CONSTRUCTION OF THE NOVEL CORE/INTERFACIAL CROSSLINKED INORGANIC/ORGANIC HYBRID MICELLE BASED ON FUNCTIONALIZED POLYHEDRAL OLIGOMERIC SILSESQUIOXANE (POSS) VIA THIOL-ENE “CLICK” CHEMISTRY

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CONSTRUCTION OF THE NOVEL CORE/INTERFACIAL CROSSLINKED INORGANIC/ORGANIC HYBRID MICELLE BASED ON FUNCTIONALIZED POLYHEDRAL OLIGOMERIC SILSESQUIOXANE (POSS) VIA THIOL-ENE “CLICK” CHEMISTRY

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ABSTRACT

Supramolecular structures formed by the spontaneous self-assembly of block copolymers in selective solvents have been the focus of academic interest over the last decade. The recent development of “living radical polymerization” synthesis methods has expanded the range of functional block polymers and improve the controllability of block length,\(^6\text{-}^{10}\) which lead spherical polymer micelles and nanoparticles into significant potential in application. However, the spontaneous dissociation of micelles under their critical micelle concentration (CMC) always limits further applications.\(^{18,19,22}\) Later, the emergence of cross-linked micelle solved this problem.\(^{21}\) By cross-linking the core or shell of micelle, it leads to the formation of robust nanoparticles, which prevent the dissociation below CMC.\(^{21,22}\)

In this work, to explore new and efficient crosslink strategy, stable spherical inorganic-organic hybrid micelles were prepared by covalent crosslinking of micellar core/interface, via thiol-ene click chemistry. Amphiphilic block copolymer, poly(ethylene oxide)-\(\text{block}\)-polystyrene with vinyl-funcitonalized polyhedral oligomeric silsesquioxanes (VPOSS) randomly distributed on the PS block (PEO-\(b\)-PS/VPOSS), was designed to form the core-crosslinked micelles by self assembly in a mixture of dimethylformamide (DMF) and water with PS/VPOSS as core and PEO as corona.
Meanwhile, another polymer, PEO-\textit{b}-PS with a VPOSS precisely located at the junction point of two blocks was synthesized to form the interfacial crosslinked micelles with VPOSS nanoparticles distributed on the interface between micellar core and shell in DMF/water solution.

The stability of the micelles were greatly enhanced by crosslinking of vinyl groups on VPOSS moieties under UV irradiation with pentaerythritol tetrakis(3-mercaptopbutylate) as crosslinking agent. The process is fast, efficient, and environmental tolerant. The crosslinked micelles can sustain their spherical morphology in organic solvent. The self assembly and crosslinking process were fully studied by Dynamic Light Scattering (DLS), and Transmission Electron Microscopy (TEM).
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CHAPTER I
INTRODUCTION

1.1 Self-assemble of Amphiphilic Block Copolymer in Solution

Supramolecular structures formed by nanoscale building blocks (NBBs) via self-assemble are attracting great attention in recent twenty years, due to their fascinating properties and immense potentials for applications.\textsuperscript{1,2} As part of the concept of “bottom-up” strategy in contrast to the “top-down” strategy which found its limit down to the scale of few nanometers,\textsuperscript{1} the self-assemble of NBBs has extended to the scales that cannot be reached by “top-down” methods and become an important approach to fabricate and process novel nano-materials.\textsuperscript{1-3}

Among many different types of NBBs, amphiphilic block copolymer stands out mainly due to its unique associative properties in both condensed state and solution\textsuperscript{2} and convenient preparation procedures especially after the recent development in anionic polymerization and controlled free radical polymerization.\textsuperscript{4,5} In last twenty years, the so-called “living radical polymerization” techniques\textsuperscript{6-10} have changed the status of chemical synthesis of polymers. Through the new established “living/controlled radical polymerization”, typically the atom transfer radical polymerization (ATRP),\textsuperscript{7,9,10} the reversible addition-fragmentation chain transfer polymerization (RAFT)\textsuperscript{8} and the nitroxide-mediated polymerization (NMP)\textsuperscript{6}, polymer chemists are capable to prepare
block polymers with well-defined compositions, narrow molecular weight distribution, and delicate architectures.\textsuperscript{5,6,10-12}

Amphiphilic block copolymers are able to self-assemble into thermodynamically stable micelles in selective solvent.\textsuperscript{13,14} Generally, micellization of block polymers in solution can be attributed to a balance of two opposing interactions: one is the interaction between the insoluble blocks which tries to attract each other to aggregate and minimize their interface with solvent molecules; the other one is the interaction between those soluble blocks which attempts to repulse each other and diffuse into solvent.\textsuperscript{14} Due to the balance of these two forces, the block polymers form unique morphologies instead of unlimitedly aggregating into a macroscopic phase or completely dissolving into an isotropic solution. Further studying in polymeric micelles reported a series of different morphologies, such as sphere, cylinder, and vesicle, by tuning the composition and concentration of block polymers, the nature of the common solvent, the selective solvent content and so on.\textsuperscript{14-16} The unique properties polymeric micelle possesses, \textit{e.g.}, good biocompatibility, low toxicity, stimuli-sensitivity, and facile preparation render them with great practical potentials in pharmaceutical applications, especially in drug delivery systems.\textsuperscript{17,18}

1.2 Crosslinked Micelles and Preparation Strategy

1.2.1 The Emergence of Crosslinked Micelles

High stability and robustness against environmental stimuli such as dilution, however, is required in many practical applications.\textsuperscript{18,19} Dilution of polymeric micelles,
*e.g.* intravenous injection, may result in the dissociation of micelles when the concentration approaches the critical micelle concentration (CMC) of the system.\(^{19}\) To circumvent this shortcoming and further extend the applications of polymeric micelles, crosslinking the individual micellar shell or core by creating covalent linkages between the polymer chains has been proposed as a viable approach to enhance the stability with respect to infinite dilution.\(^{20-22}\)

In 1996, Wooley’s group first reported the formation of the so-called shell crosslinked Knedel-like micelles. The micelles were prepared from a diblock copolymer, polystyrene-\textit{block}-poly(4-vinyl pyridine), with the aggregated polystyrene block (PS) as core and the hydrophilic poly(4-vinyl pyridine) block (PVP) as shell. The PVP block was then quaternized with p-(chloromethyl)styrene which acted as the crosslinkable agent. The crosslinking was achieved \textit{via} free radical oligomerization of those styrene groups pending on PVP block in the micellar shell. After crosslinking, the micelles were proved to be stable during the dilution of THF in solution.

1.2.2 Crosslink Strategies

Following Wooley’s pioneer work,\(^{21}\) variety of methods have been explored in this area.\(^{19,22}\) For example, a common approach is with the help of bifunctional crosslinking agents when the crosslinkable groups are introduced into polymer chains, either on the backbone, at the chain end, or as side groups.\(^{22}\) For example, Wooley’s group reported the crosslinking of hydrophilic block, poly(carboxylic acid) (PAA), by diamines in presence of carbodiimine which is used as a catalyst to activate the carboxyl group.\(^{23,24}\) Armes \textit{et al.} used the bis(2-idoethoxy)ethane (BIEE) reagent to crosslink the
block, poly(2-(dimethylamino)ethyl methacrylate) (PDMA), which is the shell of the micelle formed by poly(2-(dimethylamino)ethyl methacrylate)-block-poly(2-(N-morpholino)ethyl methacrylate) (PDMA-PMEMA)\textsuperscript{25} Another viable approach is to induce the crosslinking by radiation. Specifically, this strategy tries to create covalent linkages based on the irradiating reactive groups located in micellar shell/core through radiation\textsuperscript{22} Therefore, the small molecule crosslinking agents are no longer needed, which can be very attractive. Ding and Liu reported their work of the shell-crosslinked micelle through UV irradiation\textsuperscript{26} Their micelle was prepared based on the diblock copolymer, polystyrene-block-poly(2-cinnamoylethyl methacrylate) (PS-b-PCEMA), which contain photochemically crosslinkable functions in PCEMA block. Then, after 1-3 hours irradiation under UV light, the shell-crosslinked micelles were obtained\textsuperscript{26}

1.3 “Click” Chemistry

1.3.1 The Concept of “Click” Chemistry

The concept of “click” chemistry has been proposed by Professor K. B. Sharpless as a chemistry philosophy to describe the “ideal chemical reaction”, which should be high efficiency, with no or minimum side reactions and byproducts, easy to set up and purify, etc\textsuperscript{27} Therefore, “click” chemistry refers to a class of chemical reactions that, by the definition of Sharpless, must be modular, wide in scope, high yielding and creating only inoffensive byproducts which can be easily removed (without chromatography) and be stereospecific, simple to perform and that require benign or easily removed solvent\textsuperscript{27} Due to the advantages and prospect from the concept of “click” chemistry, it attracted
chemists to re-explore those chemical reactions which could fit more or less into the “click” society. For now, there are only several reactions which have been considered to be close enough to “click” nature. The typical examples are copper-catalyzed azide-alkyne cycloaddition \(^{28}\) (CuAAC) and thiol-ene coupling reaction. \(^{29,30}\) Then, in the following years, “click” chemistry was widely used in materials design and fabrication and making tremendous progress in this area. \(^{31-33}\)

1.3.2 Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC)

The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) was originated from the 1,3-dipolar cycloaddition which was known as the azide-alkyne Huisgen cycloaddition. \(^{34}\) Now, catalyzed by Cu(I), this reaction becomes highly regioselective and only generates the 1,4-addition product instead of a mixture of 1,4- and 1,5-addition products. \(^{35}\) And due to its high efficiency and reliability, CuAAC has also drawn great attention in fabrication of crosslinked micelles. \(^{36-39}\) In 2005, Wooley’s group reported the novel crosslinking approach based on “click” chemistry. \(^{36}\) In this work, micelles with a PAA shell and PS core was prepared by PAA-PS with the alkynyl groups partially distributed on the PAA block. By adding the multi-azide-functionalized crosslinking agent, the shell blocks of alkyne functionalized PAA were crosslinked via CuAAC “click” chemistry. \(^{36}\) This approach, though effective and robust, requires exclusion of oxygen and prolonged reaction time.
1.3.3 Thiol-ene Reaction

Thiol-ene reaction is another category of well-established “click” chemistry which gathered much interest in recent years. Thiol-ene reaction is initiated by the radical initiator; the initiating radical generate the thiol radical which reacts with the vinyl group and generate another carbon radical; then, the carbon radical further abstract a proton from next thiol group to create the next thiol radical which continue the circular reaction. Due to its click nature, tolerance of water and oxygen, and especially, short reaction time, thiol-ene reaction could be regard as a perfect candidate for preparation of crosslinked micelles.

1.4 Self-assemble Based on Functionalized Polyhedral Oligomeric Silsesquioxane (POSS)

1.4.1 Polyhedral Oligomeric Silsesquioxane (POSS)

On the other hand, in recent years, the hybrid polymeric supramolecular structures have gathered a lot of attention. Generally, they are constructed by introducing well-defined functional organic/inorganic nanoparticles with high stability and multifunctionality into polymer self-assembly. Hawker’s group use polymer micelles as template to self assemble Au particles. They prepared this amphiphilic golden nanoparticle with a Au core and amphiphilic block polymer chains, poly(styrene-b-2-vinylpyridine) attached on the surface of Au particle to form this polymer template. In solution, the block polymer self assemble to form the micelle with a PS corona and the P2VP core in which the Au nanoparticle was enclosed. However, these colloid nanoparticles can hardly be well defined and precisely functionalized. Novel building blocks with precisely defined structures and tunable functionalities are desired. There are
several candidates fitted to these requirements, for example, fullerene, polyhedral oligomeric silsesquioxane (POSS), polyoxometalate (POM), etc. Among them, polyhedral oligomeric silsesquioxane (POSS) are of great interests, due to its unique molecular structure and versatile surface functionalities. As the smallest precisely-defined silica cubic nanocage, POSS possess the hybrid inorganic-organic composition, $R_8(SiO_{1.5})_8$, where Si-O-Si, the inorganic part, constitute the silica cage and R-Si, the organic part, lead to the multiple potentially reactive and readily modified functional groups. In this way, POSS nanocage can be used as a molecular scaffold with the chemical inert core to carry diverse surface functionalities.

1.4.2 Self-assemble directed by functionalized POSS

Several groups have been focus on POSS-containing amphiphiles by grafting POSS with different functionalities to polymers or other functional nanoparticles. Ordered structures have been obtained through their self-assemble in both solution and condensed. Zhang et al. reported the synthesis of a tadpole-shaped POSS-containing hybrid poly(acrylic acid) and the formation of core-shell micelles by this molecule in aqueous solution. In our group, W-B. Zhang et al. synthesized a series of POSS end-capped poly(l-lactide) with diverse functionalities on POSS surface. Later, Yu et al. observed a variety of morphologies including spheres, cylinders and vesicles formed by polystyrene-(carboxylic acid-functionalized POSS) which is called “giant surfactant” due to its similarity with small surfactant in both molecular structure and assembly behavior in solution. Li et al. synthesized the functionalized POSS tethered by two polymeric tails with symmetric and asymmetric compositions which were later called
During the studying of POSS in our group, we found that the photo-initiated thiol-ene “click chemistry” can efficiently introduce different functionalities onto the vinyl functionalized POSS, which renders the vinyl-POSS a powerful building block to fabricate the crosslinked micelles via thiol-ene “click chemistry”.

1.5 Objective

In this work, we are going to report two kinds of POSS based crosslinked micelles: the core-crosslinked type and the interfacial crosslinked type. Specifically, to construct the core-crosslinked micelles, an amphiphilic block copolymer, poly(ethylene oxide)-b-polystyrene with vinyl-functionalized polyhedral oligomeric silsesquioxanes (VPOSS) randomly distributed on the PS block (PEO-b-PS/VPOSS), was designed. Meanwhile, the interfacial crosslinked micelles were achieved PEO-b-PS possessing a VPOSS at the junction point between the two blocks (PEO-VPOSS-PS). These two molecules were prepared by a combination of anionic polymerization, control/living polymerization, and CuAAC click reaction. Their molecular structures were fully characterized by Nuclear Magnetic Resonance, Fourier Transform Infrared Spectroscopy and Size-Exclusion Chromatography. The block copolymers were then dissolved in DMF, which is the common solvent for both blocks, followed by a slow addition of water, which is a selective solvent for PEO block, to self assemble into spherical micelles with PS core and PEO shell. Thiol-ene “click chemistry” was utilized to crosslink the core/interface of the micelle with the pentaerythritol tetrakis(3-mercaptobutylate) as crosslinking agent under UV irradiation (365 nm) at room temperature. The crosslinking process was fast and took less than 30 minutes. Through crosslinking, this inorganic-organic hybrid micelle was
stabilized and can sustain its original spherical morphology in dilution of DMF for several weeks. The morphologies were characterized by TEM and dynamic light scattering (DLS).
CHAPTER II
EXPERIMENTAL

3.1 Chemical and Solvents

The following chemicals, deuterated chloroform (CDCl$_3$, 99.8 atom% D, Aldrich), $N,N,N',N'',N'''$-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), 2,2-Dimethoxy-2-phenylacetophenone (DMPA, 99%, Aldrich), sodium azide (NaN$_3$, 99.5%, Aldrich) and pentaerythritol tetrakis(3-mercaptopentylate) (99%, Aldrich) were used as received.

Styrene (99%, Aldrich) was stirred for overnight with calcium hydride and distilled from it under vacuum for use. Cuprous bromide (CuBr, 98%, Aldrich) was purified by stirring in acetic acid overnight, washed with acetone, and dried in vacuum. The solvent, $N,N$-dimethylformamide (DMF, 99.9%, Aldrich), and toluene (Fisher Scientific, reagent grade) were purified by stirring over freshly-ground calcium hydride for 12 h and redistilled under vacuum before use.

The synthetic precursors, poly(ethylene oxide)-$b$-(polystyrene-$r$-poly(4-vinyl benzene chloride)) with azide group randomly distributed on PS block (PEO-$b$-PS/N$_3$), poly(ethylene oxide)-$b$-polystyrene with azide group at the junction point between PEO and PS blocks (PEO-(N$_3$)-PS), and VPOSS-alkyne nanoparticle were prepared according to reported procedures in our group.$^{50}$
3.2 Instrumentation and Characterization

All the samples for $^1$H and $^{13}$C nuclear magnetic resonance (NMR) were prepared in CDCl$_3$ (Aldrich, 99.8\% D). The NMR spectra were acquired by using a Varian Mercury 300 or Varian 500 NMR spectrometer. The $^1$H NMR spectra were referenced to the residual proton impurities in the CDCl$_3$ at $\delta = 7.27$ ppm. The $^{13}$C NMR spectra were referenced to $^{13}$CDCl$_3$ at $\delta = 77.00$ ppm. The average number of VPOSS nanoparticle contained on each PS block, $N_{VPOSS}$, can be obtained according to Eqn. 1 which is based on the previous work.$^{50}$

$$N_{VPOSS} = \frac{S_{VPOSS}}{S_{PEO}} \times \frac{4 \times M_{n}^{PEO}}{21 \times 44}$$  \hspace{1cm} (Eqn. 1)

where $S_{VPOSS}$ is the integration area of protons on the vinyl functional groups of POSS cage (5.82-6.21 ppm); $S_{PEO}$ is the integration area of protons in the repeat unit of poly(ethyl oxide) (3.64 ppm); and $M_{n}^{PEO}$ is referred to the calculated molecular weight of PEO block.

Infrared spectra were conducted by casting polymer films onto KBr plates from polymer solutions or by making a KBr pellet from a mixture with the sample. Meanwhile, the data were recorded on an Excalibur Series FT-IR spectrometer (DIGILAB, Randolph, MA) and then, processed using Win-IR software.

Size-exclusion chromatographic analyses (SEC) were performed using a Waters 150-C Plus instrument equipped with three HR-Styragel columns [100 Å, mixed bed (50/500/10$^3$/10$^4$ Å), mixed bed (10$^3$/10$^4$/10$^6$ Å)] and a double detector system with THF as eluent at a flow rate of 1.0 mL/min at 30 °C; the detector system consisted of a differential refractometer (Waters 410) and a laser light scattering detector (Wyatt
Technology, DAWN EOS, \( \lambda = 670 \text{ nm} \). Regular SEC calibrations were conducted with polystyrene standards (Polymer Laboratories).

Laser Light scattering experiments were conducted using a Brookhaven Instrument coupled to a BI-200SM goniometer, a BI-9000AT correlator, and an EMI-9863 photomultiplier tube for photo counting. A Meller Griot 35 mW He-Ne laser was used as the light source (632.8 nm). A cylindrical glass scattering cell with a diameter of 12 mm was placed at the center of a thermostat bath (0.01 °C) with decahydronaphthalene used for refractive index matching. The solutions were filtered into the scattering cells through syringe filters of 0.45 or 1.0 \( \mu \text{m} \) pore size. Both the scattering intensity and hydrodynamic diameter were measured at a scattering angle of 90° and a temperature of 25 °C.

Bright field images of TEM were recorded in a JEOL-1230 microscope with an accelerating voltage of 120 kV. 3 \( \mu \text{L} \) of the micelle solutions were deposited onto copper grids. After ca. 3 min, the excess solution was wicked away by a piece of filter paper. The sample was then allowed to dry under ambient conditions. TEM images were recorded on a digital CCD camera and processed with the accessory digital imaging system.

3.3 General Synthetic Procedures

3.3.1 PEO-\( b \)-PS/VPOSS

The precursors, PEO-\( b \)-PS/N\(_3\) and VPOSS-alkyne, were prepared according to the procedures reported previously in our group.\(^{50}\) PEO-\( b \)-(PS-\( r \)-PVBC-N\(_3\)) (150 mg, 0.0088 mmol), VPOSS-alkyne (45 mg, 0.062 mmol), CuBr (7 mg, 0.62 mmol) and 10 mL of
anhydrous toluene were added into reaction flask equipped with a magnetic stirrer. The mixture was degassed by three freeze-vacuum-thaw cycles. PMDETA (10 mg, 0.062 mmol) was then introduced into the mixture under nitrogen protection. After three extra freeze-vacuum-thaw cycles, the flask was stirred under room temperature for 24 h. After that the reaction mixture was concentrated and applied to the top of a column of silica gel. The column was eluted with CH$_2$Cl$_2$ first to remove the excess VPOSS. The product was then further eluted with chloroform/methanol (v:v = 90:10), which was collected, concentrated, and precipitated in an excess of ethyl ether and hexane (1:1) mixture for three times. The resulted solid was collected as a white powder (120 mg, 73 %). $^1$H NMR (CDCl$_3$, 500 MHz, ppm, δ): 6.30-7.40 (br, 430H, phenyl rings), 5.35 (br, 9H, -Ar-CH$_2$N-), 4.28 (m, 9H, -CH$_2$CH$_2$COOCH$_2$CH$_2$-), 3.64 (br, 770H, -CH$_2$CH$_2$O-), 3.08 (m, 9H, -CH$_2$CH$_2$COO-), 2.72 (m, 9H, -CH$_2$CH$_2$COO-), 1.67-2.15 (br, 87H, -CH$_2$CH(-Ar)-), 1.20-1.67 (br, 174H, -CH$_2$CH(-Ar)-), 1.20 (s, 9H, (CH$_3$)$_3$C-O-), 0.93 (m, 9H, O-COC((CH$_3$)$_2$)CH$_2$-, -CH$_2$CH$_2$COOCH$_2$CH$_2$-, -SC$_{11}$H$_{22}$CH$_3$).

3.3.2 PEO-VPOSS-PS

The synthetic precursor, PEO-(N$_3$)-PS, was prepared based on the previous work in our group.$^{50}$ The “click” reaction was carried out by a similar procedure to that of PEO-VPOSS-PS from PEO-(N$_3$)-PS. The product, PEO-VPOSS-PS, was obtained as a white powder by repeat precipitation in excess of ethyl ether and hexane (1:1) mixture. $^1$H NMR (CDCl$_3$, 500 MHz, ppm, δ): 7.80 (s, 1H, triazole group) 6.30-7.40 (br, 550H, phenyl rings), 4.28 (m, 2H, -CH$_2$CH$_2$COOCH$_2$CH$_2$-) 3.64 (br, 364H, -CH$_2$CH$_2$O-), 3.08
(m, 2H, -CH2CH2COO-), 2.72 (m, 2H, -CH2CH2COO-), 1.67-2.15 (br, 110H, -CH2CH(-Ar)-), 1.20-1.67 (br, 220H, -CH2CH(-Ar)-), 1.20 (s, 9H, (CH3)3C-O-).
4.1 Preparation of PEO-\textit{b}-PS/VPOSS

The synthetic route is outlined in Scheme 1. The block copolymer precursor, PEO-\textit{b}-PS/N3, can be easily synthesized based on previous work in our group via a combination of anionic polymerization and control/living polymerization. The precursor has an overall molecular weight of 18.5 kg/mol with PDI of 1.13. The molecular weight of PEO block was measured to be 9.0 kg/mol while PS block 9.5 kg/mol. The average azide functionality per chain was calculated to be 2.8 based on $^1$H NMR spectra. The vinyl-POSS moieties were introduced onto the polystyrene block by the copper-catalyzed azide-alkyne cycloaddition “click” chemistry (CuAAC) between azide groups on the PS block and alkyne group on VPOSS-alkyne. The product was fully characterized by $^1$H NMR, $^{13}$C NMR, FT-IR spectrometry, and SEC chromatography.
The first evidence towards success of “click” reaction comes from FT-IR spectra. Figure 3.1 shows the typical absorption peak of azide (~2100 cm\(^{-1}\)) which is obvious on the red curve (before click reaction), disappeared completely on the blue curve (after click reaction), indicating all the azide groups have been consumed.
Figure 4.1 FT-IR spectra of PEO-\textit{b-}PS/N$_3$ (red) and PEO-\textit{b-}PS/VPOSS (blue). The result was based on the sample with $M_n^{PEO} = 9.0$ kg mol$^{-1}$ and $M_n^{PS} = 9.5$ kg mol$^{-1}$.

More information about the chemical structure of the product can be obtained from $^1$H NMR, as shown in Figure 3.2. Besides the typical chemical shifts of PEO repeating units (proton \textit{b}) and PS repeating units (proton \textit{d, e,} and \textit{f}), the signals from VPOSS moieties can also be clearly observed and identified (proton \textit{h, i, j, k, l, m,} and \textit{n} in Figure 3.2). After reaction, the peaks of proton \textit{g} and \textit{h} have been shifted to 5.35 ppm and 3.05 ppm, respectively, due to the formation of triazole group (Figure 3.2). There is no residual signal at 5.00 ppm, corresponding to the protons on the carbon adjacent to azide group, indicating all the azide groups have been “clicked” with alkyne. The integration ratio between proton \textit{g, j, h,} and \textit{i} is 0.47: 0.54: 0.52: 0.49, close to 2:2:2:2 according to proposed structure. The degree of VPOSS functionality can be calculated by the integration ratio between protons on the PEO backbone (\textit{b}) and protons on the vinyl
groups of VPOSS \((l+m+n)\) based on Eqn. (1). The ratio is 49.0: 4.1, and the number of VPOSS per chain is calculated to be 3.2, close to the azide functionality in the precursor. The chemical shift of carbons on vinyl group of VPOSS was observed on \(^{13}\text{C}\) NMR at 137.1 and 128.5 ppm (Figure 3.3), further conform the structure of the product.

Figure 4.2 \(^1\text{H}\) NMR of the final product, PEO-\(b\)-PS/VPOSS. The result was based on the sample with \(M_n^{PEO} = 9.0\ \text{kg mol}^{-1}\) and \(M_n^{PS} = 9.5\ \text{kg mol}^{-1}\).
Figure 3.4 shows the SEC chromatograph of PEO-\textit{b}-PS/VPOSS and its precursor, PEO-\textit{b}-PS/N\textsubscript{3} as well as the pure PEO. The SEC characterization gives a symmetrical and narrow distribution of both molecules (PDI, 1.13 and 1.07, respectively). Obvious shifts of the curves to the small elution volume conform the molecular weight increasing in each reaction steps. After covalently linking POSS onto PS block, the polydispersity slightly increases, which can be explained by the presence of POSS nanoparticles. Actually, vinyl benzyl chloride (VBC) monomer was copolymerized with styrene to form a random distribution of VBC among PS repeating units. Because of similar molecular weights of two monomers and high overall molecular weight of block polymer, the difference between individual polymer chains is very small. However, this difference was greatly enlarged after grafting VPOSS particle onto the polymer chain due to its bulky
volume and relative high molecular weight (~700 g/mol), and therefore increases the polydispersity.

Figure 4.4 SEC chromatography of PEO, PEO-\textit{b}-PS/N3, and PEO-\textit{b}-PS/VPOSS. The result was based on the sample with $M_n^{PEO} = 9.0$ kg mol⁻¹ and $M_n^{PS} = 9.5$ kg mol⁻¹.

Another target molecule, PEO-\textit{b}-PS/VPOSS with a different PS molecular weight was synthesized to be the contrast group. The molecular characterizations of both of two products are summarized in Table 3.1.

<table>
<thead>
<tr>
<th>Label</th>
<th>$M_n^{all}$ kg mol⁻¹</th>
<th>$M_n^{PEO}$ kg mol⁻¹</th>
<th>$M_n^{PS}$ kg mol⁻¹</th>
<th>PDI</th>
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<tr>
<td>PEO-\textit{b}-PS/VPOSS</td>
<td>19.8</td>
<td>9.0</td>
<td>9.5</td>
<td>1.17</td>
</tr>
</tbody>
</table>

(a, b, c) Molecular weight was calculated by $^1$H NMR; (d) Polydispersity of the precursors, measured by SEC;
4.2 Formation of the core-crosslinked micelle

4.2.1 Preparation and characterization of PEO-$b$-PS/VPOSS micelle

PEO-$b$-PS/VPOSS micelle was prepared in a mixture of DMF and water. Since DMF is a common solvent for both blocks, PEO-$b$-PS/VPOSS was first dissolved in anhydrous DMF with a concentration of 0.25\% \textit{wt} as stock solution. Then water, which is a selective solvent of PEO block, was gradually adding into the solution. As a result, it will induce the formation of micelle due to amphiphilic nature of block polymer at room temperature. Figure 3.5a shows the image of spherical micelles formed by PEO-$b$-PS/VPOSS in the DMF/water solution at 11\% water content under a bright field TEM. Over a broad range of water content (from 11\% to 28\%), only spherical micelle can be observed (Figure 3.6). The spheres have an average diameter around 18 nm with a narrow distribution according to TEM characterization (Figure 3.5a). The micelle was further characterized by dynamic light scattering (DLS), which can provide size and morphological information in solution based on a spherical structure. The DLS results also gave a narrow distribute but relatively larger size (~ 30nm) compared with TEM picture (Figure 3.5b). The reason is that TEM observations were carried out in the solid state after the micelles had dried while DLS measurement was conducted directly in solution. The difference was mainly due to the collapse of the micellar corona during drying.
4.2.2 Formation of the core-crosslinked micelle

Crosslinking of the core of micelle was achieved by thiol-ene “click” reaction between vinyl groups on VPOSS nanoparticles and thiol groups on the crosslink agent, pentaerythritol tetrakis(3-mercaptopbutylate). An excess amount of pentaerythritol tetrakis(3-mercaptopbutylate) was added to consume all the vinyl groups to achieve
maximum of crosslinking density. 2,2-Dimethoxy-2-phenylacetophenone (DMPA) was used as photo-initiator to initiate the reaction by generating free radicals under UV irradiation. The mixture of micellar solution, DMPA, and pentaerythritol tetrakis(3-mercaptopbutylate) was stirred for 10 minutes to achieve homogenous solution. The mixture was then stirred under UV irradiation (365 nm) for 30 minutes at room temperature to complete the crosslink process (Scheme 3.1). After crosslinking, the TEM shows that the morphology of micelle was essentially unchanged and spherical micelle was observed with similar diameter (Figure 3.7a). DLS results exhibit another broad distribution with much lower concentration and larger average diameter, comparing with the previous one. This can be mainly attributed to the aggregation of micelles after thiol-ene crosslinking process (Figure 3.8).
To demonstrate the success of the crosslinking process and the stability of the micelle, the micelle solution after UV radiation was diluted with anhydrous DMF 6 times, 18 times, and 110 times to reach water content of 2 %, 0.7 %, and 0.1 %, respectively, and then incubated for one week at room temperature. At the same time, a control experiment was performed by diluting the uncrosslinked micelles with DMF to reach water content of 0.7%. In all the crosslinked cases, spherical micelle with similar size can still be clearly observed under TEM (Figure 3.7b-d). However, the typical micelle can hardly be identified in the control experiment (Figure 3.9).

![TEM pictures](image)

Figure 4.7 TEM picture of PEO-b-PS/VPOSS after crosslink (a), and diluted with anhydrous DMF to reach water content of 2 % (b), 0.7 % (c), and 0.1 % (d). The scale bar is 100 nm.
Figure 4.8 DLS result of the PEO-b-PS/VPOSS micelles after crosslink.

Figure 4.9 TEM picture of PEO-b-PS/VPOSS before crosslink and diluted with anhydrous DMF to 0.7% water content. The scale bar is 100 nm.
Since excess pentaerythritol tetrakis(3-mercaptopbutylate) was added and therefore all the vinyl groups were expected to be consumed, $^1$H NMR can provide further evidence towards the success of the thiol-ene click reaction. The crosslinked micelle solution was dialyzed against water for 2 days to remove DMF and small molecules, such as pentaerythritol tetrakis(3-mercaptopbutylate) and residual of initiators. The solution was then subjected to freeze dry and white powder was obtained. The $^1$H NMR spectrum was shown in Figure 3.10, in which the chemical shift of vinyl group (multi-peaks at 5.8-6.2 ppm) disappeared completely, which conform the success of thiol-ene reaction.

![Figure 4.10 $^1$H NMR of the crosslinked micelles dialyzed from DMF.](image)

4.3 Preparation of PEO-VPOSS-PS

The synthetic route is shown in Scheme 3.2. The “click” precursor, PEO-(N$_3$)-PS, can be obtained according to previous work in our group. A series of azide functionalized precursors with different block lengths were synthesized via a combination of anionic polymerization and atom transfer radical polymerization (ATRP). The
synthetic results for all products are shown below in Table 3.2. As shown in the synthetic route, the “click” reaction between VPOSS-alkyne and PEO-(N\textsubscript{3})-PS is similar to the previous reaction to synthesize PEO-\textit{b}-PS/VPOSS. The major difference is the number and location of the azide groups in the precursor. For PEO-\textit{b}-PS/N\textsubscript{3}, the azide functionalities are randomly introduced on the PS block with the number of 2 to 3 per chain; while only one azide group per chain which is located at the junction point of the PEO and PS blocks in the case of PEO-(N\textsubscript{3})-PS. Therefore, after “click” reaction, comparing with the randomly distributed VPOSS in the case of PEO-\textit{b}-PS/VPOSS, each molecule will have a well-defined structure with one vinyl-POSS particle grafted on the same exact point of the polymer chain. Based on this molecular design, during the formation of micelle, the VPOSS moieties can distribute on the interface between polystyrene core and poly(ethylene oxide) corona. Then, after crosslinking process, the interfacial crosslinked micelle with both unbonded core and corona can be obtained. The product molecules were characterized by $^1$H NMR, $^{13}$C NMR, FT-IR spectrometry, and SEC chromatography.
Scheme 4.3 Synthetic Route of PEO-VPOSS-PS

As an example, the characterizations of PEO-VPOSS-PS-1 are discussed to demonstrate the synthesis. Figure 3.11 shows the FI-IR spectra of the product and precursor, from which the typical absorption peak of azide (~2100cm⁻¹) (Figure 3.11, red) was found to be completely disappeared (Figure 3.11, blue), indicating all the azide groups have been consumed.
In Figure 3.12, the $^1$H NMR spectrum gives more accurate information to support the proposed molecular structure. The broad peak around 3.65 ppm belongs to the typical resonance of the protons of the PEO repeat units (proton $b$) and the signal from polystyrene can be clearly observed around 6.30 – 7.40 ppm (phenyl rings, proton $i$) and 1.20 – 2.15 ppm (proton $c, d$). With known of the molecular weight of PEO block, the molecular weight of PS can be calculated from the ratio of the $^1$H signal integration of the two blocks. The multiple peaks at 5.87 – 6.20 ppm which can be attributed to the vinyl groups on VPOSS cage (proton $h, n, m$), along with the presence of the chemical shifts at 2.70 ppm, 3.02 ppm, and 4.26 ppm corresponding to proton $f, g, e$, indicate the success of this “click” reaction. However, due to the high molecular weight of the
polymer and low resolution of those characteristic signals for the VPOSS moiety and the
“click” linkage, it is difficult to obtain the accurate integration ratio of them. Similar with
the case of PEO-\(b\)-PS/VPOSS, the observation of peaks at 137.1 and 128.2 on \(^{13}\)C NMR
which are corresponding to the vinyl group of VPOSS further conform the structure of
the product (Figure 3.13).

Figure 4.12 \(^{1}\)H NMR of PEO-VPOSS-PS. The result was based on the sample with \(M_{n}^{PEO}\)
= 4.0 kg mol\(^{-1}\) and \(M_{n}^{PS} = 11.4\) kg mol\(^{-1}\).
Figure 4.13 $^{13}$C NMR of PEO-VPOSS-PS. The result was based on the sample with $M_n^{PEO} = 4.0$ kg mol$^{-1}$ and $M_n^{PS} = 11.4$ kg mol$^{-1}$.

The SEC chromatography was used to measure the molecular weight and polydispersity of the block copolymers. Figure 3.14 shows the GPC results for the final product, PEO-VPOSS-PS, its precursor PEO-(N$_3$)-PS, and the original polymer, PEO. The SEC traces give narrow distributes for all the products. A clear shift can be observed from PEO to the “click” precursor, PEO-(N$_3$)-PS, which is due to the formed polystyrene block during ATRP. Then, after VPOSS functionalization, the retention volume essentially remains unchanged, which can be explained by the relative low molecular weight increment for one VPOSS (~700 g/mol).
Figure 4.14 SEC chromatography of PEO (black), PEO-(N$_3$)-PS (red), and PEO-VPOSS-PS (blue). The result was based on the sample with $M_n^{PEO} = 4.0$ kg mol$^{-1}$ and $M_n^{PS} = 11.4$ kg mol$^{-1}$.

Table 4.2 Molecular Characterization of PEO-VPOSS-PS.

<table>
<thead>
<tr>
<th>Label</th>
<th>$M_n^{all}$/kg mol$^{-1}$</th>
<th>$M_n^{PEO}$/kg mol$^{-1}$</th>
<th>$M_n^{PS}$/kg mol$^{-1}$</th>
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<td>1.10</td>
</tr>
</tbody>
</table>

(a, b, c) Molecular weight was calculated by $^1$H NMR;
(d) Polydispersity of the precursors, measured by SEC.

4.4 Formation of the interfacial crosslinked micelle

The PEO-VPOSS-PS interfacial crosslinked micelle was prepared by a similar procedure as the case of PEO-$b$-PS/VPOSS which has been described above. First, PEO-VPOSS-PS was dissolved in anhydrous DMF to prepare the stock solution with a
concentration of 0.2% wt. With the slow addition of water, the spherical micelle can be obtained at room temperature. The morphology and size of the micelle were characterized under a bright field TEM. Then, an excess amount of the crosslink agent, pentaerythritol tetrakis(3-mercaptopbutylate) and the photo-initiator, 2,2-Dimethoxy-2-phenylacetophenone (DMPA), were added into the micelle system to perform the thiol-ene “click” reaction between the VPOSS located on the interface between the PEO corona and PS core. Under the UV irradiation (365 nm) for 30 minutes at room temperature, the crosslinked micelles can be prepared. The micelle solution was diluted with an excess amount of DMF and characterized under TEM.

Micelles were prepared in DMF/water solution from the sample, PEO-VPOSS-PS-1, with $M_n^{\text{PEO}} = 4.0 \text{ kg mol}^{-1}$ and $M_n^{\text{PS}} = 11.4 \text{ kg mol}^{-1}$, and then, crosslinked by thiol-ene reaction. First, this molecule formed micelles in the solution with water content of 13.7% and then, the TEM was applied to characterize them (Figure 3.15). The result shows a mixture of spheres and cylinders in the micellar system, which mainly due to the larger PS fraction which lead to a morphological transformation from sphere to cylinder. After photo-crosslinking under UV irradiation for 0.5 hour, these crosslinked micelles formed by PEO-VPOSS-PS-1 were not as intact as micelles as in the previous case. Figure 17b shows that after crosslinking and diluting with DMF, a portion of PS chains were dissolved and diffusing out of the micellar core and floating around the surface of micelles. The micelles were partly deformed but still kept the essential spherical shape. It is probably due to that the interface is partially crosslinked. Different from the core-crosslinked micelles discussed in section 3.2, there is only one POSS nanoparticle on each block polymers. In this case, the interface may not be fully covered with POSS
particles, and thus the interface was not fully crosslinked. After diluting with DMF, ‘cracks’ will form on the interface. The PS will escape from core since DMF is a good solvent. It can only dangle around the interface, however, due to the covlanet bonds and other limitations.

Figure 4.15 TEM picture of PEO-VPOSS-PS before crosslink with the water content of 13.7% (a), and after crosslinking, dissolved in anhydrous DMF (b). The scale bar is 100 nm. The result was based on the sample, PEO-VPOSS-PS-1, with $M_n^{PEO} = 4.0$ kg mol$^{-1}$ and $M_n^{PS} = 11.4$ kg mol$^{-1}$. 
In summary, a novel approach towards preparation of the vinyl-POSS containing core/interfacial crosslinked micelles via the high efficient photo-initiate thiol-ene “click” chemistry has been proposed and disuccsed. Two types of molecules with POSS cage randomly distributed on the PS block (poly(ethylene oxide)-block-polystyrene/VPOSS) and POSS cage at the junciton point of block polymer (poly(ethylene oxide)-VPOSS-polystyrene), were synthesized to construct the core and interfacial crosslinked micelle, respectively. TEM and dynamic light scattering (DLS) confirm that after crosslink, the stability of micelles was greatly enhanced. It was found that thiol-ene click chemistry provides a facile and efficient approach towards crosslinked hybrid micelles.


