, red fluorescence) to the toluene phase. As a result, larger CdSe NPs assembled on the surface of existing stabilized droplets, displacing the smaller 2.8 nm NPs (Figure 1.10.b). This displacement is unique to NPs when thermal fluctuation is dominant and provides a strong support to the "Pieranski equation".

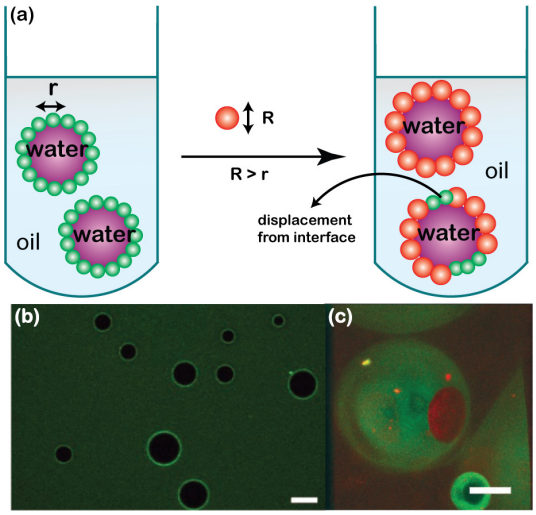

Figure 1.10. (a) Schematic of size selective displacement from interface. Confocal Microscopy images of (b) 2.8 nm CdSe stabilized droplets (c) Droplets after addition of 4.6 nm CdSe NPs. Scale Bar, 20 µm

1.3.2.2. Wettability of NPs. Another key parameter which governed the interfacial assembly of NPs is wettability; dictated by three phase contact angle (θ) [83]. This is the angle between the tangents to the NPs and the liquid-liquid interface measured through one of the liquids in each point of the three phase contact line where NP and two liquids meet. The relation between contact angle and interfacial tensions can be derived by Young's equation; $\cos\theta = {}^{\gamma_{po} - \gamma_{pw}}/_{\gamma_{ow}}$ The affinity of the particles for the respective solvents is a significant determinant, as indicated by $\gamma_{p/o}$ and $\gamma_{p/w}$ of above equation. Generally, hydrophilic NPs ($\gamma_{po} > \gamma_{pw}$, θ < 90°) stabilize oil-in-water emulsion and hydrophobic NPs ($\gamma_{po} > \gamma_{pw}$, θ > 90°) are used to stabilize water-in-oil emulsions. Only particles with

intermediate wettabilty ($\gamma_{po} = \gamma_{pw}$, θ = 90°) produce thermodynamically stable emulsions (Figure 1.11.a). Extending this concept, Reincke *et. al.* showed that 4-mercaptobenzoic acid capped Au NPs (~ 8nm) can be attached to and detached from the liquid/liquid interface and subsequently redispersed in the aqueous bulk phase by changing the pH [84]. When NPs were introduced to the water-heptane interface, no interfacial attachment of the NPs was observed due to their extreme hydrophilic nature. After adjusting the pH (~2) by addition of dilute HCl, Au NPs became protonated and slowly migrated to the interface and formed a purple color film (Figure 1.11.b). The reversible nature of the interfacial self-assembly was tested by adjusting the aqueous solution pH to 9. As a result the color of the aqueous solution turned red, similar to the original solution, confirmed the detachment of the Au NPs from the interface.

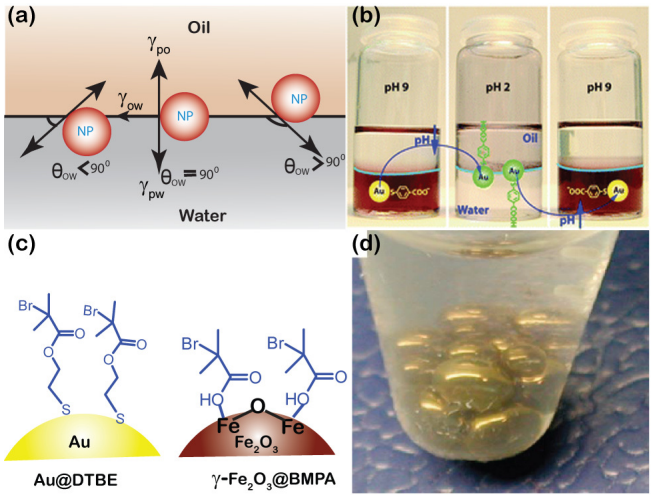

Figure 1.11. (a) NPs of different wettability at the interface (b) reversible attachment/detachment of Au NPs (c) 2-bromo-2-methylpropionate functionalized NPs. (d) Emulsion stabilized by Au NPs of intermediate wettability

The wettability of NPs can also be tuned by proper selection of capping ligands [85]. Surface modification of NPs by 2-bromo-2-methylpropionate ligand (Figure 1.11.c) has a contact angle very close to 90° and as a result the NPs stay exactly at the middle of the interface and effectively stabilize the emulsions droplets (Figure 1.11.d).

1.3.3. Interparticle interaction at oil-water interface

Interaction between adsorbed particles at the liquid-liquid interface exhibit a broad range of behavior and play a decisive role during self-assembly process. Various effective interfacial forces such as capillary force, solvation force, electrostatic force, Van der Wall force, and fluctuation force are responsible for manipulating the interparticle interaction and represent a current challenge in this area [86]. In addition to these physical forces, chemical interaction between the adsorbed particles is also crucial to stabilize the NPs at the curved interface and to fabricate MCs. In order to seize the thermally activated escape of NPs, it's necessary to trap the NPs at the interface during the process of self-assembly. Recent research has been focused on the fabrication of stable and robust MCs by crosslinking of NPs at oil-water interface.

1.3.4. Crosslinking of NPs at liquid-liquid interface

Recently, significant advances have been made in the area of colloidal microcapsules engineering through chemical crosslinking of the particles assembled at the oil-water interface. Crosslinking helps NPs to form a 2-D network structure at the emulsion interface and provides robustness to the MCs. The most straightforward way of crosslinking thethe NPs at the oil-water interface is to link their surface capping ligands via chemical bond formation. Sophisticated ligand design and surface functionalization of NPs are very important for this purpose. These crosslinking strategies can be grouped into two categories: (i) via covalent interactions between NPs and (ii) via non-covalent interactions between NPS.

1.3.4.1. Covalent interaction between NPs. Surface functionalized NPs offer ample opportunity to tailor interfacial interaction and utilize different chemistries to arrest the self assembled structure at the liquid-liquid interface via judicious choice of ligands. Covalent crosslinking between ligands provides appreciable mechanical integrity and structural stability to the NPs assemblies. In their earlier work, Lin et al created ultrathin NPs membrane [87] by crosslinking CdSe quantum dots (~ 3nm) at toluene-water interface via polymerization of vinyl benzene moieties.

High efficiency of the copper(I) catalyzed Huisgen type [3+2] "Click" cycloadditions under ambient conditions prompted Rotello group to evaluate this reaction for the crosslinking of NPs at the interface of water-in-oil emulsions (Figure 1.12). In this strategy, alkyne and azide functionalized Fe_3O_4 NPs were co-assembled at the interface and covalently linked using the Cu(I) catalyst present in the aqueous microdroplets (Figure 1.12.a). This methodology provides dense crosslinking of NPs on the colloidosome shell, resulting in high stability of the colloidosomes that allowed their transfer into water [66]. Furthermore, the permeability of these colloidal containers can be expected to be low because of small nanoparticle size and dense crosslinking.

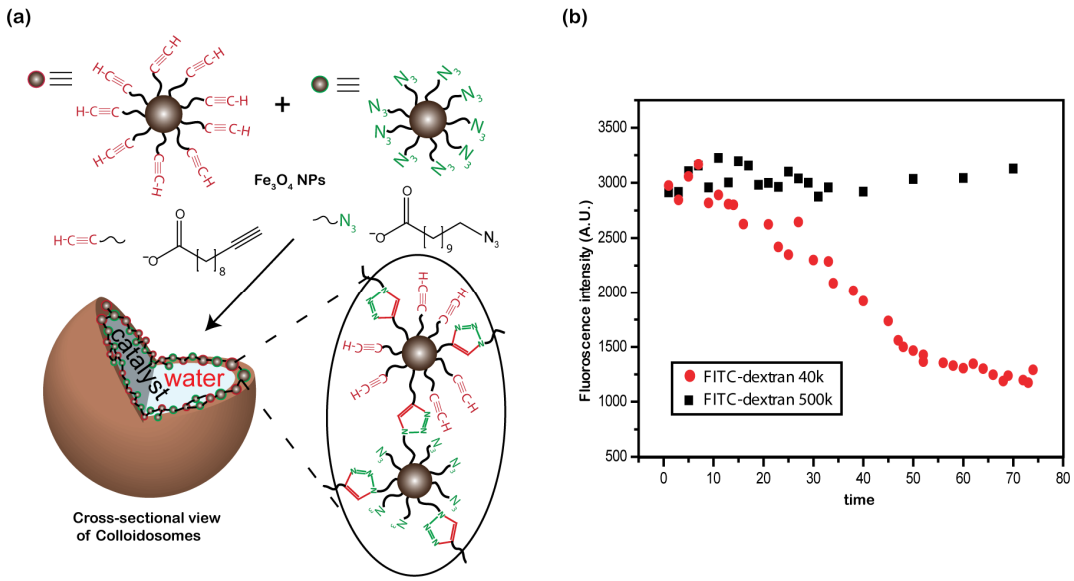

Figure 1.12. (a) Formation of magnetic colloidosomes synthesis through self-assembly at water-in-oil interfaces followed by interfacial crosslinking of NPs via click chemistry and cross-sectional view of a colloidosome. (b) Size selective release of fluorescent dyes from the colloidosomes

Indeed, different sized fluorescent dyes were shown to have distinctive permeability out of the colloidosomes in water based on size exclusion processes. For example, while the rate of release of a small dye like riboflavin was very fast, dyes bound to a high molecular weight dextran polymer did not diffuse out from the colloidosomes (Figure 1.12.b).

1.3.4.2. Noncovalent interaction between NPs. Noncovalent interaction mediated self-assembly is an attractive alternative compared to covalent strategies, opening up the potential for the fabrication of dynamic systems. For example, molecular recognition provides a noncovalent coupling between two complementary molecules or surfaces functionalized with such complementary molecules. The 'tailored interactions' between building blocks via molecular recognition along with the 'dynamic nature' of self-assembly process provides a promising tool to create novel functional materials and molecular assemblies [88]. In a recent work, Rotello and Sanyal reported the fabrication of colloidal microcapsules via "host-guest" type molecular recognition at the liquid-liquid interface [89]. This strategy is used to create stimuli-responsive colloidal microcapsules at oil-water interfaces using molecular recognition between appropriately functionalized gold nanoparticles (Figure 1.13.a). Water-soluble β-cyclodextrin-capped gold nanoparticles and organo-soluble adamantyl functionalized gold nanoparticles were self-assembled at the water-toluene interface via specific "host-guest" molecular interactions to provide robust microcapsules. Multivalent interactions of the complementary ligands on the NPs surface provide lateral stability to these capsules; no stabilization was observed when either NPs was used alone.

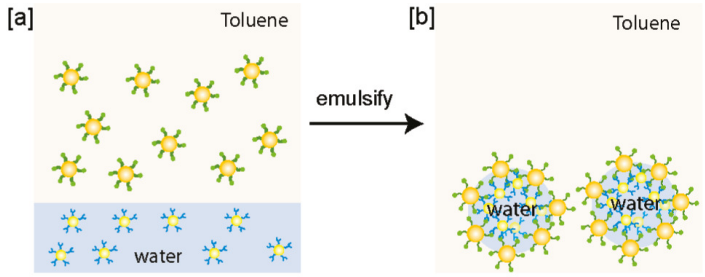

Figure 1.13. (a) NP1 and NP2 dispersed in water and toluene, respectively. (b) Fabrication of colloidal microcapsule via recognition mediated crosslinking

2. AIM OF THE STUDY

This thesis is composed of three parts. In the first part, the use of dendritic scaffolds to encapsulate flavin derivatives and tuning their electrochemical behavior using molecular recognition is studied (Figure 2.1). Three generations of dendrons containing diaminopyridine (DAP) unit at their focal point were utilized to probe the supramolecular encapsulation of monomeric and polymeric flavin units. The DAP moiety on the dendrons binds to monomeric and polymeric flavins to produce supramolecular structures. The resultant encapsulated supramolecular assemblies demonstrate distinctly different redox behavior as a function of encapsulation. Monomeric flavins exhibit reversible, redox-modulated behavior consistent with previous flavin model systems [90]. Polymeric flavins, however, demonstrate diffusion limited redox behavior and site isolation when bound to increasing DAP dendrimer generations. The effective encapsulation of polymeric flavins via supramolecular interaction provides a potential tool to modulate redox processes in various systems including artificial enzymes, light harvesting systems, molecular wires, and light-emitting diodes.

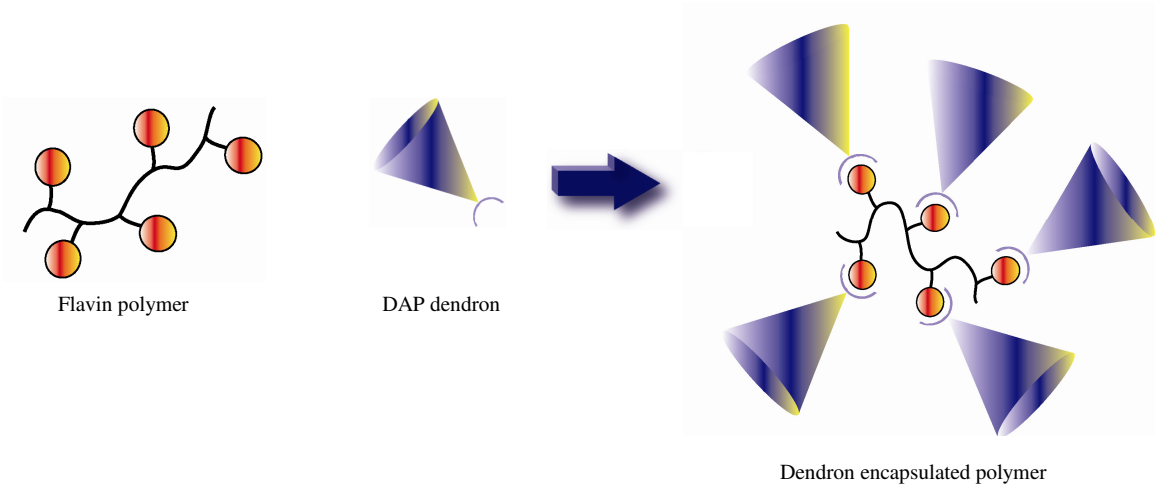

Figure 2.1. General scheme of a schematic representation of encapsulation of flavin polymer

In the second part, goal is to fabricate water-dispersible functional polymeric microspheres. Self-assembled microspheres were arrested via an effective crosslinking method which is [3+2] Huisgen Cycloaddition (Figure 2.2.a-b) [60, 61]. ‘‘Click’’ chemistry has a wide application area in polymer [91, 92] and dendrimer [63, 64] synthesis, in the formation of colloidosomes [65] and in the functionalization of micelles and nanoparticles [65, 93]. The copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes is a highly efficient coupling procedure and therefore it is very suitable for the further functionalization of microspheres. Beside of this efficiency, this type of ‘‘click’’ reaction is highly selective, thereby tolerating the presence of other functional groups. Polymer building blocks carrying both recognition units that involve in non-covalent interactions and reactive units that can be crosslinked to capture the self-assembled structures were synthesized. After crosslinking, pegylation was performed to overcome solubility problem of polymer in solvents like methanol and water (Figure 2.2.c). Another noteworthy point is the ability to further functionalize these microspheres [61, 94]. This was demonstrated by immobilization of a fluorescent dye, BODIPY and attachment of specific ligands such as biotin enzyme immobilizationbiotin.

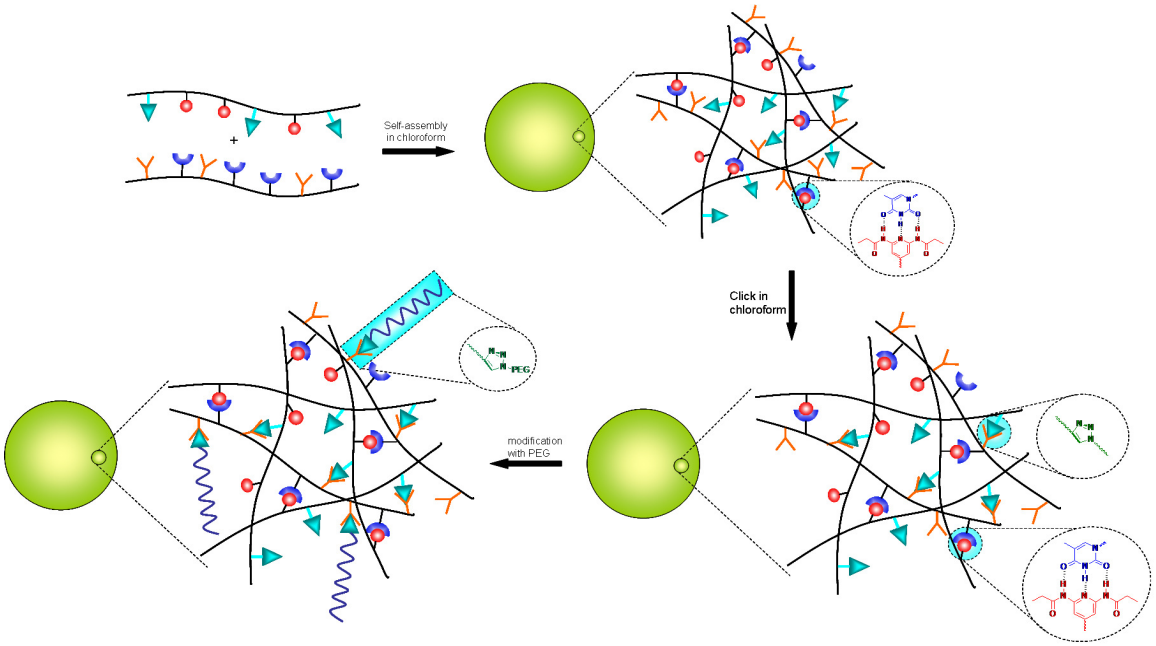

Figure 2.2. Schematic illustration of (a) the self-assembly of microspheres via molecular recognition, (b) their subsequent crosslinking and (c) pegylation via click chemistry

In the last part, fabrication of stimuli-responsive colloidal microcapsules at the oil-water interface using molecular recognition between β-cyclodextrin functionalized gold nanoparticles and adamantyl-functionalized iron oxide nanoparticles is shown. β-cyclodextrin is water soluble, thus β-cyclodextrin-coated gold nanoparticles are nicely soluble in water. Adamantyl-functionalized gold nanoparticles are organic soluble. β-cyclodextrin functionalized gold nanoparticles and adamantyl-functionalized iron oxide nanoparticles self-assemble at the water-toluene interface via specific host-guest molecular interactions and results in formation of microcapsules (Figure 2.3).

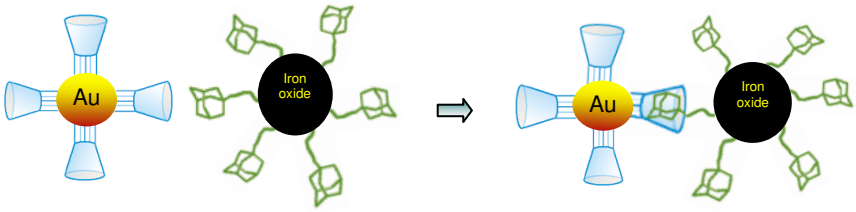

Figure 2.3. Schematic illustration of host-guest molecular interaction between adamantane functionalized iron oxide and β-cyclodextrin functionalized gold nanoparticles

3. EXPERIMENTAL STUDIES

3.1. Methods and Materials

Monomers (styrene and 4-chloromethylstyrene) were purified from the inhibitor using short alumina plugs. 2,2-azobisisobutyronitrile (AIBN) were purchased from Aldrich Chemical Co. 2,2-Azoisobutyronitrile (AIBN) was purified by recrystallization from ethanol. Poly(ethylene glycol) monomethyl ether (PEG, MW 2000) was purchased from Alfa Aesar. Fluorescein (FITC) conjugated streptavidin is obtained from Pierce and used as received. BodipyC10Br was synthesized according to literature procedure [95]. Bodipy-azide was synthesized according to literature procedure [96]. Biotin azide was synthesized according to the literature procedure [97]. 2,6-Dipropamidopyrid-4-one (DAP) was synthesized as previously published [49].

Solutions utilized in electrochemical experiments were prepared using reagent grade CH_2Cl_2 dried via distillation over CaH_2. Tetrabutylammonium perchlorate (TBAP, obtained from SACHEM, electrometric grade) was dissolved in $CHCl_3$, washed with distilled water, recrystallized twice from ethyl acetate and dried for several days under high vacuum. Triethylamine was distilled over CaH_2. All chemicals were reagent grade and were used as received from manufacturer (Merck, Aldrich, Alfa Aesar, and Riedel de Haen) unless otherwise noted. Dry solvents (CH_2Cl_2, THF, toluene) was obtained from ScimatCo Purification System, other dry solvents were dried of molecular sieves. Column chromatography was performed using silicagel-60 (43-60 nm). Thin layer chromatography was performed using silica gel plates (Kiesel gel 60 F254, 0.2mm, Merck). Plates were viewed under 254 nm UV lamp. Infrared spectroscopy was carried out on Thermo Scientific Nicolet 380 FTIR spectrophotometer. ^1H NMR (operating at 400 MHz) and was recorded on Varian Mercury-MX in $CDCl_3$ as solvent at the Advanced Technologies Research and Development Center at Boğaziçi University.

3.2. Synthesis

3.2.1. Electrochemistry

All electrochemical experiments were carried out on a Cypress System potentiostat. A 1 mm platinum button and a gold-plated electrode were utilized as working and reference electrodes, respectively. A silver wire pseudo reference electrode was used and all potentials are referenced versus the ferrocene/ferrocenium couple. The sweep rate was 100 mV/s and the studies were run on an argon-purged temperaturecontrolled cell. Solutions of flavin/flavin polymer and the flavin/flavin polymer-DAP complexes were prepared maintaining a constant concentration of the cofactor, with the receptors added to saturation. The solutions were degassed by bubbling argon through them for at least 10 minutes, at which time cyclic and square wave voltammograms were recorded.

3.2.1.1. Cyclic Voltammetry. CV traces were recorded for a CH_2Cl_2 blank, then for a solution of the flavin or flavin polymer and ferrocene (as a reference), and finally for the same samples containing excess DAP. Differences in halfwave potentials were determined using square-wave voltammetry. All scans were recorded at a sweep rate of 100 mV S^{-1}.

3.2.2. Molecular dynamics simulation (Amber force field)

Molecular dynamic simulations were performed on the flavin/flavin polymer with DAP dendrons using MacroModel (Maestro v8.0) from Schrodinger, Inc. Amber* force field was chosen from the subsystem “Dynamics” and the calculations were performed in a continuum of chloroform as the solvent. Electrostatic treatment was set to the constant dielectric setting of 1.0. The external cutoffs were automatically set to 8.0 (Van der Waals), 20.0 (electrostatics), and 4.0 (hydrogen bonding). There were no constraints placed on the molecule. The method used was TNCG (Truncated Newton linear Conjugate Gradient), with the maximum number of iterations at 500. Convergence was based on a gradient and the threshold was set to 0.0500. Stochastic dynamics were used, and all the bonds were shaken during the calculation. The simulation temperature was performed over the range of 1000K-100K (decreasing). The time steps (fs) were set to 1.5, the equilibrium time (ps) set to 1.0, and the simulation time (ps) set to 10.0.

3.2.3. Synthesis of Building Blocks

3.2.3.1. Synthesis of alkyne functionalized flavin 1. To a solution of 4, 5-dimethyl-1, 2-phenylene diamine (7.3 mmol) and Et_3N (14.6 mmol) in THF (20 mL) at 60 °C was added 6-chlorohexyne (7.3 mmol) and an excess of NaI. The reaction was allowed to proceed overnight at 60 °C. Upon cooling the reaction mixture was washed with saturated NaCl solution, and the organic layer was then removed, dried with anyhydrous Na_2SO_4, filtered, and reduced under reverse pressure. The resulting mixture was then purified using flash column chromatography (hexanes/ethyl acetate 1:1), resulting in the mono alkylated, alkyne functionalized diamine derivative as a reddish oily product (4.4 mmol, 61% yield). In a round bottom flask was combined the purified alkyne functionalized diamine derivative (5.7 mmol), alloxan monohydrate (5.7 mmol) and boron oxide (11.5 mmol) in acetic acid (20 mL). The above mixture was then heated to 60 °C for 3 hours. The mixture was then cooled, and precipitated into H_2O. The mixture was then extracted with CH_2Cl_2 (3 x 25 mL), the organic layers were combined, washed with brine, anhydrous Na_2SO_4, filtered, and reduced under reverse pressure onto silica gel. The crude product was then purified using flash column chromatography (10:1 CH_2Cl_2/THF). The columned product was then recrystallized from absolute ethanol yielding flavin 1 (3.3 mmol, 59% yield after recrystallization, mp 279-282 °C). ^1H NMR ($CDCl_3$,δ, ppm) = 8.40 (s, 1H), 8.08 (s, 1H), 7.50 (s, 1H), 4.74 (br t, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.38-2.34 (m, 2H), 2.02 (dt, *J* = 11.2, 5.2 Hz, 2H), 1.82-1.77 (m, 2H), 1.26 (s, 1H) (Figure A.1).

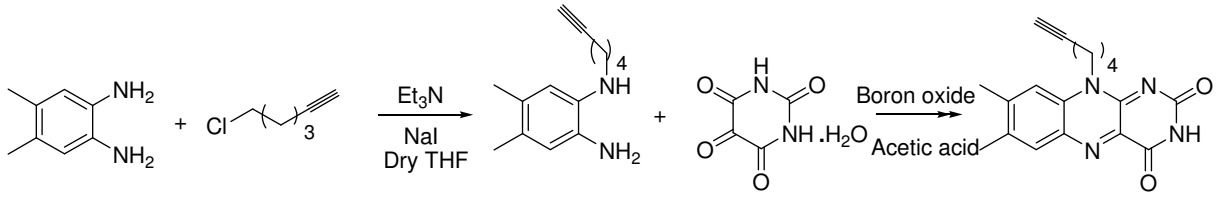

Figure 3.1. Synthesis of alkyne functionalized flavin 1

3.2.3.2. Synthesis of control N-methylated, alkyne functionalized flavin 2. To a solution of flavin 1 (0.462 mmol) and K_2CO_3 (1.84 mmol) in DMF (5 mL) at 60 °C was added MeI (0.924 mmol) and the reaction was allowed to proceed overnight. Upon cooling, the reaction was quenched with H_2O and extracted with $CHCl_3$ (3 x 25 mL). The organic

layers were combined, washed with brine, anhydrous Na_2SO_4, filtered, and reduced under reverse pressure onto silica gel. The crude product was then purified using flash column chromatography (15:1 CH_2Cl_2/THF) yielding control *N*-methylated, alkyne functionalized flavin 2 (0.420 mmol, 91% yield, mp 260-263 °C). ^{1}H NMR ($CDCl_3$,δ, ppm) = 8.07 (s, 1H), 7.47 (s, 1H), 4.73 (br t, 2H), 3.52 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.38-2.34 (m, 2H), 2.02 (dt, *J* = 11.2, 5.2 Hz, 2H), 1.82-1.77 (m, 2H), 1.26 (s, 1H) (Figure A.2).

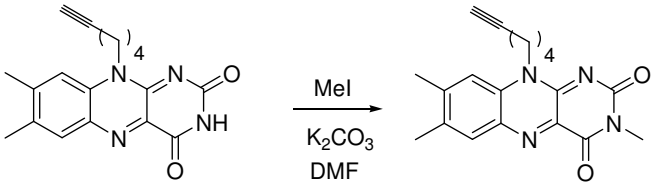

Figure 3.2. Synthesis of control N-methylated alkyne functionalized flavin 2

3.2.3.3. Flavin functionalized copolymers. Compound chloromethylstyrene/styrene copolymer was synthesized according to the previously reported literature procedure [49].

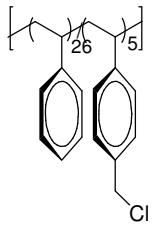

Figure 3.3. Chemical structure of copolymer of styrene-chloromethylstyrene polymer

3.2.3.4. Azide functionalized polystyrene polymer 3. To a solution of chloromethylstyrene copolymer (0.2 mmol) in DMSO (10 mL) was added an excess of NaN_3 (2 mmol, ~10 eq. azide per polymer chain). The reaction was allowed to proceed overnight. The polymer was then precipitated from H_2O. The crude polymer was then filtered, washed with copious amounts of H_2O, and allowed to dry yielding azide functionalized polystyrene polymer 3 (0.196 mmol, 98% yield). ^{1}H NMR ($CDCl_3$, δ, ppm) = 7.20-6.30 (br m, 25H), 4.24 (br s, 2H), 2.00-1.20 (br m, 19H) (Figure A.3).

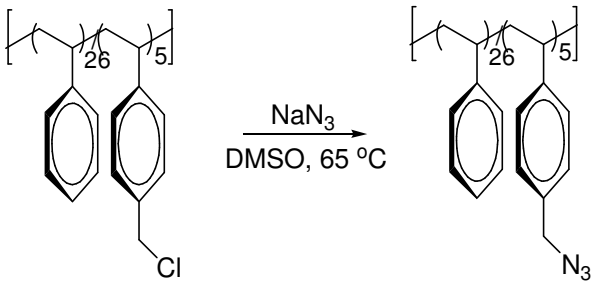

Figure 3.4. Synthesis of azide functionalized polystyrene polymer 3

3.2.3.5. Flavin functionalized polystyrene polymer 4. To a solution of polymer 3 (40 µmol) and flavin 1 (0.24 mmol) in DMSO (5 mL) was added CuI (cat.). The reaction was allowed to proceed for 3 hours whereupon the polymer was precipitated into a stirring solution of saturated $NH_4^+Cl^-$. The dark, reddish brown DMSO mixture instantaneously yielded highly fluorescent polymer 4. The polymer was then filtered, washed with copious amounts of H_2O, and dried resulting in flavin functionalized polystyrene polymer 4 (36 µmol, 90% yield). ^{1}H NMR ($CDCl_3$,δ, ppm) = 9.27 (s, 1H), 8.02 (s, 1H), 7. 57 (s, 1H), 7.40-6.25 (br m, 25H), 5.40 (br s, 1H), 4.73 (br t, 1H), 4.73 (br t, 2H), 3.52 (s, 3H), 2.58 (s, 3H), 2.43 (s, 3H), 2.84 (br s, 2H), 2.59 (br s, 2H), 2.43 (br s, 2H), 2.15-0.82 (br m, 19H) 1.26 (s, 1H) (Figure A.4).

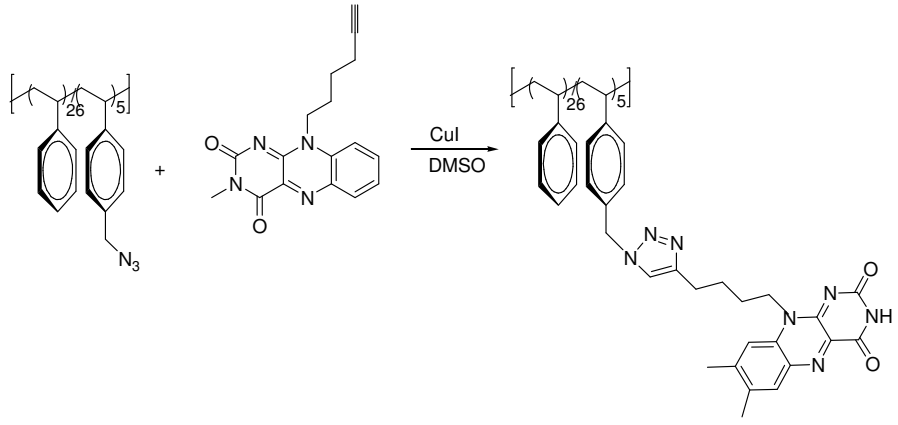

Figure 3.5. Synthesis of flavin functionalized polystyrene polymer 4

3.2.3.6. Control N-methylated flavin functionalized polystyrene polymer5. To a solution of polymer 3 (40 µmol) and control flavin 2 (0.24 mmol) in DMSO (2 mL) was added CuI

(cat.). The reaction was allowed proceed for 3 hours whereupon the polymer was precipitated into a stirring solution of saturated $NH_4^+Cl^-$. The dark, reddish brown DMSO mixture instantaneously yielded highly fluorescent polymer 5. The polymer was then filtered, washed with copious amounts of H_2O, and dried resulting in control *N*-methylated flavin functionalized polystyrene polymer 5 (37 μmol, 93% yield). ^1H NMR ($CDCl_3$,δ, ppm) = 8.05 (s, 1H), 7. 55 (s, 1H), 7.41-6.35 (br m, 25H), 5.36 (br s, 1H), 4.73 (br t, 1H), 3.50 (br s, 3H), 3.83 (s, 2H), 2.58 (s, 3H), 2.43 (s, 3H), 2.15-0.75 (br m, 19H) (Figure A.5).

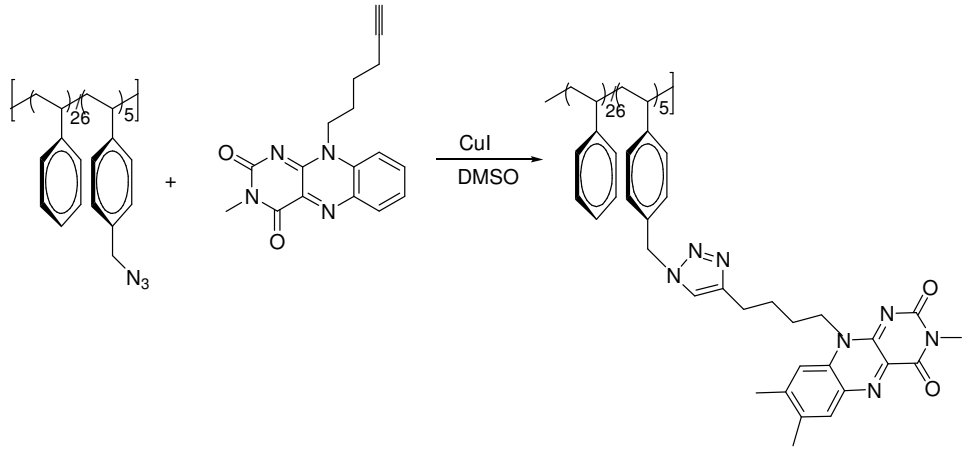

Figure 3.6. Synthesis of control N-methylated flavin functionalized polystyrene polymer5

3.2.3.7. Synthesis of DAP Dendrons. The poly (aryl ether) bromide dendrons reported here were synthesized by the adaptation of the procedures used by Fréchet and Hawker [5, 57]. The poly (aryl ether) azide dendrons were synthesized according to literature [63]. DAP-OH was prepared according to reported literature [57].

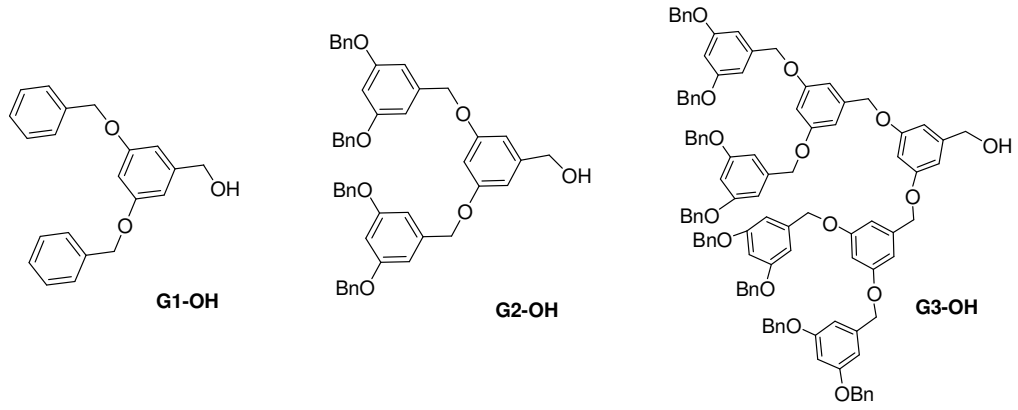

Figure 3.7. G1, G2 and G3 polyaryl dendrons

3.2.3.8. Representative procedure for G2-DAP-dendron. A solution of G2-bromide (0.131 g, 0.16 mmol), DAP-OH (0.040 g, 0.18 mmol), 18-crown-6 (0.002 g, 0.008 mmol) and anhydrous K_2CO_3 (0.033 g, 0.24 mmol) in dry acetone (6 mL) was refluxed under N_2 for 18 h. Then, the reaction mixture was filtered to remove K_2CO_3, and the filtrate evaporated under *vacuo*. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate/ hexane (1:1) as eluent to obtain DAP G2-dendron as a waxy solid. (0.127 g, 83 % yield). ^{1}H NMR ($CDCl_3$,δ, ppm) = 7.63 (s, 2H), 7.46 (s, 2H), 7.40 – 7.27 (m, 20H), 6.67 (d, *J* = 2.1 Hz, 4H), 6.65 (d, *J* = 2.1 Hz, 2H), 6.55 (t, *J* = 2.1 Hz, 2H), 6.53 (t, *J* = 2.1 Hz, 1H), 5.07 (s, 2H), 5.04 (s, 8H), 4.99 (s, 4H), 2.37 (q, 4H), 1.22 (t, *J* = 7.5 Hz, 6H) (Figure A.6).

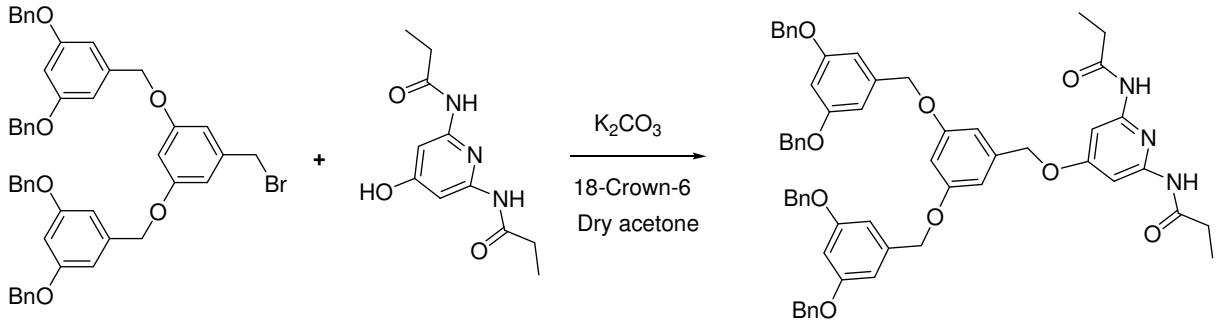

Figure 3.8. Synthesis of G2-DAP-dendron

Above procedure was followed to obtain G1-DAP-dendron. ^{1}HNMR ($CDCl_3$,δ, ppm) = 7.63 (s, 2H), 7.49 (br s, 2H), 7.42 - 7.28 (m, 10H), 6.67 (d, *J* = 2.2 Hz, 2H), 6.56 (t, *J* = 2.2 Hz, 1H), 5.05 (s, 2H), 5.04 (s, 4H), 2.39 (q, 4H), 1.20 (t, *J* = 7.5 Hz, 6H) (Figure A.7).

Above procedure was followed to obtain G3-DAP-dendron. ^{1}HNMR ($CDCl_3$,δ, ppm) = 7.63 (s, 2H), 7.46 (s, 2H), 7.40 - 7.26 (m, 40H), 6.66 (d, *J* = 2.4 Hz, 14H), 6.55 (m, 7H), 5.04 (s, 2H), 5.00 (s, 16H), 4.96 (s, 4H), 4.95 (s, 8H), 2.32 (q, 4H), 1.18 (t, *J* = 7.6 Hz, 6H) (Figure A.8).

3.2.4. Characterization of polystyrene copolymer

Number-averaged molecular weights (M_n) and polydispersity indexes (PDI) of the parent polymer in THF solution was determined from gel permeation chromatograms (GPCs) acquired on an in-house built GPC system using PL Caliber data collection software, three-column set (Polymer Labs, Inc.; PLgel 5 mm columns, 300 mm_7.5 mm, 103, 104 and 105 A° pore size), with an RI detector (Waters 403). The system was calibrated with respect to polystyrene standards (Polymer Labs, Inc.). S_{Cl} content was calculated according to ^{1}H NMR peak integration (using a Bruker AC-200 spectrometer operating at 200.13MHz for ^{1}H) to an estimated error of 5% S_{Cl} content. NMR spectra were taken in $CDCl_3$ with the exception of ^{1}H NMR of DAP taken in DMSO.

3.2.5. Scanning Electron Microscopy

Pegylated polymersomes were lyophilized and scanning electron microscopy was used to characterize the morphology. Images were taken using ESEM-FEG/EDAX Philips XL-30 (Philips, Eindhoven, The Netherlands) instrument using an accelerating voltage of 10 kV.

3.2.6. Poly(styrene-p-(chloromethyl)styrene)

AIBN (800 mg, 4.88 mmol) was added to a solution of styrene (4.8 g, 46.08 mmol) and p-(chloromethyl)styrene (7 g, 45.9 mmol) in chlorobenzene (80 mL). The reaction mixture was heated at 80 °C for 20 h. The reaction mixture was then cooled to room

temperature and added to cold methanol (300 mL); white solid (7.67 g, 65%) was precipitated in the presence of vigorous mixing. The precipitate was collected by filtration, and washed with methanol. The product (parent polymer) was dried in vacuo. ^{1}H NMR ($CDCl_3$, δ, ppm) = 7.3-6.2 (br m, 12H), 4.49 (br s, 2H), 2.0-1.2 (br m, 8H) (Figure A.10). $M_{n\text{-}GPC}$= 5578 , PDI=1.41, CMS:St=1:1.

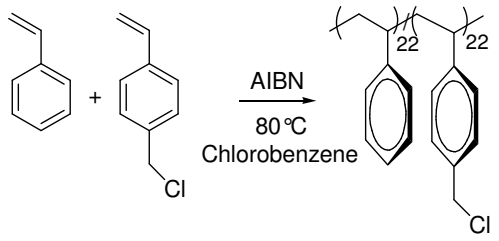

Figure 3.9. Synthesis of poly(styrene-*p*-(chloromethyl)styrene)

3.2.7. Synthesis of Polymer I (PS-DAP-Az)

3.2.7.1. Synthesis of Azide Polymer. The parent polymer P(S_{Cl}-co-S) (500mg, 0.0896 mmol 1.97mmol) was dissolved in 3mL of N,N-dimethylformamide (DMF) and sodium azide (25 mg, 0.4 mmol) was added into the reaction mixture. The reaction mixture was stirred at 70 ^{o}C for 18 h. The product was concentrated in vacuo and precipitated in methanol (100 mL) after cooling to room temperature. The white solid product was filtered and dried in vacuo. ^{1}H NMR ($CDCl_3$, δ, ppm) = 7.25-6.20 (br m, 22H), 4.51 (br s, 3H), 4.23 (br s, 2H), 2.21-0.85 (br m, 15H) (Figure A.11).

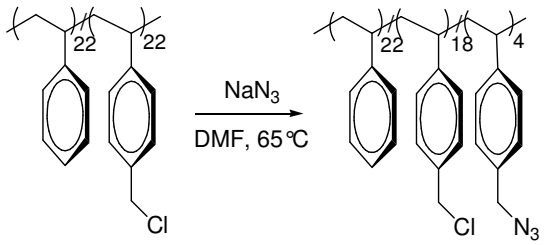

Figure 3.10. Synthesis of azide polymer

3.2.7.2. Synthesis of DAP polymer. The azide polymer (150 mg, 0.484 mmol), K_2CO_3 (100 mg, 0.726 mmol) and Dap (57.3 mg, 0.242 mmol) were dissolved in 3 mL of N,N-

dimethylformamide (DMF). The reaction mixture was kept at 70 ^{o}C for 16 h. The reaction was cooled to room temperature and K_2CO_3 was filtered and the polymer was precipitated in 150 mL methanol. The precipitate was collected and dried in vacuo. ^{1}H NMR ($CDCl_3$, δ, ppm) = 7.29-6.19 (br m, 24H), 5.01 (br s, 2H), 4.50 (br s, 2H), 4.22 (br s, 2H), 2.38 (br s, 4H), 1.79 (br s, 6H), 1.79-0.82 (br m, 18H) (Figure A.12).

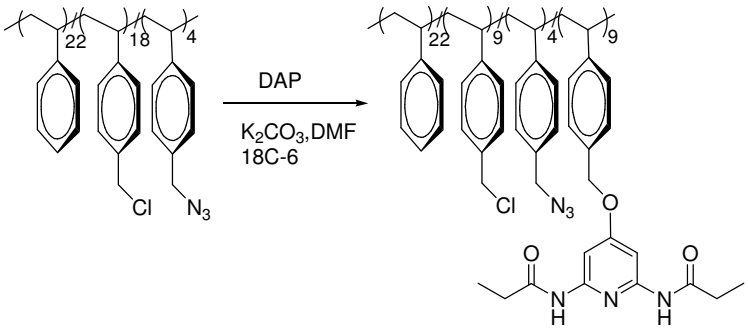

Figure 3.11. Synthesis of DAP polymer

3.2.8. Synthesis of Polymer II (PS-THY-Alk)

3.2.8.1. Synthesis of Alkyne polymer. The parent polymer (500 mg, 0.0896 mmol, 1.97 mmol), propargyl alcohol (22.11 mg, 0.3944 mmol) and sodium hydrate (NaH) (18.93 mg, 0.789 mmol) were dissolved in dry tetrahydrofuran (THF, 10 mL) and the parent polymer (500 mg, 0.0896 mmol, 1.97 mmol) was added into the reaction mixture which was heated to 65 ^{o}C for 16 h. After reaction, polymer was precipitated in 200 mL methanol and the precipitate was collected and dried in vacuo. ^{1}H NMR ($CDCl_3$, δ, ppm) = 7.23-6.20 (br m, 22H), 4.52 (br s, 4H), 4.12 (br s, 2H), 2.45 (br s, 4H), 2.12-0.82 (br m, 15H) (Figure A.13).

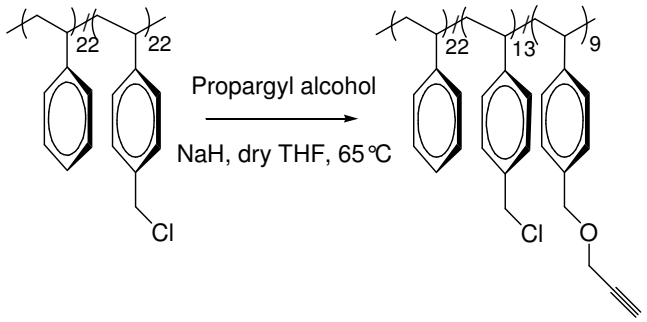

Figure 3. 12. Synthesis of alkyne polymer

3.2.8.2. Synthesis of Thy polymer. The alkyne polymer (100 mg, 0.34 mmol), thymine acetic acid (32 mg, 0.17 mmol), K_2CO_3 (23 mg, 0.17 mmol) and N,N-dimethylformamide (DMF, 2 mL) were reacted at 65 ^oC for 16 h under nitrogen atmosphere. Solvent was evaporated under vacuo and the polymer was precipitated in distilled water. Precipitate was filtered and washed with water. The product was dried in lyoflizer. ^1H NMR ($CDCl_3$, δ, ppm) = 7.23-6.20 (br m, 22H), 5.12 (br s, 2H), 4.51 (br s, 19H), 4.12 (br s, 5H), 2.47 (br s, 1H), 2.13-0.80 (br m, 65H) (Figure A.14).

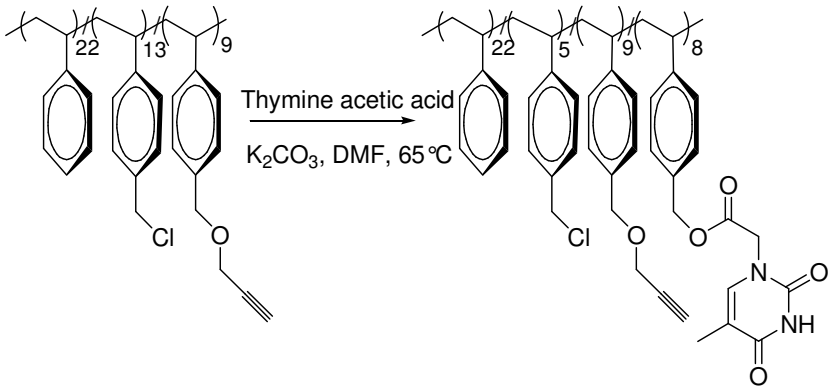

Figure 3.13. Synthesis of Thy polymer

These random copolymer P(S_{Cl}-co-S-co-S_{N3}) and P(S_{Cl}-co-S-co-S_{Alkyne}) scaffolds were converted using previously established methods to DAP-functionalized polymer P(S_{Cl}-co-S-co-S_{N3}-co-S_{DAP}) and Thy-functionalized polymer P(S_{Cl}-co-S-co-S_{Alkyne}-co-S_{Thy}) [48].

3.2.9. Representative Polymersome Fabrication

3.2.9.1. Representative Polymersome Crosslinking. 2 mg DAP polymer and 2 mg Thy polymer were dissolved in 1 mL $CHCl_3$ separately, then mixed together. 0.5 mg Cu(I)Br was weighed and put in a vial containing 0.5 mL $CHCl_3$. Pentamethyldiethylenetriamine (PMDETA) (50 microliter, 41.5 mg, 0.24 mmol) was used to dissolve Cu(I)Br. Dissolved cupper solution was added onto the microsphere solution. The reaction mixture was stirred at room temperature for 6 h. Clicked microspheres were checked under microscope in chloroform.

3.2.10. Synthesis of Iron NPs and Place Exchange Reaction

3.2.10.1. Synthesis of NPs. 0.86 g (4.32 mmol) of $FeCl_2.4H_2O$ and 2.34 g (8.66 mmol) of $FeCl_3.6H_2O$ were dissolved under argon atmosphere in 80 mL of milliQ water with vigorous stirring. The solution was purged with argon for 5 min to remove any oxygen present in the milliQ water. A black precipitation was formed after the addition of NH_4OH (10 mL) to the reaction solution. The pH of the reaction mixture was retained at 10-12. This precipitate was further incubated at 90 ºC for 20 min. The reaction mixture was then cooled down to room temperature and washed with milliQ water several times to remove any un-reacted chemicals and decrease the pH of the solution to 7-8. 15 mL aqueous solution of oleic acid (1g) and 5 mL of NH_4OH were added to the NP precursor in argon atmosphere. Then the reaction mixture was sonicated for 20 min. A clear reddish-brown color solution was formed. The reaction mixture was incubated at 100 °C for 3h. Aqueous dispersion of the NPs was precipitated using acetone. The black colored precipitation was redispersed in hexane. Excess ligands were removed by re-precipitating using ethanol and dispersion in hexane. Purification was performed twice and NPs were dispersed in hexane or dichloromethane.

3.2.10.2. Place Exchange Reaction to Get ADA Functionalized Iron Nanoparticles. Oleic acid coated iron oxide nanoparticles (50 mg) are dissolved in 1 mL DCM. 150 mg adamantine 1-carboxylic acid is dissolved in 1.5 mL DCM. Two solutions are mixed and nitrogen is purged. To purify, nanoparticles are precipitated twice in ethanol and collected with the aid of a magnet. Purified ADA coated iron nanoparticles are kept in DCM.

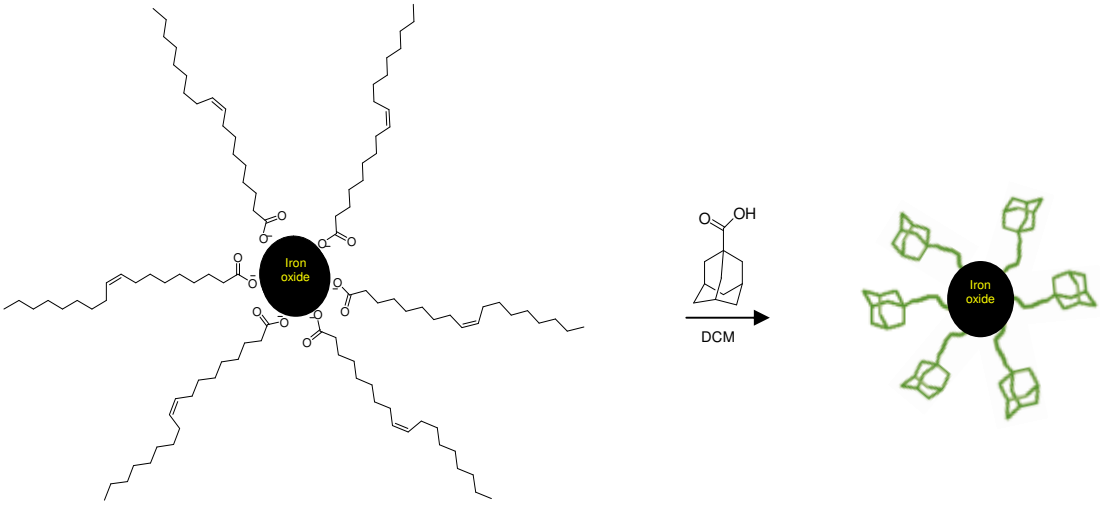

Figure 3.14. Synthesis of adamantane coated iron oxide nanoparticles

3.2.10. Synthesis of Cyclodextrin Functionalized Au Nanoparticles

3.2.10.1. Synthesis of Per iodo β cyclodextrin. To a solution of Ph_3P (6.91 g, 26.4 mmol) in dry DMF (30 mL), I_2 (6.98 g, 27.6 mmol) was added over 15 mins. Heat evolved during this addition and the solution increased in temperature from RT to approximately 50 °C. Dry D-cyclodextrin (2.00 g, 10.2 mmol) was then added to this dark brown solution and the temperature was raised to 70 °C using an oil bath. The solution was stirred at this temperature for 20 h. The heat was removed, and the solution was concentrated to 1/3 of its original volume. To this residue, NaOMe in MeOH (3.00 M, 10.3 mL) was added where the reaction was cooled in ice/salt slurry and the mixture was stirred for 30 mins. The reaction mixture was then poured into MeOH (150 mL) to form a precipitate, which was then washed with MeOH 6-7 times by successive dispersions and centrifugations. 1H NMR spectrum was in agreement with the literature data.

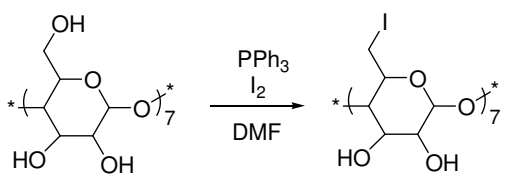

Figure 3.15. Synthesis of Per iodo β cyclodextrin

3.2.10.2. Synthesis of Per thio β cyclodextrin. Per iodo cyclodextrin (0.500 g, 0.26 mmol) was dissolved in DMF (6 mL); thiourea (0.156 g, 2.05 mmol) was then added and the reaction mixture heated to 70 ^{o}C under a nitrogen atmosphere. After 19 h, the DMF was removed under reduced pressure to give yellow oil, which was dissolved in water (25 mL). Sodium hydroxide (0.135 g, 3.37 mmol) was added and the reaction mixture heated to a gentle reflux under a nitrogen atmosphere. After 1 h, the resulting suspension was acidified with aqueous $KHSO_4$ and the precipitate filtered off, washed thoroughly with distilled water, and dried. To remove the last traces of DMF, the product was suspended in water (25 mL) and the minimum amount of potassium hydroxide added to give a clear solution; the product was then reprecipitated by acidifying with aqueous $KHSO_4$. The resulting fine precipitate was carefully filtered off and dried in the freeze-drier. ^{1}H NMR spectrum was in agreement with the literature data.

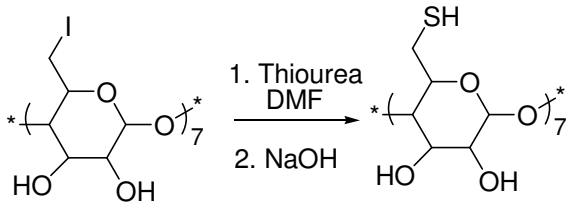

Figure 3.16. Synthesis of per thio β cyclodextrin

3.2.10.3. Synthesis of Cyclodextrin Functionalized Au Nanoparticles. CD-functionalized Au nanoparticles were synthesized according to a literature procedure. $HAuCl_4$ (90 mg, 0.27 mmol) was dissolved in DMSO (10 mL). This solution was mixed quickly with a solution of $NaBH_4$ (123 mg, 3.25 mmol) and per thio cyclodextrin (100 mg, 0.08 mmol) in DMSO (10 mL). The reaction mixture turned deep-brown immediately, and was allowed to continue for 24 h. At this point, CH_3CN (20 mL) was added to precipitate the nanoparticles, which were collected and purified by centrifugation, followed by washing with CH_3CN:DMSO (1:1 v/v, 30 mL) and ethanol (30 mL), dissolution in water, and freeze-drying. ^{1}H NMR spectrum was in agreement with the literature data.

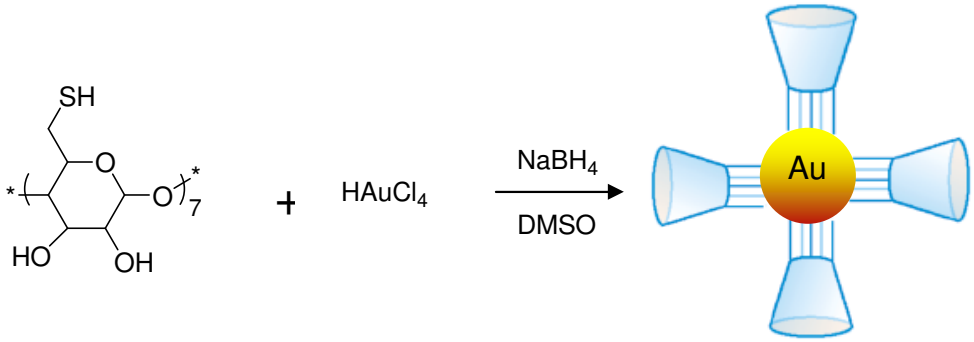

Figure 3.17. Synthesis of Cyclodextrin Functionalized Au Nanoparticles

4. RESULTS AND DISCUSSION

4.1. Recognition Mediated Polymer Encapsulation

Monomeric and polymeric flavins were synthesized using a previously reported procedure [98]. Briefly, polymeric flavin was synthesized by reacting the monomeric alkyne flavin derivative with azide functionalized polymer via Huisgen 1,3-dipolar, ‘‘click’’ cycloadditions (Figure 4.1).

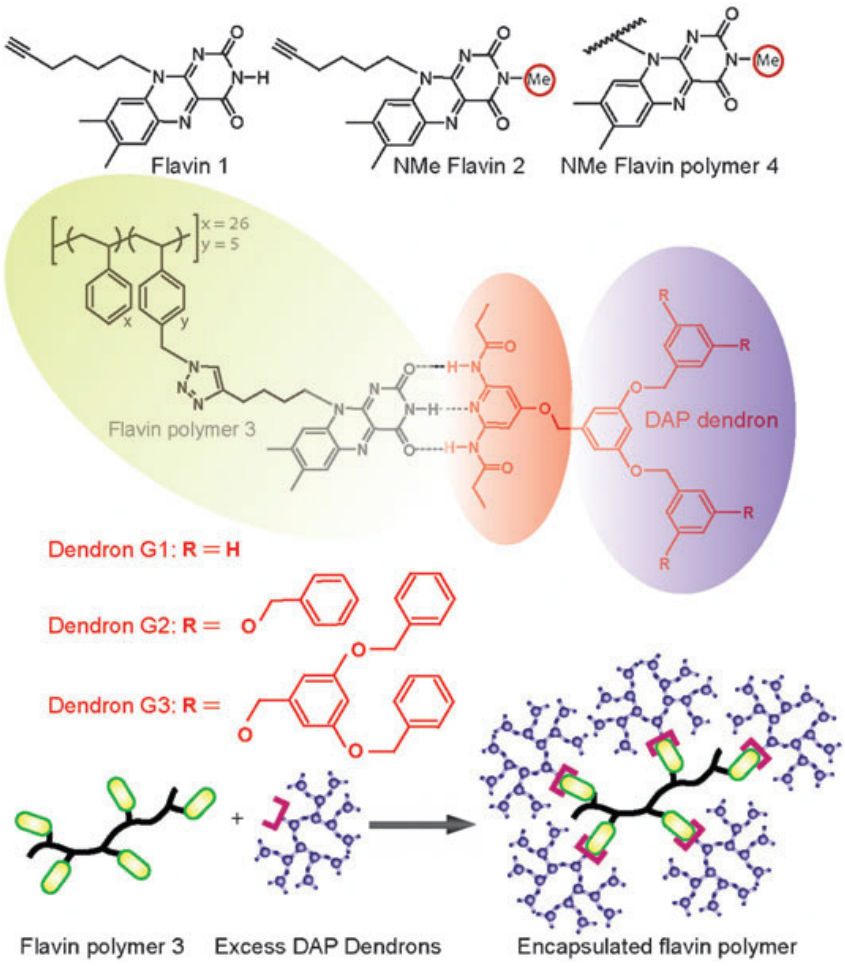

Figure 4.1. Alkyne-functionalized flavin 1, control N-methylated flavin 2, flavin polymer 3 exhibit specific three-point hydrogen bonding interactions with complementary dendrons, control polymer 4, and a schematic representation of encapsulation of flavin polymer

The association constant (Ka(ox)) of flavin 1 and flavin polymer 3 with complementary DAP dendrons was quantified via fluorescence titrations in $CHCl_3$. The fluorescence intensity of flavin was monitored upon addition of guest DAP dendrons (Figure 4.2).

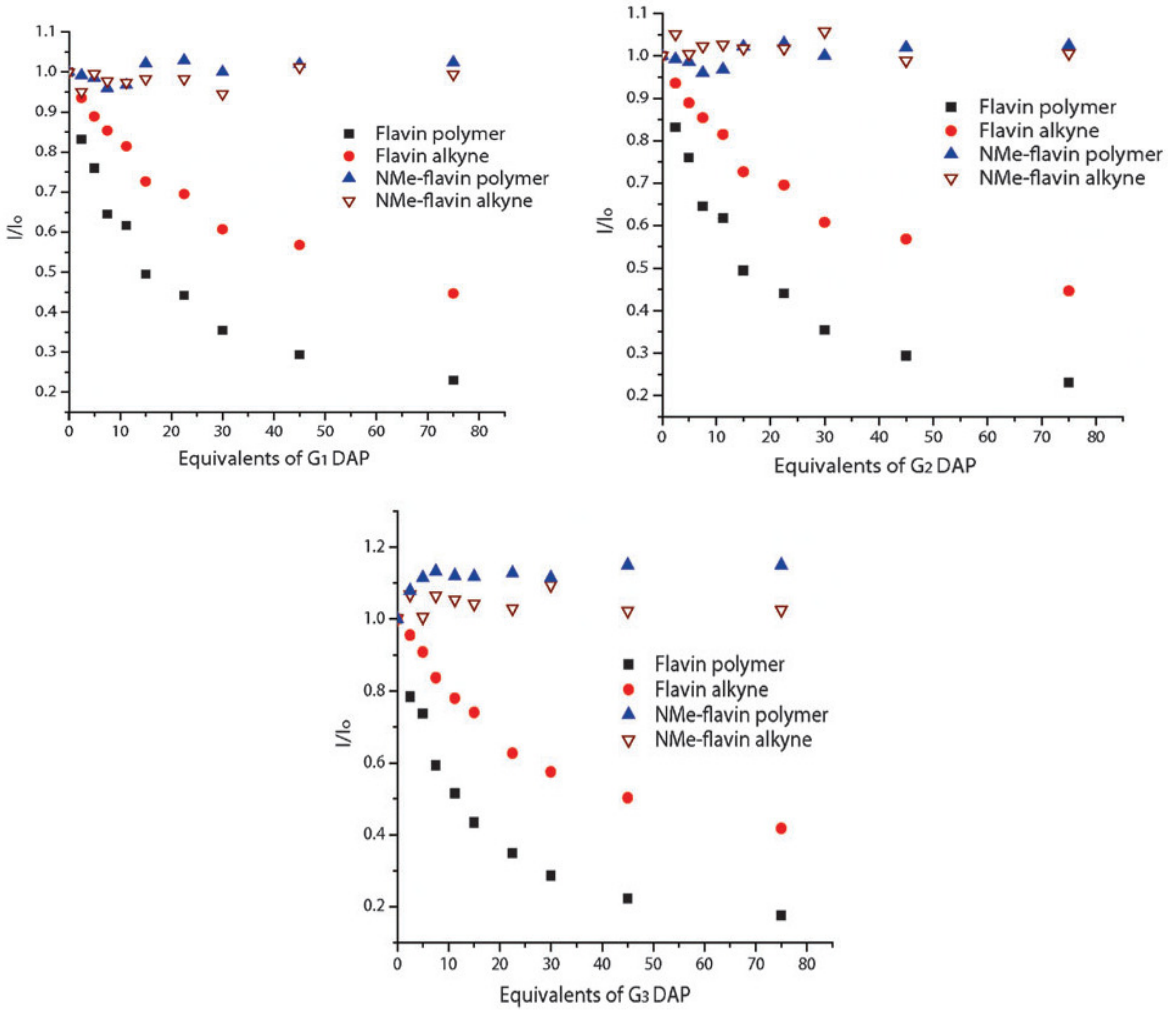

Figure 4.2. Inverse Stern–Volmer plot showing a dramatic quenching of flavin 1 and flavin-functionalized polymer 3 fluorescence upon addition of DAP dendrons, whereas interactions with control N-methylated flavin 2 and control polymer 4 show no fluorescence quenching (50 mM, lex = 445 nm, lem = 460–650 nm)

Fluorescence titrations of flavin 1 in the presence of increasing concentrations of DAP dendrons showed a dramatic quenching of fluorescence, indicative of three point hydrogen bonding between flavin and DAP complexes [99]. Flavin 1 demonstrated

relatively similar binding constants (K_a(ox) = 400 M^{-1}) for increasing generations of DAP dendrimer, suggesting that the flavin–DAP complex was independent of dendron size. N-Methylated flavin 2, which cannot participate in hydrogen bonding interactions, was used as a control and showed no quenching of fluorescence upon subsequent additions of excess DAP dendrons.(Figure 4.2). In contrast to the monomeric flavin, fluorescence titrations of flavin functionalized polymer 3 in the presence of increasing concentrations of DAP dendrons exhibited significant quenching of flavin fluorescence corresponding to K_a(ox) = 600, 700, 550 M^{-1}, respectively, for the G1, G2, and G3 DAP dendrons (Figure 4.2). No substantial change in binding affinity was observed for increasing DAP dendrimer generations. However, the enhanced binding affinity recorded for polymer 3 as compared to flavin 1 was attributed to the cooperative non-covalent interactions including hydrogen bonding and p-stacking within the polymeric–dendritic supramolecular complex. As expected, N-methylated flavin polymer 4 did not show fluorescence quenching upon additions of DAP Dendron (Figure 4.2).

The redox behavior for the supramolecular complexes was determined in CH_2Cl_2 through cyclic voltammetry (CV). Cyclic voltamograms were obtained for 1, 2, polymer 3, polymer 4 using tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte. The half wave reduction potential was calculated for flavin 1 and polymer 3 ($E_{1/2}$(unbound)) along with the corresponding potentials for 1 and polymer 3 in the presence of DAP ($E_{1/2}$(bound)). Flavin 1 showed a single reduction wave followed by two characteristic return oxidation waves typical for an electrochemical–chemical–electrochemical (ece) process (Figure 4.3).

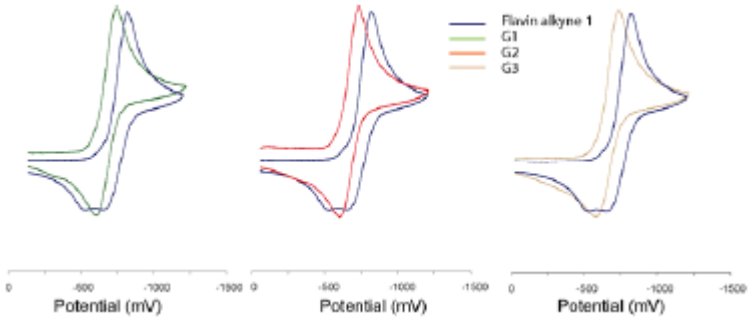

Figure 4.3. CV traces of flavin alkyne 1 with G1,G2 and G3 DAP dendrons at 4 equivalents

Upon addition of DAP dendrons, flavin 1 became fully reversible with the disappearance of the second oxidation wave (Figure 4.3). A significant positive shift in the half wave reduction potential ($\Delta E_{1/2}$) was observed ($\Delta E_{1/2}$) to be 60 ±5 mV for the dendrons (Table 4.1).

Table 4.1. Half-wave potential (mV) and association constants (M^{-1}) for monomeric and polymeric flavin systems.

Flavin	Dendron	K_a(ox)[b]	$E_{1/2}$(u)[c]	$E_{1/2}$(b)[d]	$\Delta E_{1/2}$	K_a(red)
Flavin 1	G1	400	-1280	-1225	55	3400
	G2	400	-1280	-1215	65	5000
	G3	350	-1280	-1225	55	3000
Polymer 3	G1	650	-1250	-1190	60	6500
	G2	700	-1250	-1180	70	11000
	G3	550	-1250	-1190	60	5700

[a] Half-wave potential ($E_{1/2}$) was taken from square-wave voltammetry measurements ($E_{1/2}$ ±5 mV vs. ferrocene).[b] Neutral association constants (K_a(ox)) determined via fluorescence spectroscopy.[c] Reduction potential of the unbound flavin species.[d]Reduction potential of the bound flavin species with DAP guest. Association constants have the error range of ≤50.

No shift in the half wave reduction potential ($\Delta E_{1/2}$) was observed for the dendrons when NMe flavin was used (Table 4.2).

Table 4.2. Half-Wave Potential (mV) and Association Constants (M^{-1}) Associated with NMe flavin Systems

Flavin system	$K_a(ox)^b$	$E_{1/2}(u)^c$	$E_{1/2}(b)^d$	$\Delta E_{1/2}$	K_a(red)
NMe Flavin 2	0	-1350	0	0	0
	0	-1350	0	0	0
	0	-1350	0	0	0
Polymer 4	0	-1350	0	0	0
	0	-1350	0	0	0
	0	-1350	0	0	0

Hence, the DAP dendrimers modulate the flavin redox behavior which is consistent with previous flavin model systems [86, 100]. Polymer 3 demonstrated fully reversible electrochemical behavior as well (Figure 4.4).

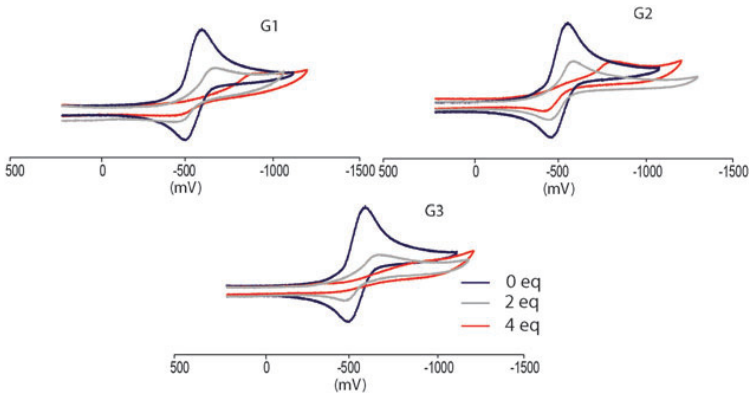

Figure 4.4. CV traces of polymeric flavin 3 exhibiting different flavin redox behaviors in the presence of G1, G2 and G3 DAP dendrons

The flavin units appended to the polymer produced isolated redox behavior, preventing flavin–flavin proton transfer and the disappearance of a second oxidation wave [101, 102]. However, upon addition of 4 equivalents of DAP dendrons, polymer 3 exhibited distinctly different electrochemical behavior from its monomeric counterpart (Figure 4.4). A drastic change in peak shape was observed for polymer 3. The signal was significantly smaller and broader for each corresponding dendrimer generation, indicating

limited electron diffusion as a function of dendrimer size. The peak to peak distances were 200, 225, 440 mV for G1, G2 and G3 respectively. The broadening of the peak to peak distance and the dramatic decrease in the current indicate a slow rate of electron transfer from the flavin to electrode, indicating the effective isolation and encapsulation of appended flavins from outside interfering species (Figure 4.4). Surprisingly, the shift in the polymeric flavin redox potential was not significantly different than the monomeric flavin systems. A positive shift of 60–70 mV was observed for the reduction potential of polymer 3 for all three DAP dendrimer generations. The shifts in reduction potential were only slightly larger than the shifts recorded for the monomeric flavin 1. Thus, the cooperative non-covalent interactions appeared to modulate the flavin redox potential while the size of the complex determined the encapsulation of the flavin unit. Association constants in the radical anionic states (K_a(red)) were extrapolated by using the shifts in reduction potentials ($\Delta E_{1/2}$) of 1 and polymer 3 and the association constants (K_a(ox)) through the following relationship.

$$K_a(red) = K_a(ox)e^{\{(nF/RT)(E1/2(bound)-E1/2\ (unbound))\}}$$

There was no change in the CV traces when Nme flavin polymer system was used (Figure 4.5).

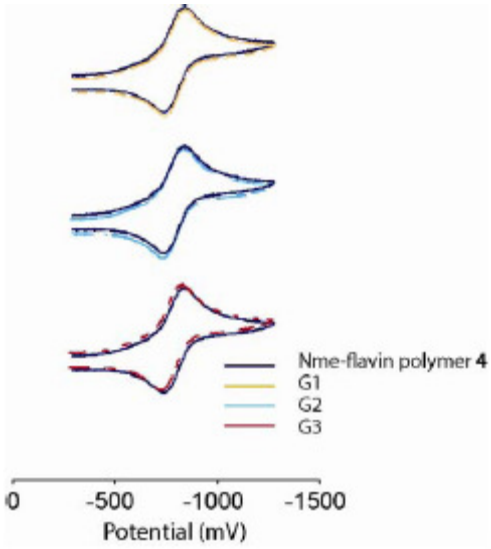

Figure 4.5. CV traces of NMe flavin polymer 4 with G1, G2 and G3 DAP dendrons at 2 equivalents

The association constant for the G2 dendron with the polymer bound flavin in reduced state showed a 15.7-fold increase in binding. However, the monomeric flavin showed an 8.5-fold increase in the binding in the reduced state (Table 4.1).

Molecular modeling studies clearly predicted the formation of encapsulated flavin inside the self-assembled structure through hydrogen bonding and aromatic interactions between the flavin polymer 3 and DAP dendron G3 (Figure 4.6).

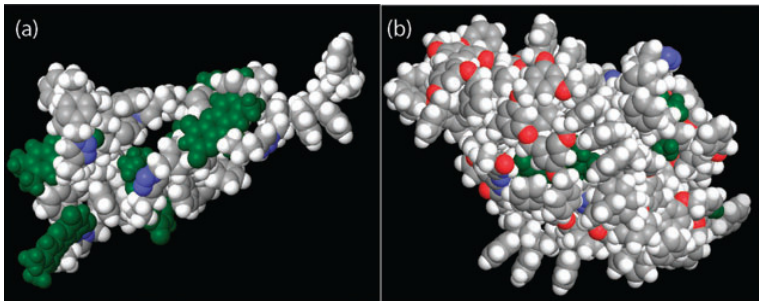

Figure 4.6. Molecular dynamics simulation (Amber force field) of (a) polymeric flavin 3 and (b) polymeric flavin 3 with G3 DAP dendrons. (Flavin moieties are highlighted in green)

Analogous molecular models of flavin polymer 3 with DAP dendrons G1 and G2 have also shown encapsulation of flavin units, while monomeric flavin does not demonstrate any encapsulation of flavin units (Figure 4.7 and Figure 4.8).

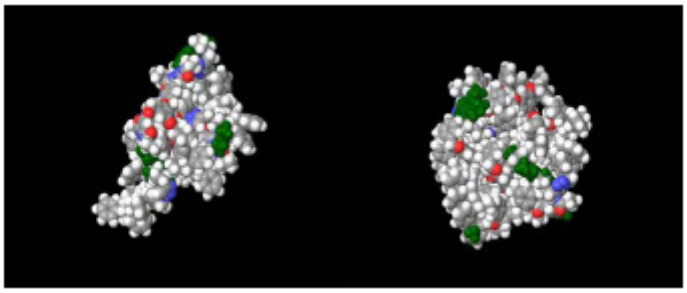

Figure 4.7. Polymer Flavin 3 with G1, and G2 DAP dendron respectively

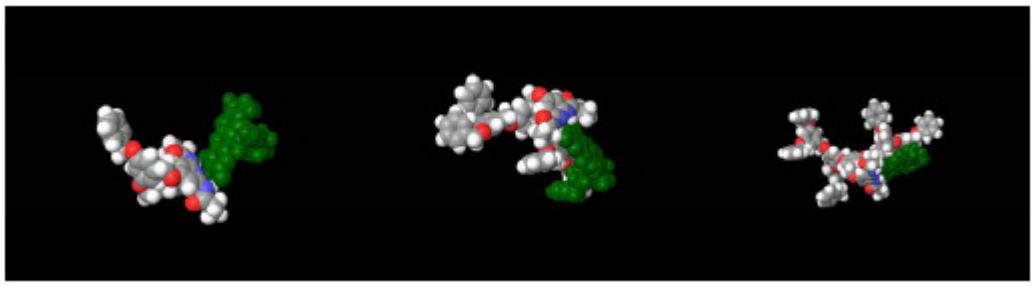

Figure 4.8. Flavin alkyne 1- G1 DAP, G2 DAP and G3 DAP dendron do not show shielding of flavin moiety (highlighted in green)

Dynamic light scattering experiments corroborated the expected diameter change for the flavin polymer upon addition of DAP dendrons observed in the molecular modeling simulations. The diameter increases (from 4.6 nm to 7.9 nm) as the generation of dendron increased for the flavin polymer 3 whereas the control polymer 4 did not show any appreciable change in diameter (Figure 4.9).

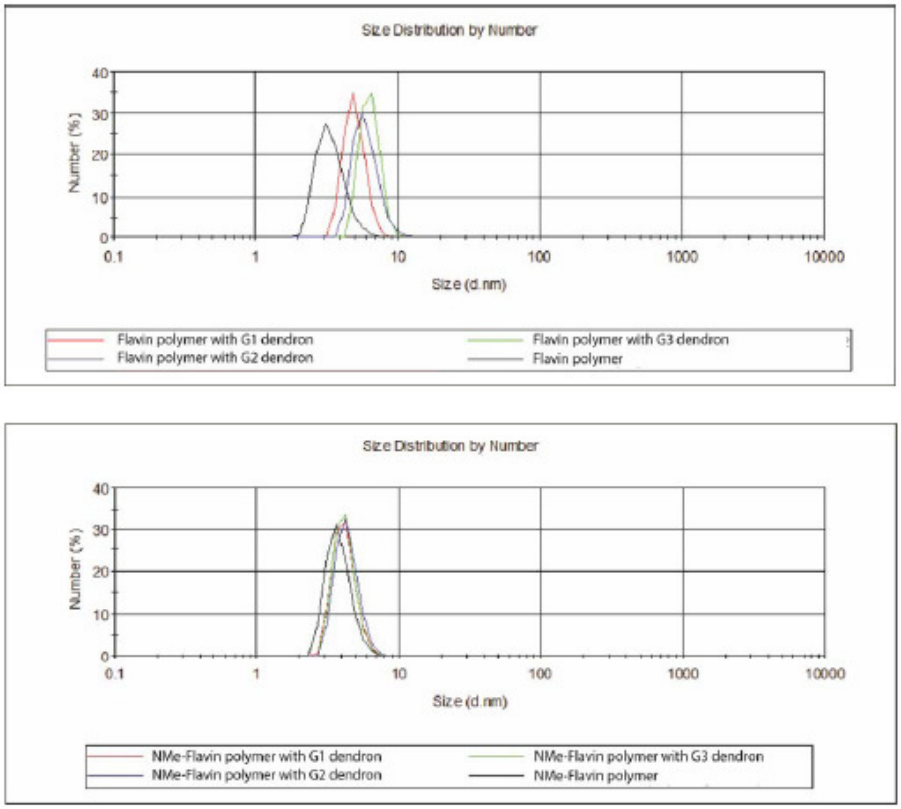

Figure 4.9. Dynamic light scattering of flavin polymer and N-methyl flavin polymer upon addition of dendrons

4.2. Fabrication of Stable Polymersomes via Self-Assembly and Crosslinking

$P(S_{Cl}\text{-co-}S\text{-co-}S_{N3}\text{-co-}S_{DAP})$ and $P(S_{Cl}\text{-co-}S\text{-co-}S_{Alkyne}\text{-co-}S_{Thy})$ were used for these studies, synthesis steps of them were explained in the experimental part (Figure 4.10). In these polymers, the chloromethyl groups provide attachment sites for functionalization with recognition units (DAP and Thy functionalities) and reactive units (azide and alkyne functionalities). Synthesis of parent polymer, $P(S_{Cl}\text{-co-}S)$ random copolymer was conducted using azobisisobutyronitrile (AIBN) initiated free radical polymerization in chlorobenzene.

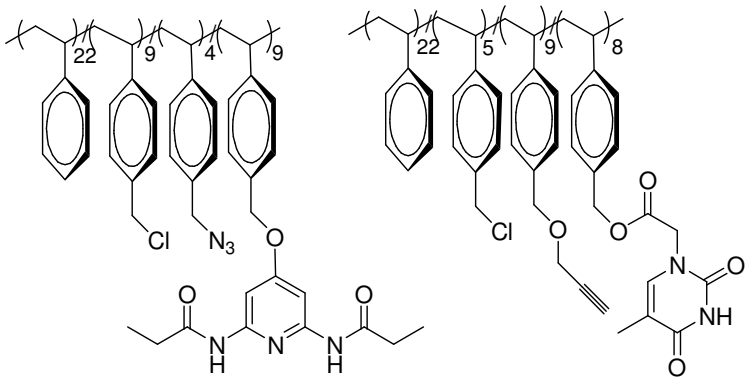

Figure 4.10. General structure of copolymers used in this study

In the NMR spectrum of DAP polymer, CH_2 protons near chlorine were seen at 4.4 ppm. After azide functionalization, a new peak at 4.2 ppm was appeared. Peak at 5 ppm was due to CH_2 protons near DAP units.

In the NMR spectrum of Thy polymer, peak at around 2.5 ppm was coming from alkyne proton. After Thy functionality, a peak at 5 ppm appeared.

4.2.1. Self-assembly of Copolymers

Microspheres were obtained upon mixing of solutions of DAP polymer and Thy polymer in chloroform ([Thy polymer] = [DAP polymer] = 2 mg/mL^{-1}). Immediate Turbidity observed upon mixing of polymers indicated microsphere formation. Microsphere formation was observed under optical microscope (Figure 4.11.a). When

protic solvents like methanol and THF were used, it was observed that microspheres were no longer stable. This was expected due to the disruption of three point hydrogen bonding between DAP and Thy units.

4.2.2. Making Microspheres Stable

To obtain stable microspheres not only in non-competing solvents but also in competing solvents and to preserve microsphere stability over time, these self-assembled systems should be arrested via some covalent crosslinking approaches (Figure 4.11.b). In this study to reach this goal, [3+2] Huisgen cycloaddition reaction was chosen as a method of crosslinking.

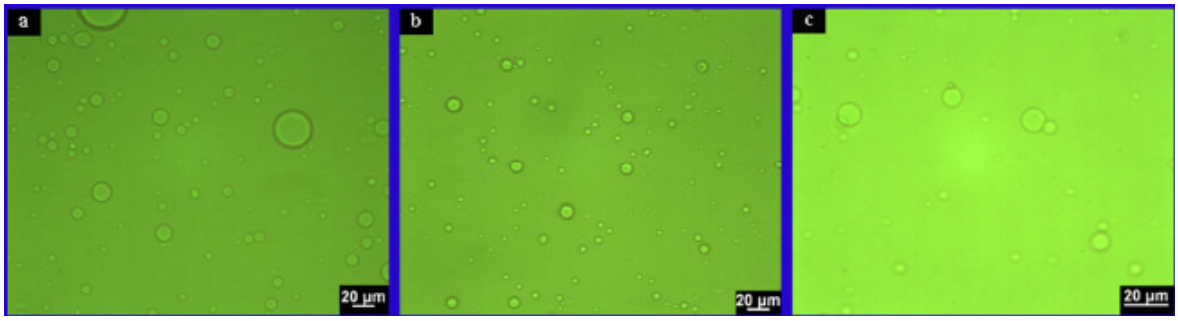

Figure 4.11. DIC micrographs (X20) of spherical aggregates formed by P(S_{Cl}-co-S-co-S_{N3}-co-S_{DAP}) with P(S_{Cl}-co-S-co-S_{Alkyne}-co-S_{Thy}) (a) before click reaction in chloroform, (b) after click reaction in chloroform, (c) after click reaction in 70% THF and 30% methanol

4.2.3. Making water soluble microspheres

After the click reaction, presence of microspheres was checked in 70% THF and 30% methanol (Figure 4.11.c). Successful crosslinking of microspheres was evident due to the recreation of structures in a such polar and H-bonding competing solvents. In control systems i.e non-crosslinked microspheres, the structures disrupt and dissolve upon addition of methanol.

In order to render these structures water dispersible, unreacted triple bonds on Thy polymer were modified with PEG. After 6 h clicking the microspheres, PEG 2k azide (4mg, 0.002 mmol) dissolved in 0.5 mL $CHCl_3$ was added into the reaction mixture and the reaction was continued for 10 h.

After pegylation, chloroform was evaporated and microspheres were dissolved in 2 mL of water. To remove copper and unreacted PEG 2k azide dialysis was performed for 18 h in water. For dialysis a cellulose membrane with MWCO (molecular weight cut off) 3500 was utilized. After dialysis, microspheres were suspended in water and were checked under optical microscope. It was seen that microspheres were easily dispersible in water (Figure 4.12.a).

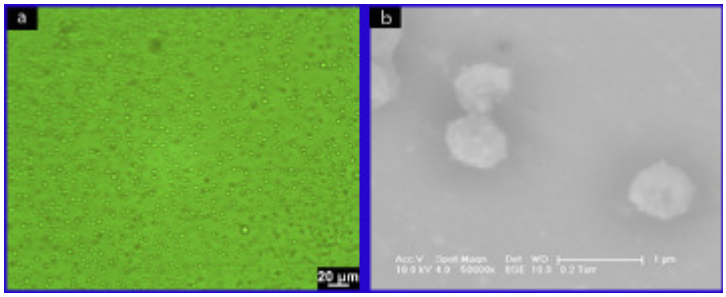

Figure 4.12. Pegylated microspheres in water and SEM image of pegylated microspheres

4.2.4. Scanning Electron Microscopy

Pegylated polymersomes were lyophilized and scanning electron microscopy was used to characterize the morphology. Images were taken using ESEM-FEG/EDAX Philips XL-30 (Philips, Eindhoven, The Netherlands) instrument using an accelerating voltage of 10 kV (Figure 4.12.b). Size of the microspheres were close to 1µm, commensurate with optical microscopy measurements.

Thermal reversibility is one of the important characteristics of self-assembled materials. Before crosslinking, as the temperature increases, a remarkable and continuous decrease in absorbance value of microsphere solution in chloroform at 700 nm was observed, while the absorbance of clicked microspheres did not show any remarkable

change (Figure 4.13.c). At 20 °C both solutions before and after click reaction have very turbid appearances. Heating the non-clicked microspheres resulted in nearly total loss of turbidity, whereas clicked microspheres did not lose their turbidity (Figure 4.13.a-b). This experiment reinforces the stability of these microspheres after crosslinking.

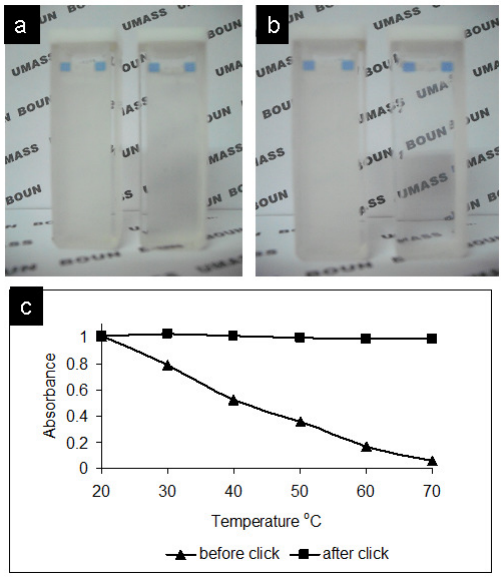

Figure 4.13. Microsphere solutions in chloroform (a) after click and before click at 20 °C (b) after click and before click at 70 °C, (c) UV graph at 700 nm at different temperatures

4.2.5. Fuctionalization of Microspheres

In this study, the appended azide and alkyne functionalities on the polymers served two purposes. One was crosslinking the microspheres to arrest self assembled structures. Second was to decorate microspheres with functional molecules such as fluorescence dyes and enzymes to proof their functionalizable structures (Figure 4.14). The former one was achieved and resulted in stable microspheres even in water. For the second purpose as a fluorescence dye, bodipy bearing azide functionality was used.

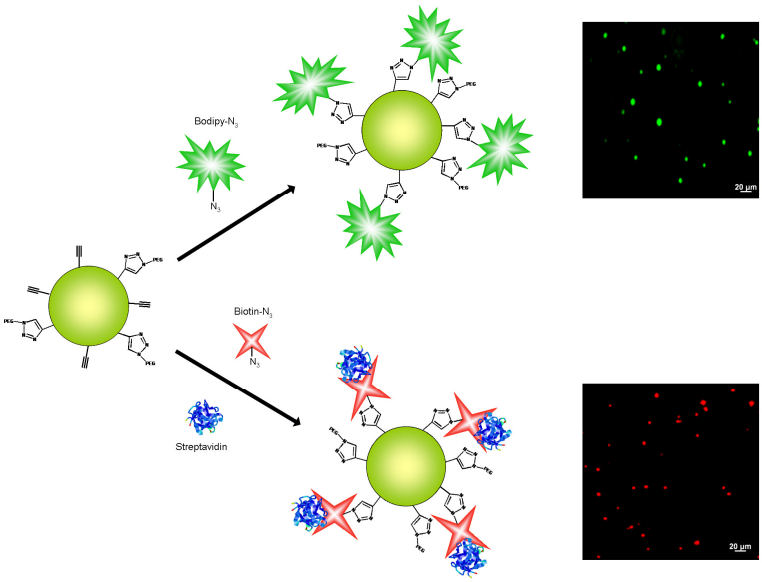

Figure 4.14. Funtionalization of microspheres with bodipy azide and biotin azide and immobilization of streptavidin on biotin functionalized microspheres

4.2.6. Functionalizing microspheres with biotin- streptavidin and biotin-extravidin

Biotin azide (0.5 mg) was dissolved in 0.5 mL chloroform and added into pegylated microsphere solution before dialysis. The reaction was kept at room temperature for 16 h. The reaction mixture was dialysized for 18 h in water to get rid off unbound biotin azide. Streptavidin solution (100 ppm) and extravidin solution (100 ppm) was added separately and fluorescence microscope was used to get fluorescence pictures (Figure 4.15.a-b).

Water soluble microsphere solution before dialysis was taken and bodipy azide (0.2 mg) dissolved in 0.2 mL chloroform was added. The reaction mixture was kept at room temperature for 16 h. Dialysis in water for 18 h was performed to remove unbound BODIPY. Fluorescence images were taken (Figure 4.15.c-d).

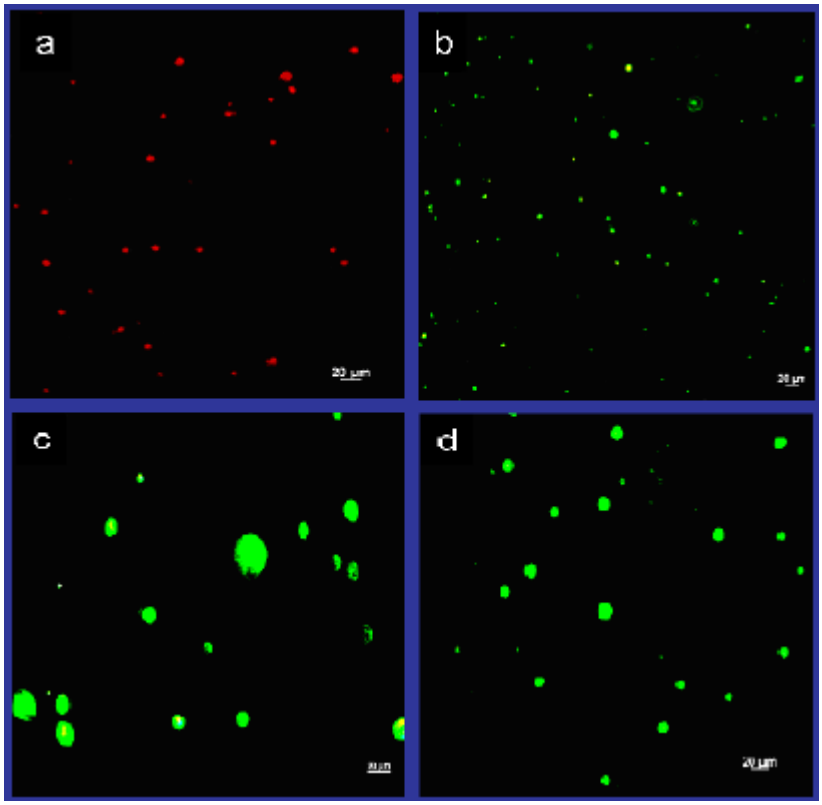

Figure 4.15. Fluorescence micrographs of microspheres (a) biotin-extravidin functionalized (x20), (b) biotin-streptavidin functionalized (x20), (c) bodipy functionalized (x40), and (d) bodipy functionalized (x20). All scale bars are 20 micrometer

IR spectrums of microspheres before and after crosslinking were taken. It was observed that after click reaction there was a remarkable decrease in azide and alkyne peaks (Figure 4.16).

Experiments will be repeated using DIC (Differential Interface Contrast Microscopy) for accurate size distribution.

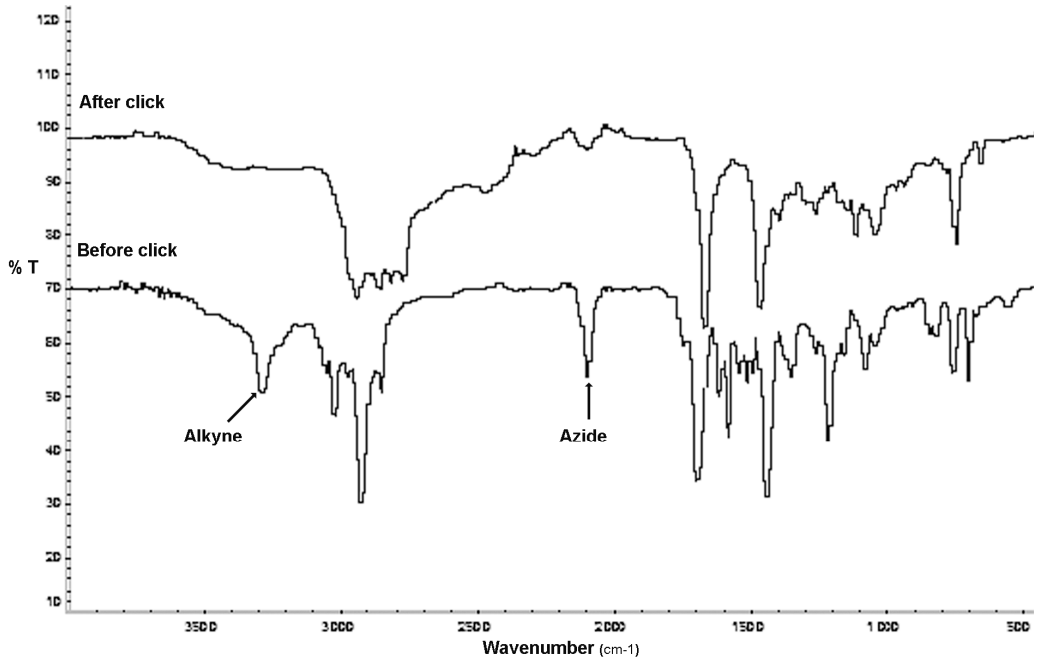

Figure 4.16. IR spectrum of microspheres before and after click reaction

4.3. Fabricaiton of Colloidosomes via Self-Assembly at the Liquid-Liquid Interface

For colloidosome fabrication, literature was followed to obtain the required CD coated nanoparticles. Synthesis of the adamantane functionalized iron oxide nanoparticles was achieved by place exchange reaction of oleic acid coated iron oxide nanoparticles with adamantane-1-carboxylic acid (3 eq. by weight) in dichloromethane.

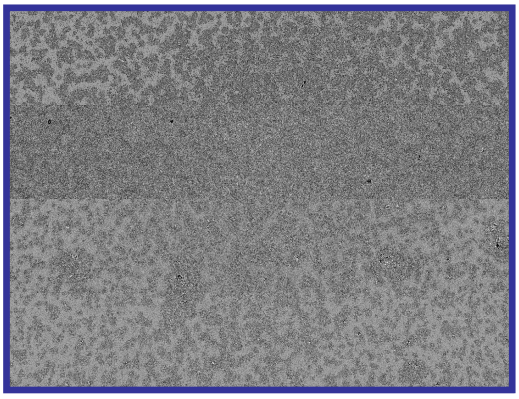

Figure 4.17. TEM image of ADA functionalized iron oxide NPs

According to TEM images average particle size is about 5 nm (Figure 4.17).

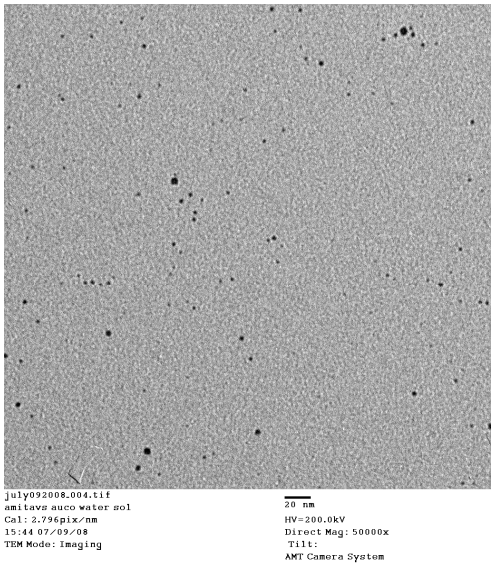

Figure 4.18. TEM image of CD functionalized Au NPs

According to TEM images average particle size is about 2 nm (Figure 4.18).

4.3.1. Fabrication of the Microcapsules

4.3.1.1. Synthesis of the Microcapsules in Toluene. 15 μL of aqueous CD functionalized Au NP solution was added into 0.3 mL solution of AD functionalized iron oxide NPs in toluene. The mixture was emulsified by shaking vigorously for a few seconds. Consequently, toluene was removed by a pipette as much as possible and fresh toluene was added for a few times. Last step was repeated until the toluene phase became colorless (Figure 4.19).

4.3.1.2. Synthesis of the Microcapsules in Methyloleate. Methyl oleate is a pale yellow oily liquid. It is a fatty acid ester. When compared to toluene, it is non-toxic. Same procedure was applied, instead of toluene, methyloleate as oil was used (Figure 4.19).

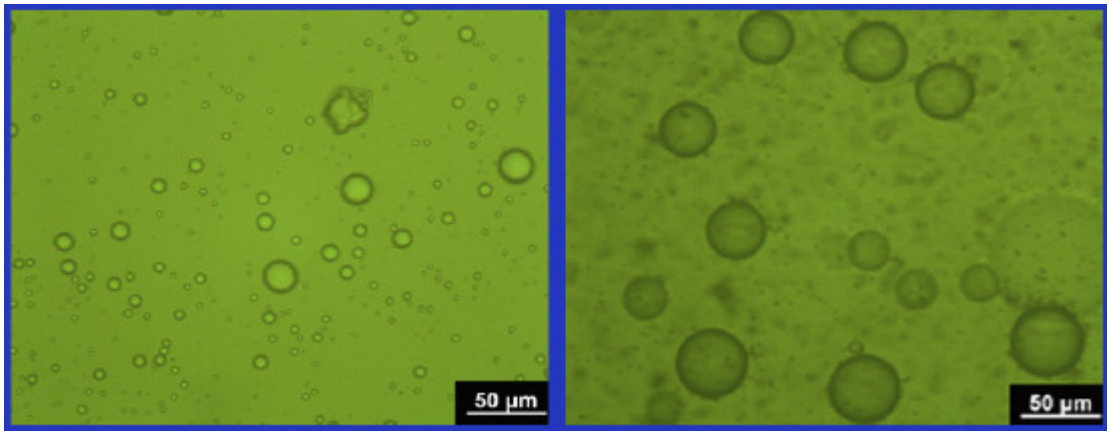

Figure 4.19. Microcapsules water in toluene and water in methyl oleate

4.3.1.3. Synthesis of the Microcapsules in Water. To a 0.3 mL aqueous CD functionalized Au NP solution, 15 µL solution of AD functionalized iron oxide NPs in toluene was added. The mixture was emulsified by shaking vigorously for a few seconds. Then, toluene was removed by a pipette as much as possible and fresh water was added without destroying the microcapsules (Figure 4.20). Instead of toluene, methyl oleate can also be used (Figure 4.20).

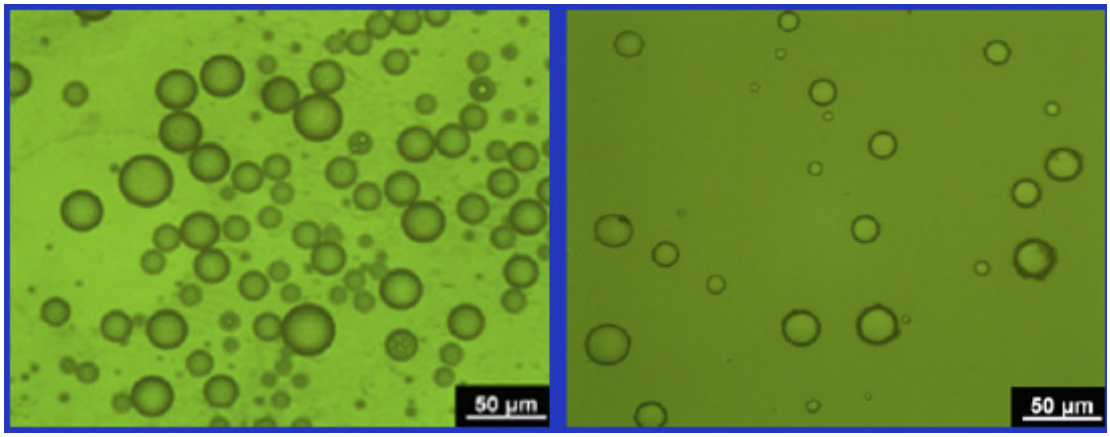

Figure 4.20. Microcapsules toluene in water and methyl oleate in water

In the TEM image of the microcapsules, close packed assembly of the nanoparticles can be observed (Figure 4.21).

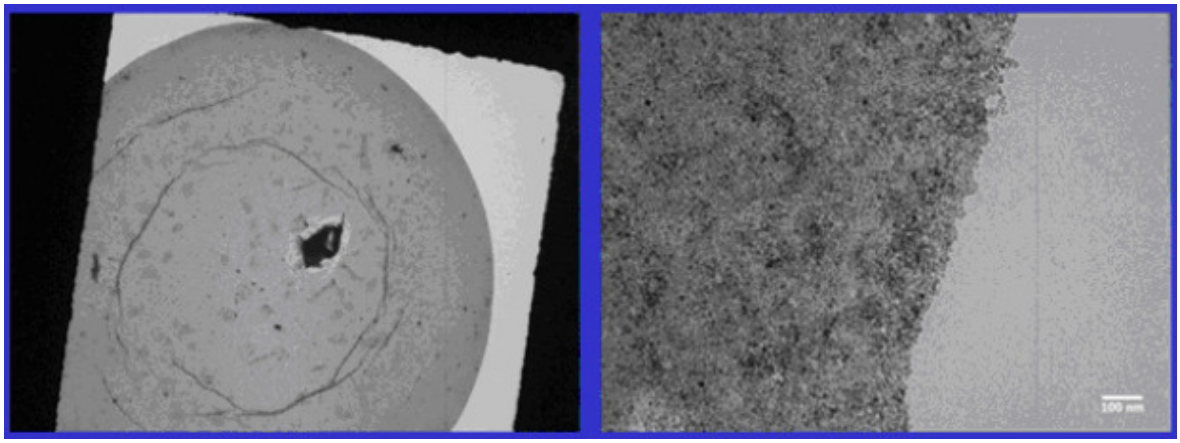

Figure 4.21. TEM image of the microcapsules

Encapsulation of hydrophobic materials such as polystyrene based polymers within the microcapsule is possible. This was demonstrated by addition of a flavin dye tagged polystyrene polymer to the oil phase. During the fabrication of macrocapsules via toluene in water system, a few drops from the flavin polymer solution (2mg/mL) were added and the vial was shaken. Successful encapsulation of hydrophobic fluorescent polymer was evident from the fluorescence micrographs (Figure 4.22).

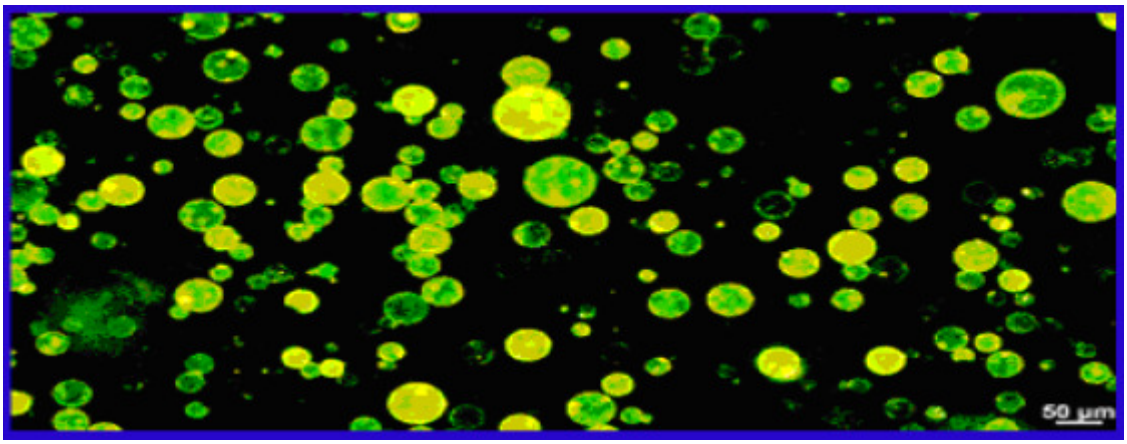

Figure 4.22. Fluorescence micrograph of microcapsules encapsulating flavin units appended a 3500-5000 mwt polystyrene polymer

After the fabrication of macrocapsules via toluene in water system, a drop of adamantane functionalized lissamine dye solution in water was added. Due to the presence of the adamantane functionality on the dye, host-quest interactions with cyclodextrin groups on the microcapsule surface occur. Hence the dye gets localized on the surface of the microcapsules, as evident from the fluorescent micrographs.

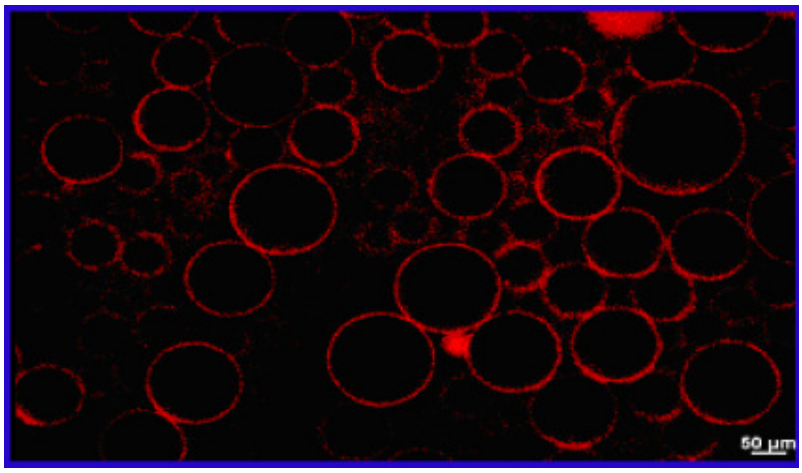

Figure 4.23. Fluorescence micrograph of microcapsules encapsulating adamantane functionalized lissamine dye at the cross section

5. CONCLUSIONS

Insulation or encapsulation of polymers using a dendron based jacket can be accomplished by utilizing formation of supramolecular dendronized polymers. This can be done by incorporation of specific hydrogen bonding units along the side chain of the polymer. Dendrons containing complementary hydrogen bonding recognition units at their focal point will interact with the polymer backbone. Encapsulation of redox active flavin units attached to the polymeric backbone via formation of specific supramolecular complexes was used to demonstrate this approach. Modulation of the redox behavior was used as a tool to monitor the efficiency of the encapsulation process. At higher equivalents of DAP appended dendrons, a significant insulation of redox activity of polymeric flavin was observed due to the encapsulation of flavin. This supramolecular modulation of polymer motif could be potentially used in the creation of insulated molecular wires.

As a conclusion for second part, a new strategy for the construction of stable microspheres via self-assembly was developed. Copolymers of styrene and chloromethyl styrene were synthesized and functionalized with DAP and Thy groups that provide non-covalent interactions necessary for formation of self-assembled structures. Additionally, the polymers were also decorated with azide and alkyne functionalities that can be utilized for cross-linking. First, microsphere formation was achieved in chloroform via three point hydrogen bonding between complementary DAP and Thy units and then efficient Huisgen click reaction at room temperature was applied to arrest the self-assembled structures. Obtained stable microspheres were rendered water solubile via surface pegylation. Further functionalizations of these microspheres were undertaken with fluorescent dyes and ligands for bioimmobilization.

As a final conclusion, microcapsules were prepared by non-covalent crosslinking water soluble cyclodextrin functionalized gold nanoparticles, and toluene and methyl oleate soluble adamantane functionalized iron oxide nanoparticles at the oil-water interface. Fabrication of microcapsules was possible by both oil in water and water in oil systems. Encapsulation of flavin tagged polymer within the microcapsules and surface modification of the microcapsule surfaces by adamantane functionalized lissamine dye

using ‘host-guest’ chemistry demonstrates the ability to load and modify these containers as deemed necessary for application at hand.

APPENDIX A: SPECTROSCOPY DATA

^{1}H NMR and IR spectroscopy of the synthesized products are included. Necessary expansions were made on the NMR data.

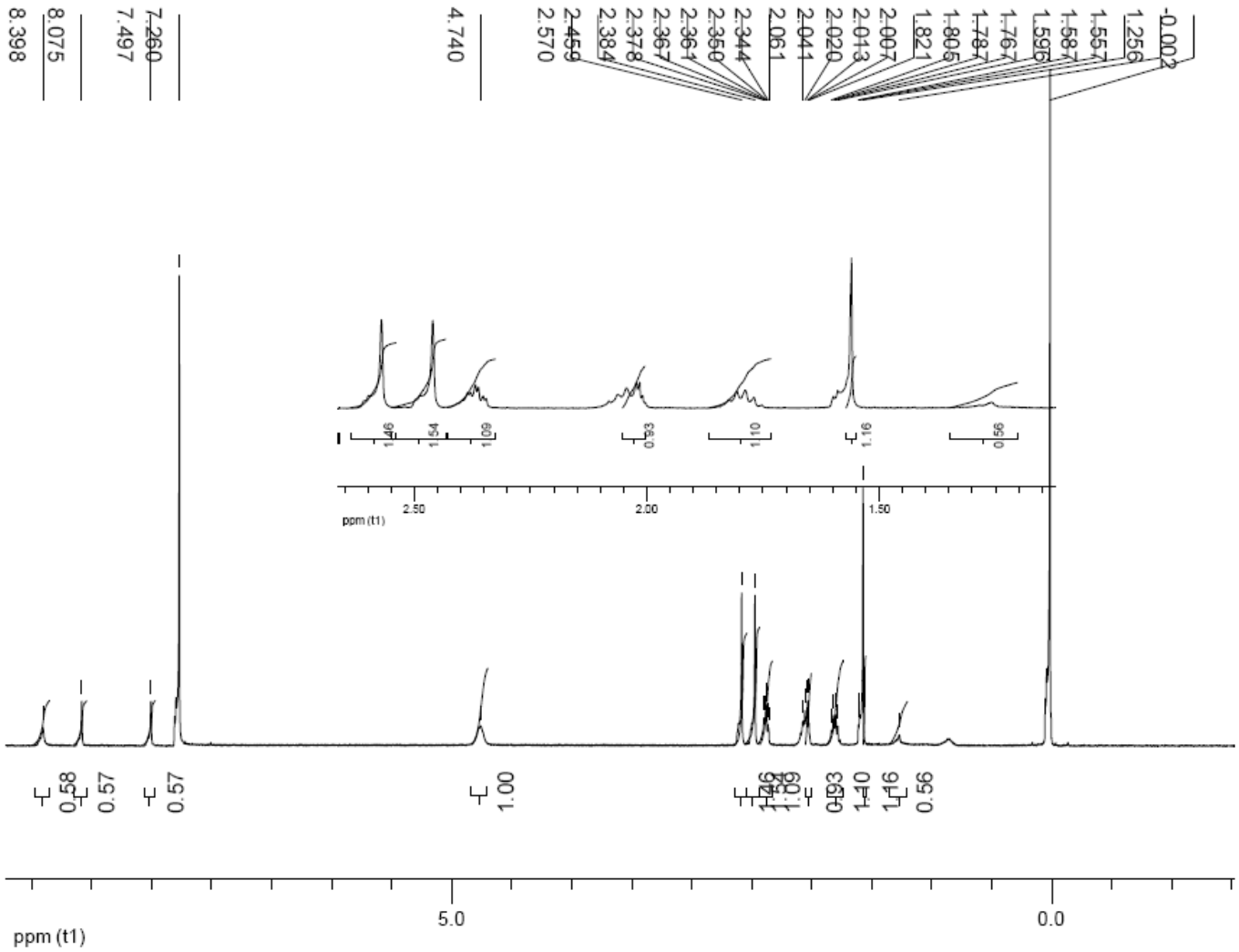

Figure A. 1. ^{1}H-NMR of alkyne functionalized flavin 1

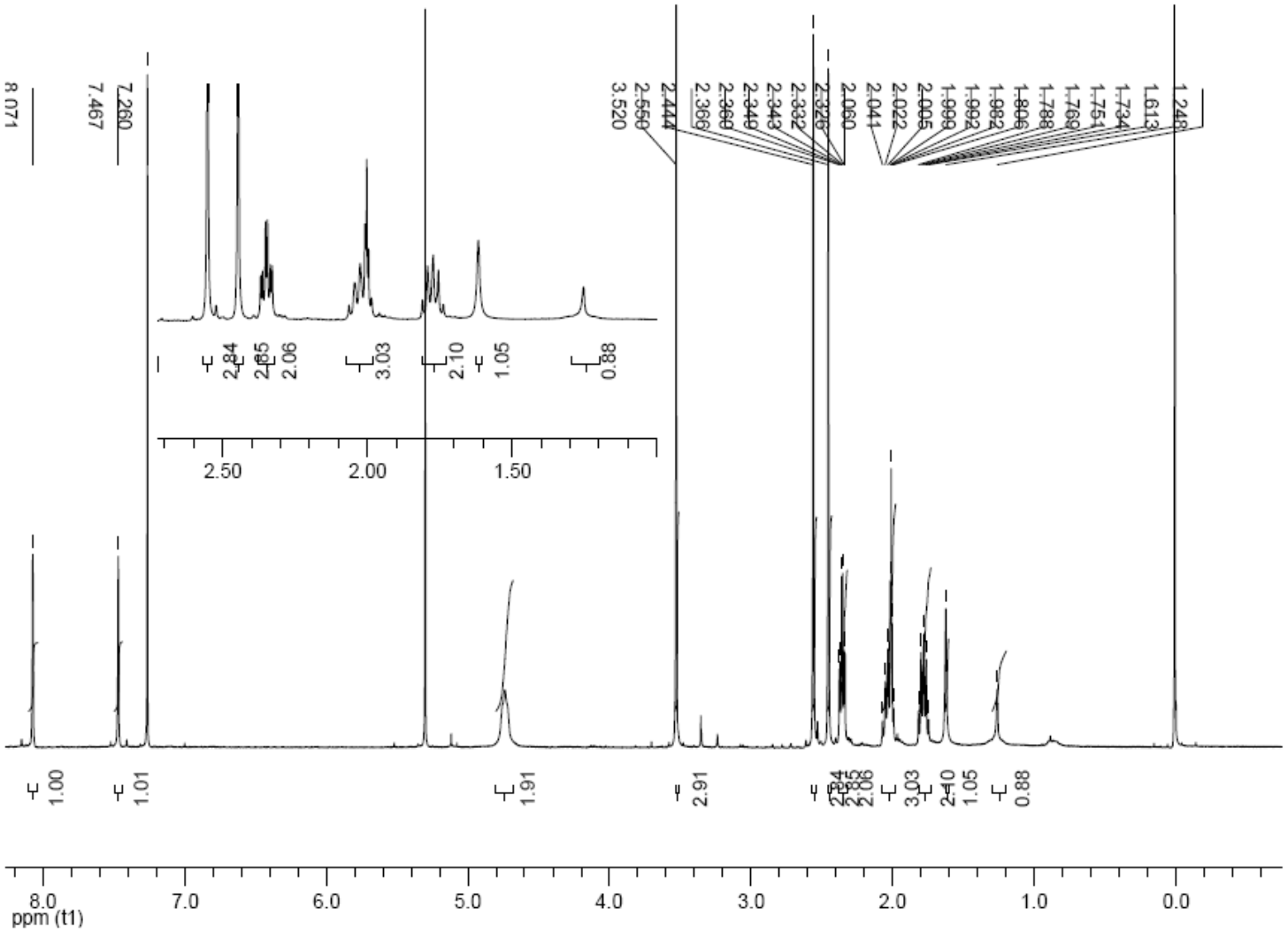

Figure A.2. ^{1}H-NMR of N-methylated alkyne functionalized flavin 2

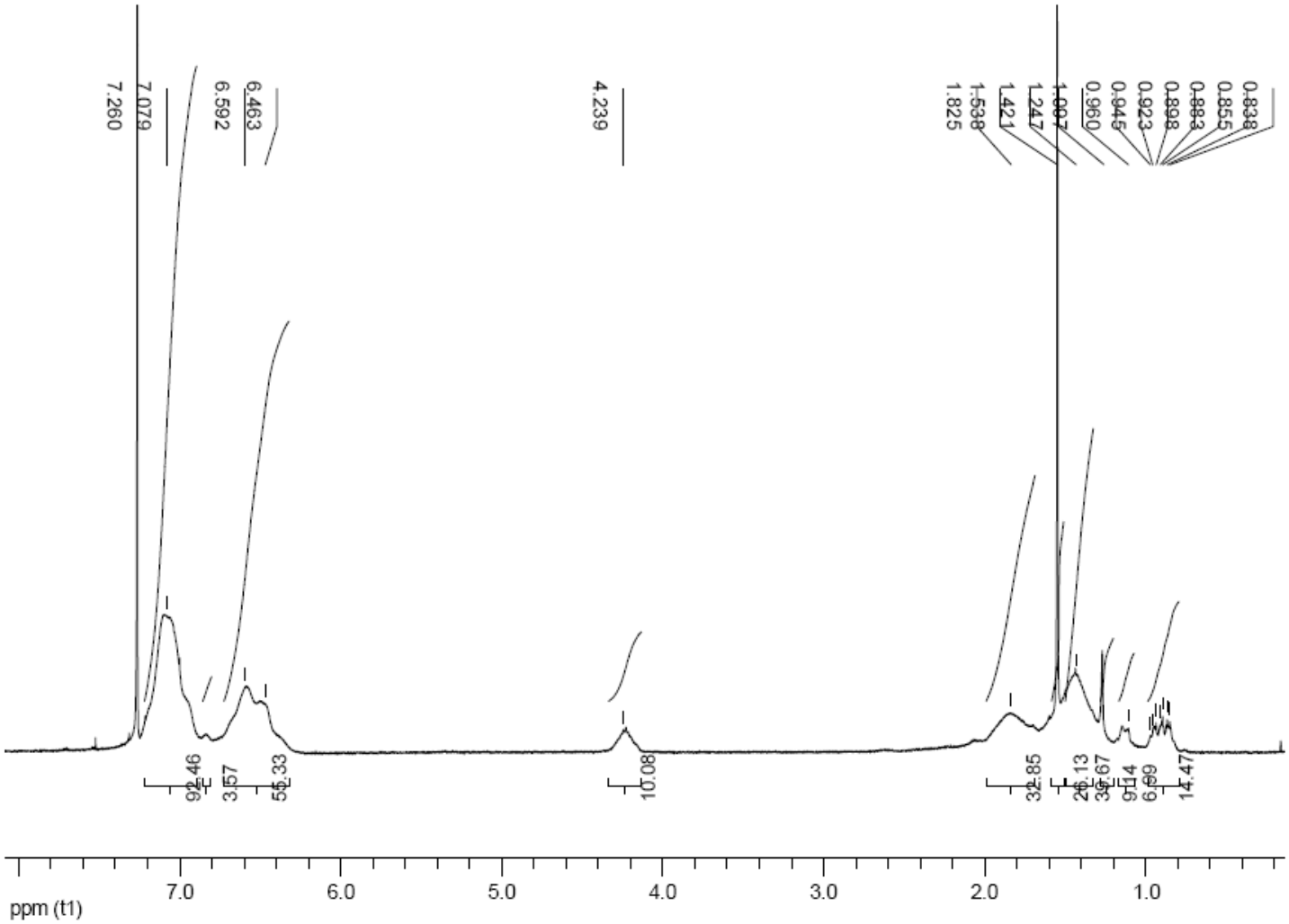

Figure A.3. ^{1}H-NMR of azide functionalized polystyrene polymer 3

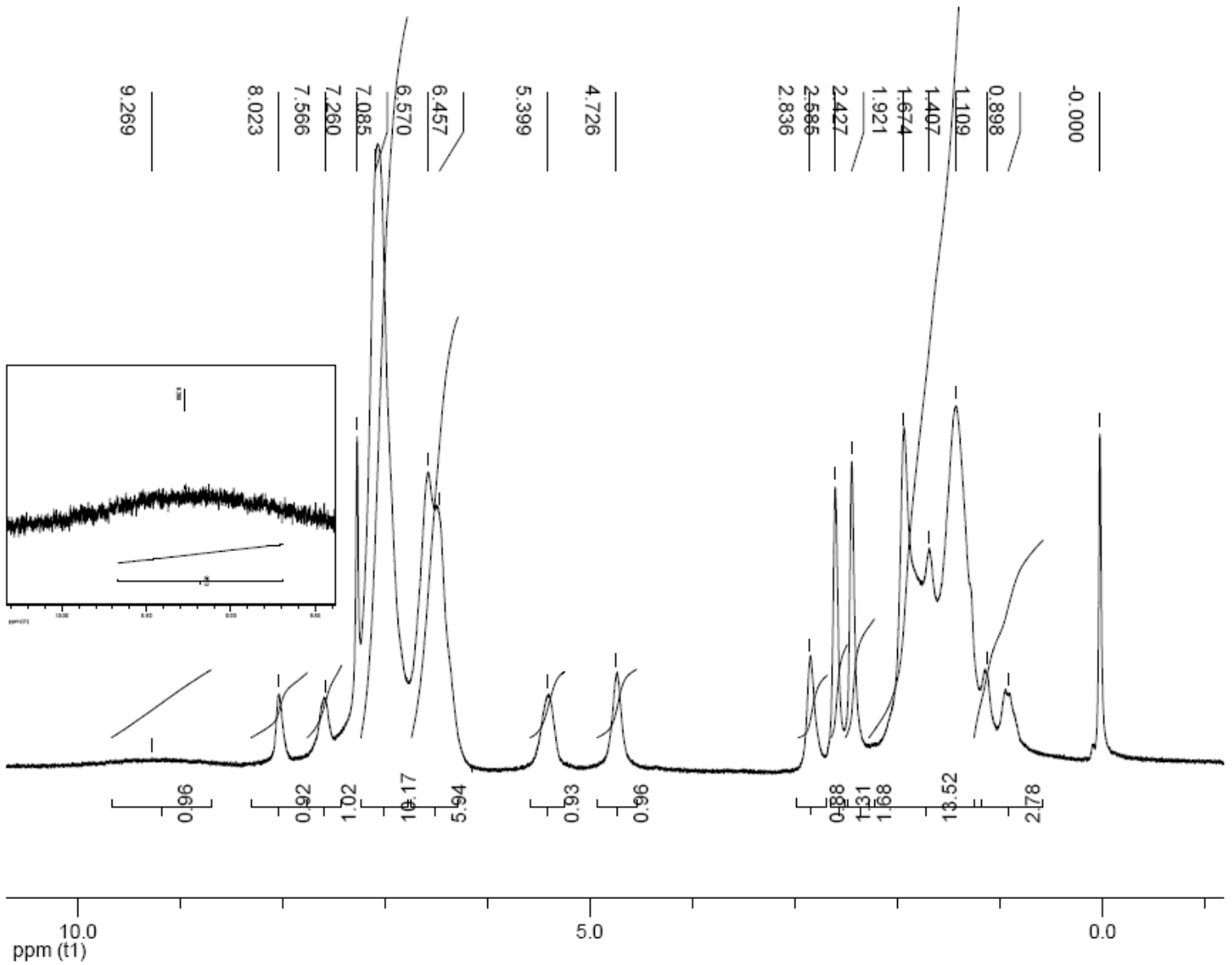

Figure A.4. ^{1}H-NMR of flavin functionalized polystyrene polymer 4

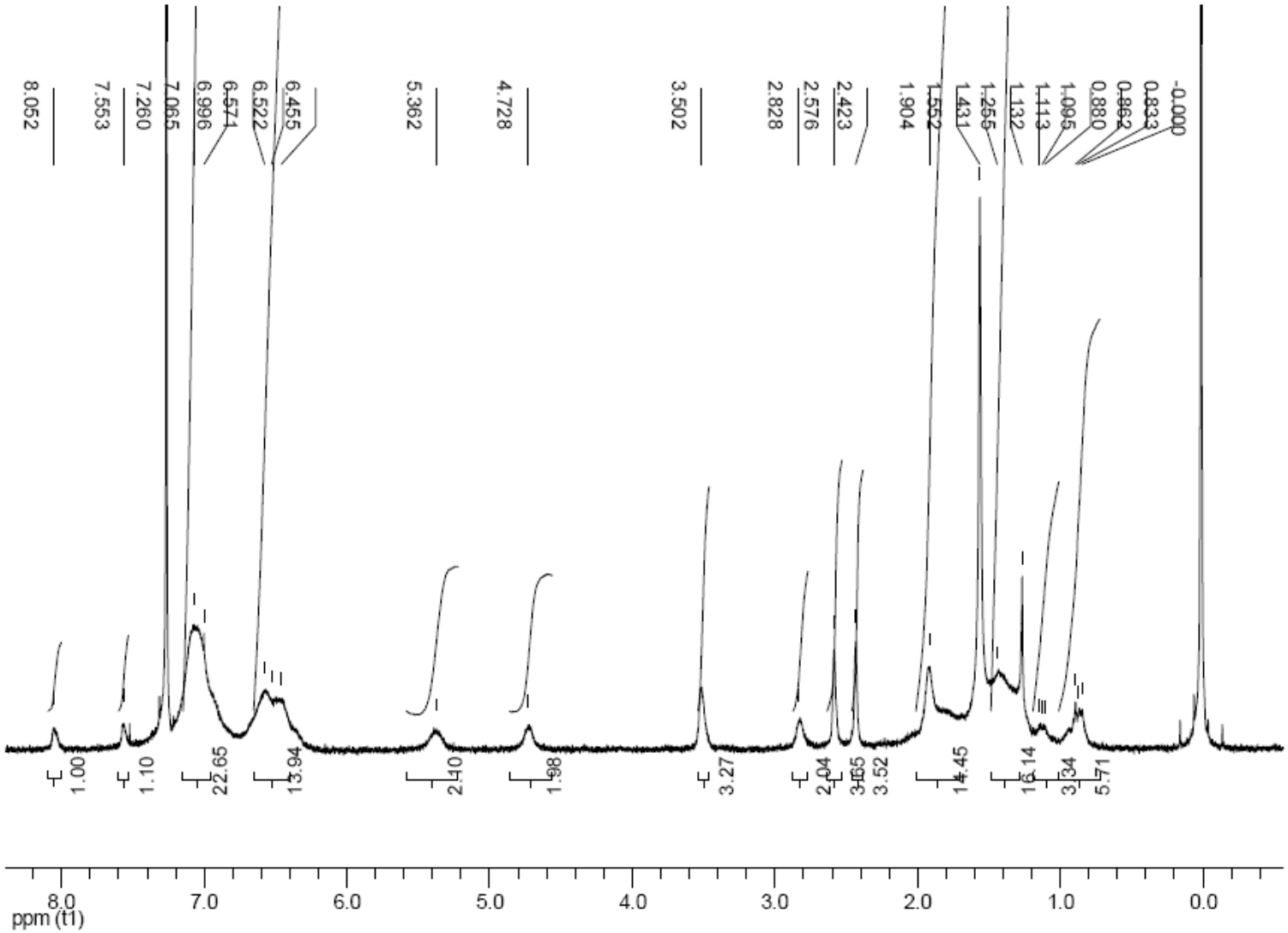

Figure A.5. ^{1}H-NMR of N-methylated flavin functionalized polystyrene polymer 5

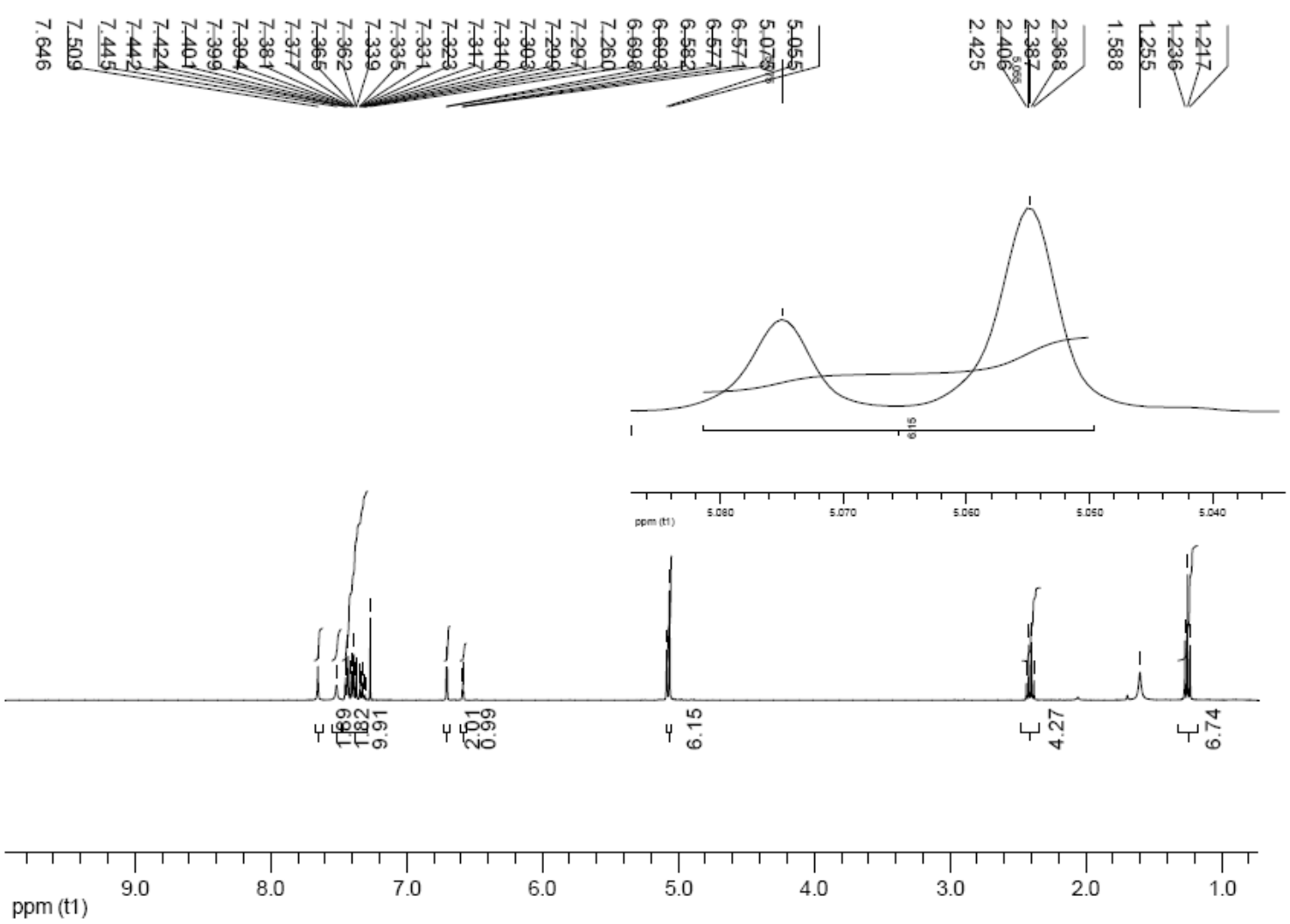

Figure A.6. ^{1}H-NMR of G1-DAP-dendron

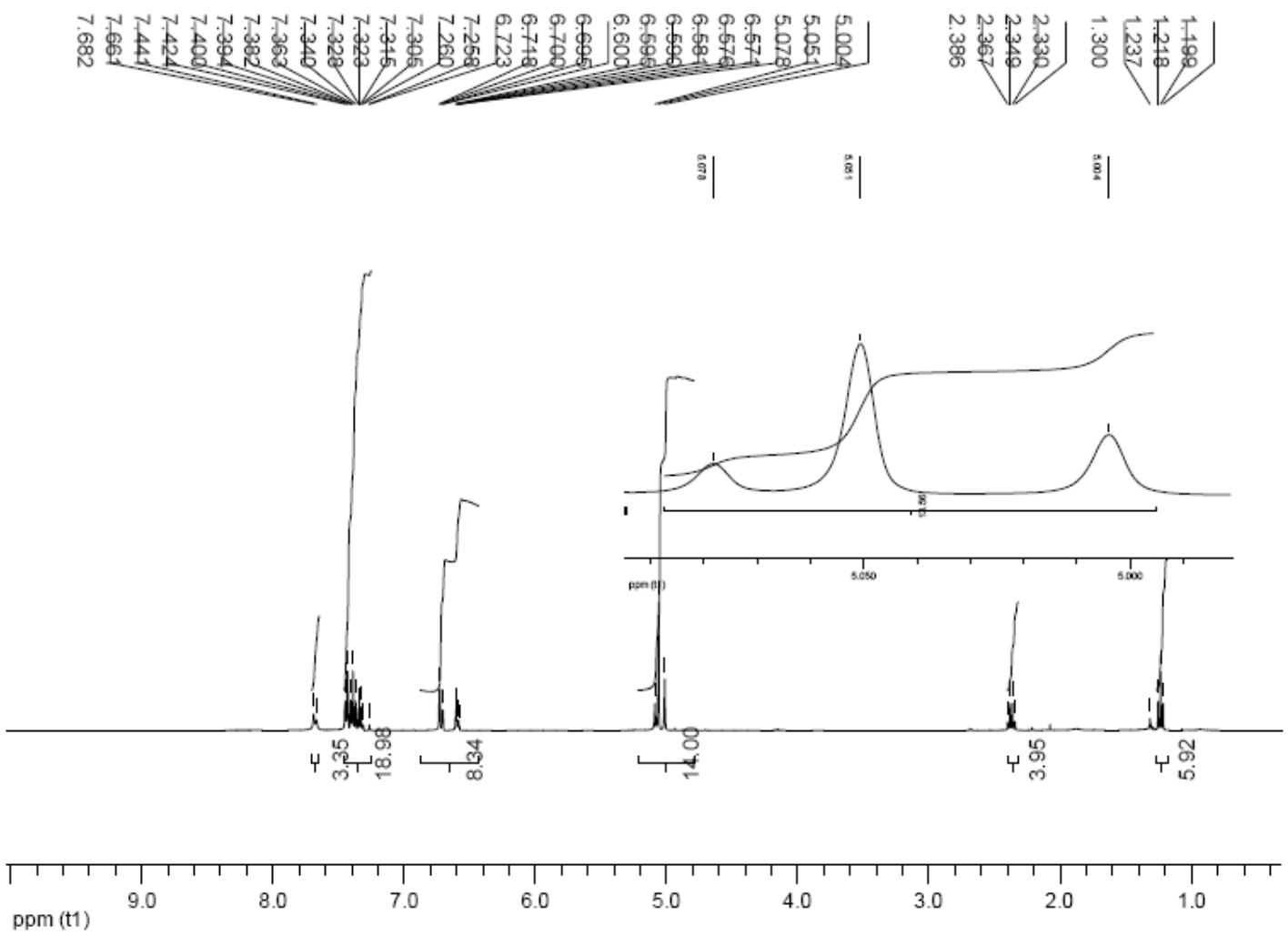

Figure A.7. ^{1}H-NMR of G2-DAP-dendron

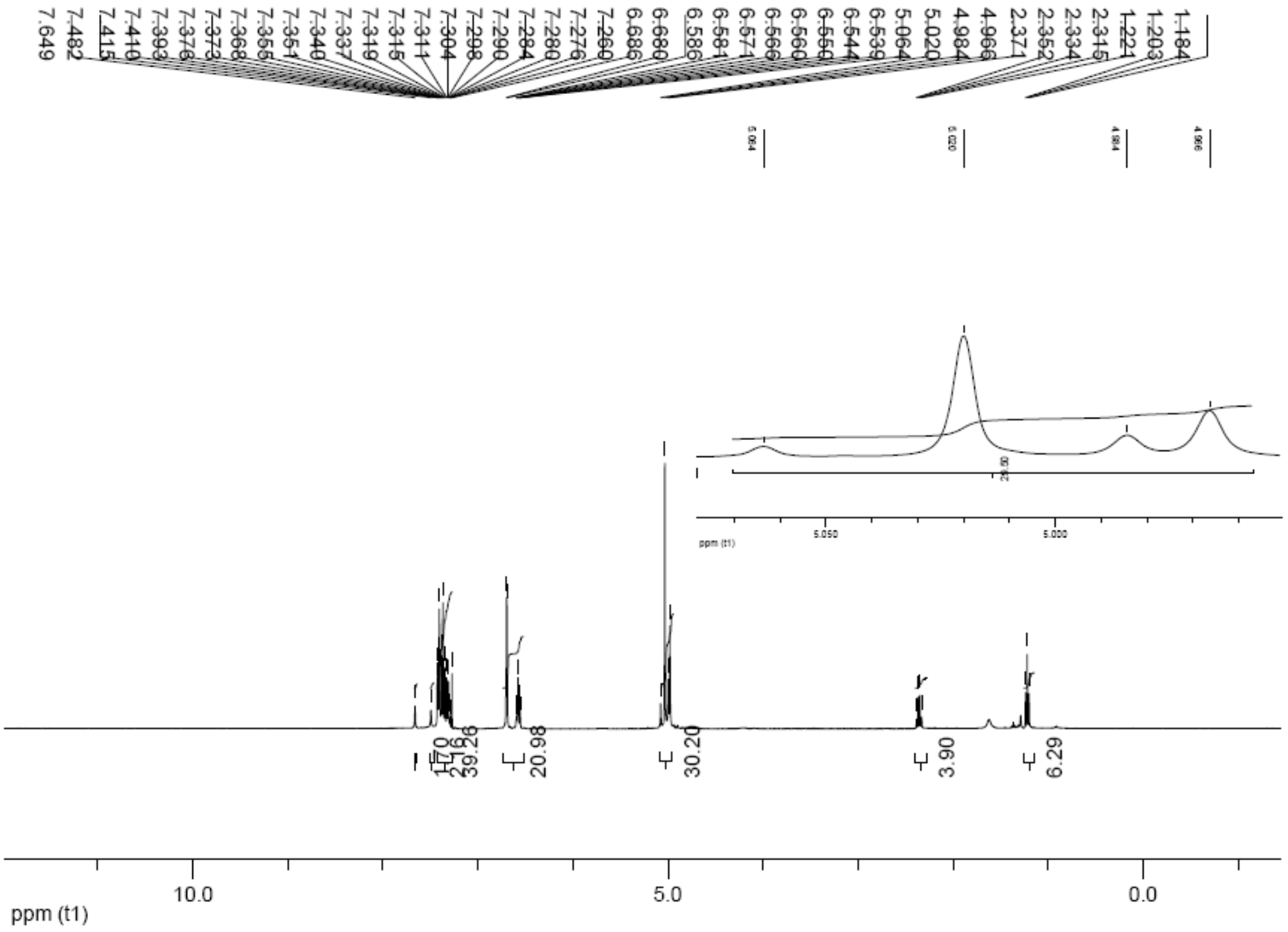

Figure A.8. ^{1}H-NMR of G3-DAP-dendron

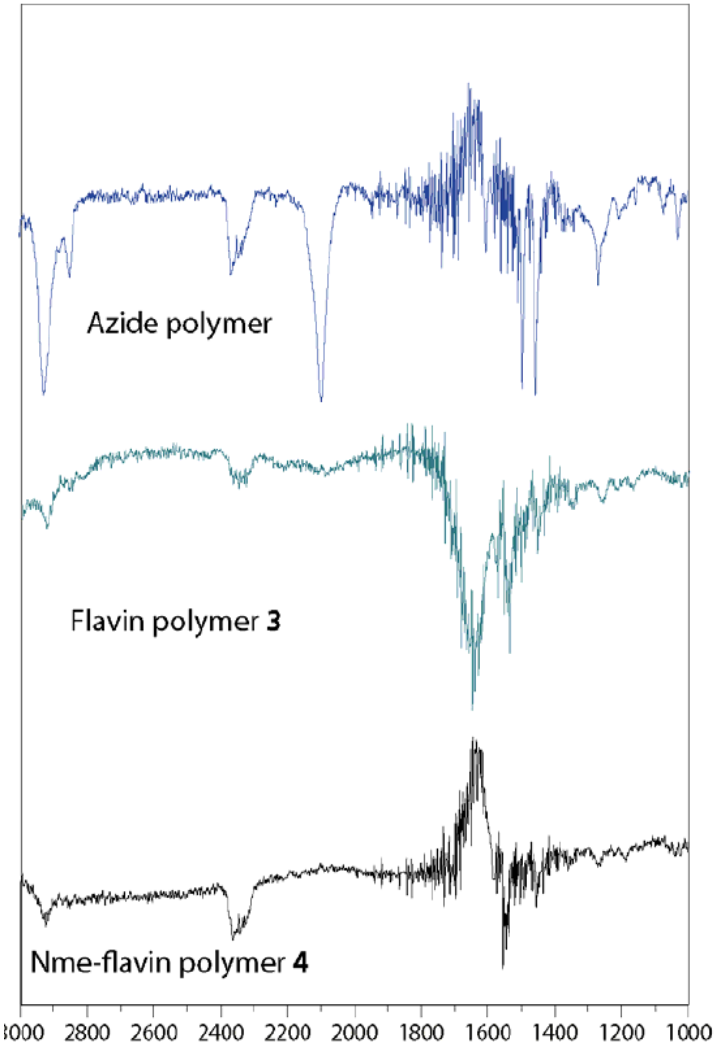

Figure A.9. IR spectrum of azide polymer, flavin polymer 3 and NMe-flavin polymer 4

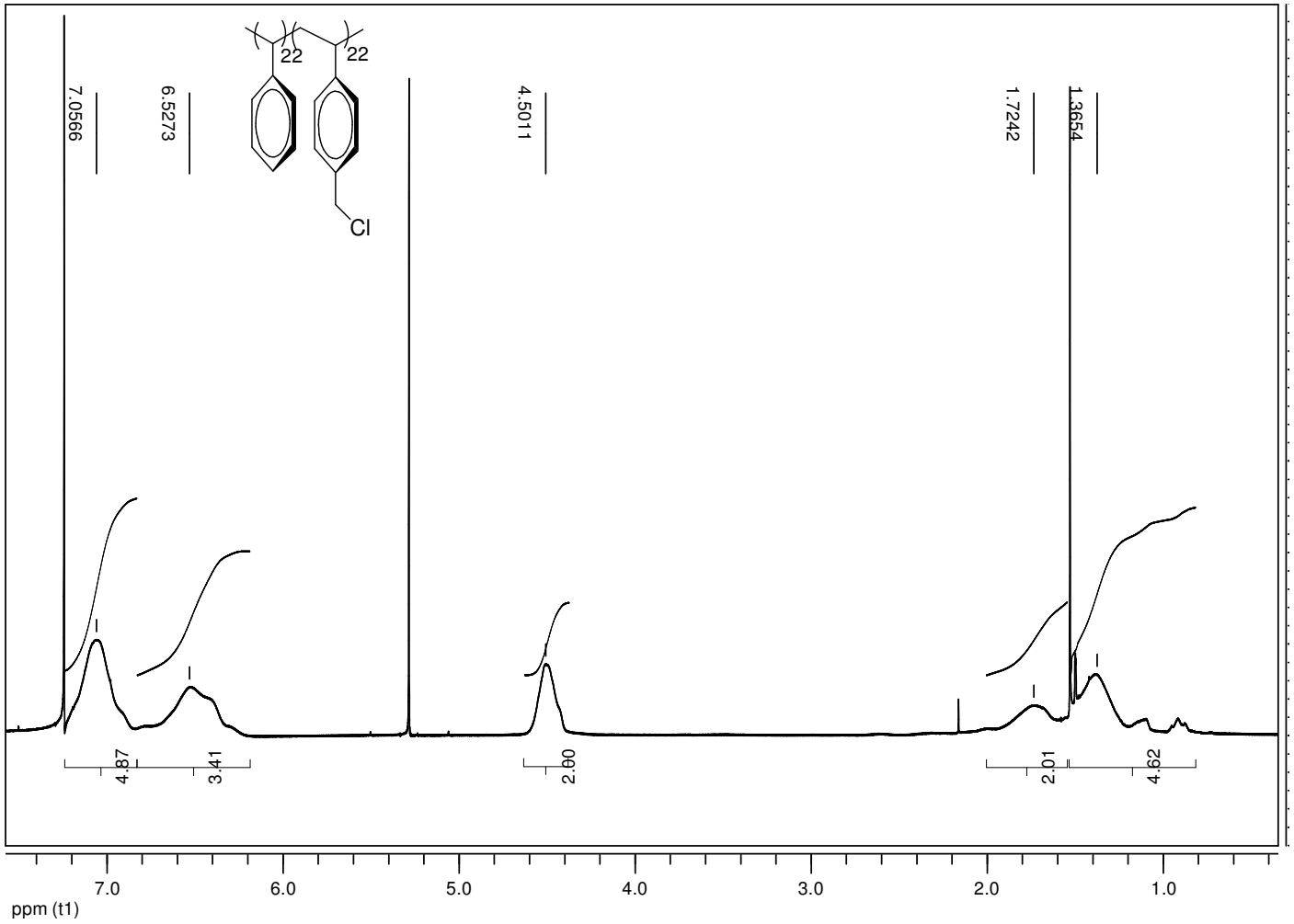

Figure A.10. ^{1}H-NMR of poly(styrene-*p*-(chloromethyl)styrene)

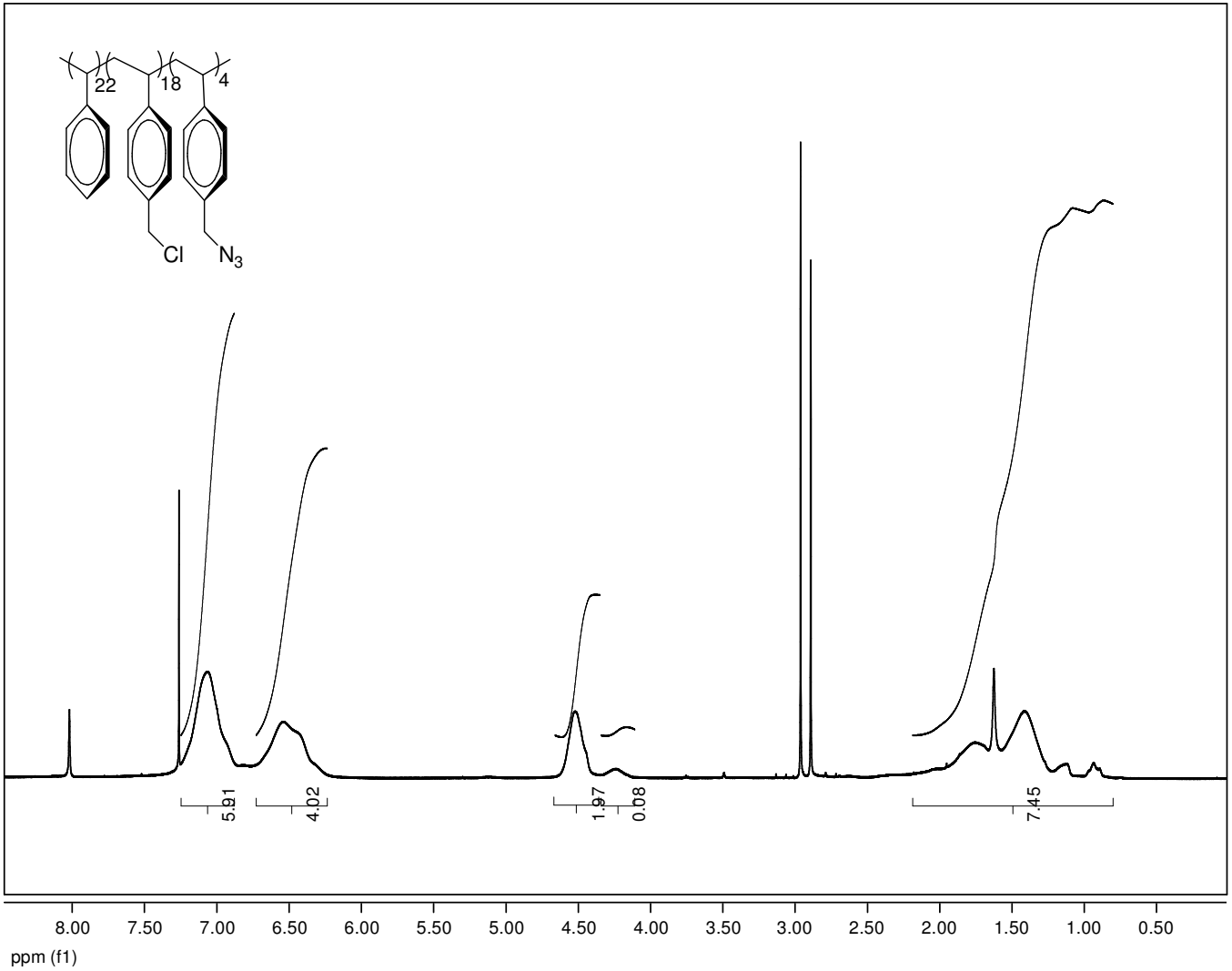

Figure A.11. ^{1}H-NMR of azide polymer

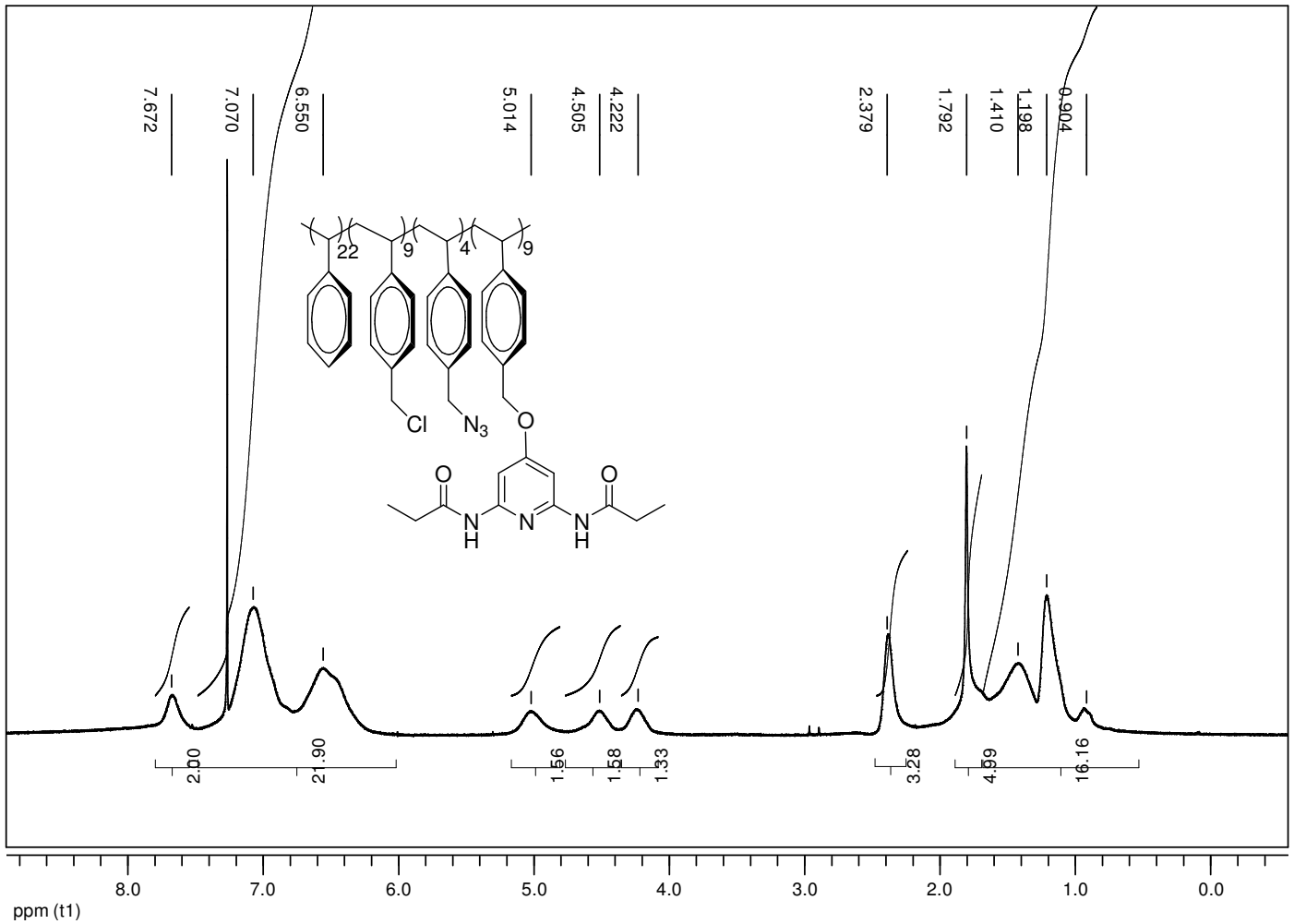

Figure A.12. ^{1}H-NMR of polymer I (PS-DAP-Az)

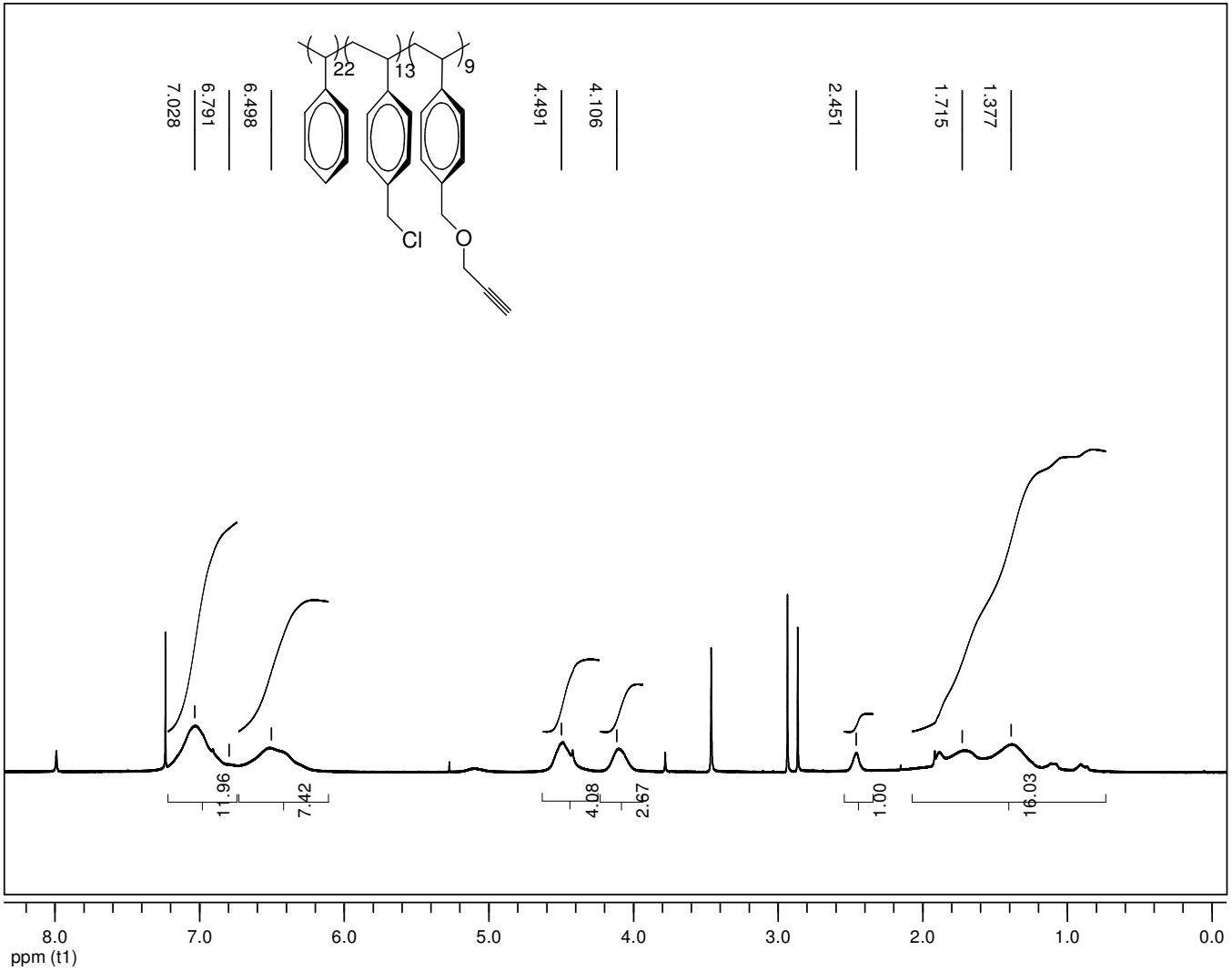

Figure A.13 ^{1}H-NMR of alkyne polymer

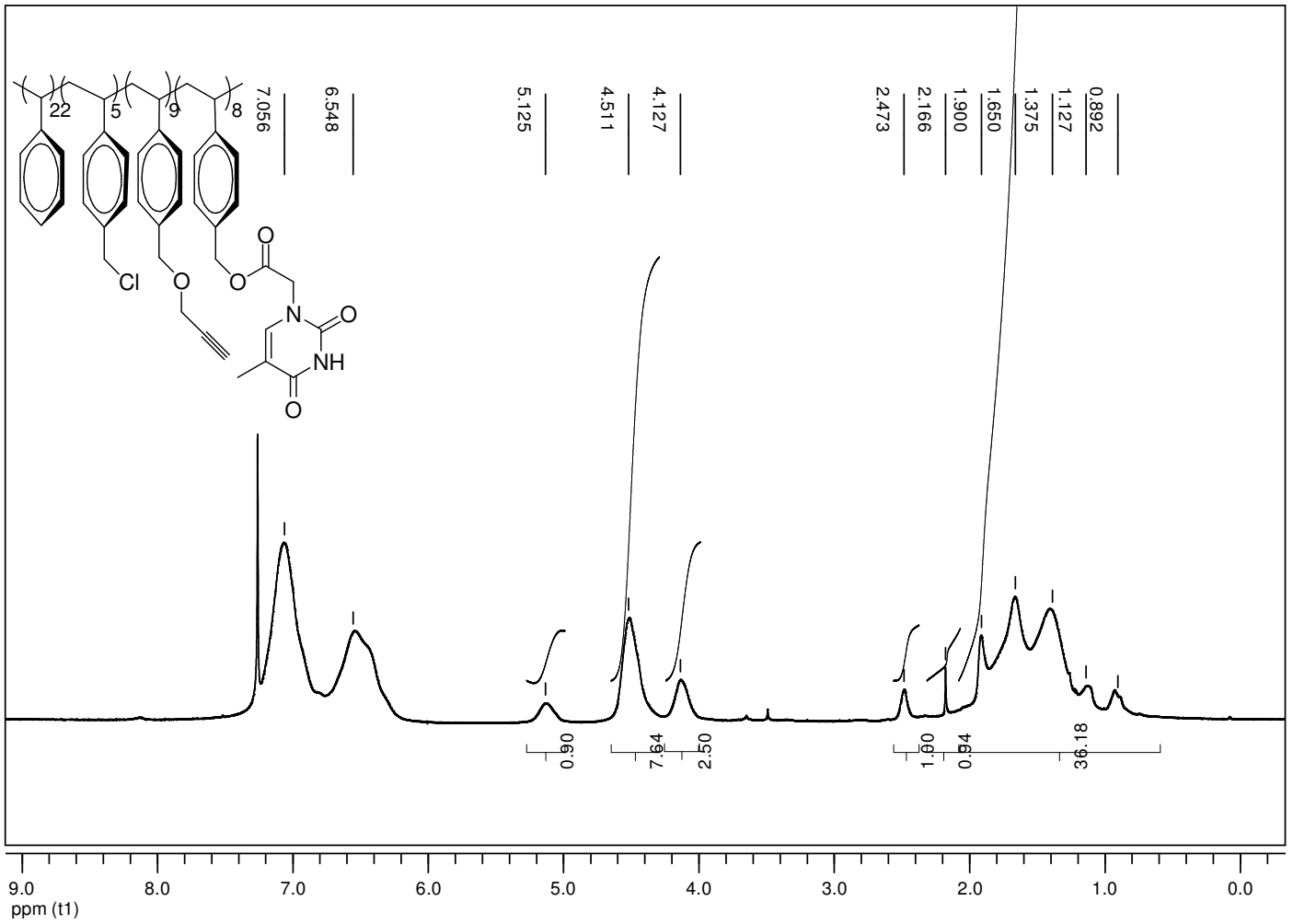

Figure A.14. ^{1}H-NMR of polymer II (PS-THY-Alk)

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