

Synthesis of Amphiphilic Star Block Copolymer with Photosensitive Core by ATRP

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Abstract: Well-defined photo and pH-sensitive amphiphilic star block copolymers were synthesized by copper based atom transfer radical polymerization, which consisted of a hydrophilic pH sensitive shell and photosensitive hydrophobic core structure. For this, photosensitive *n*-butyl acrylate (*n*BA) star polymer was synthesized with a multi-functionalized initiator including Pd-coordinated porphyrin in combination with CuBr and 4,4'-dinonyl-2,2'-bipyridyl (dNbpy) (PDI < 1.09). This hydrophobic photosensitive *n*BA star polymer was then used as a macroinitiator and polymerized with *N,N'*-dimethylamino ethyl methacrylate (DMAEMA) in the CuCl/CuCl₂/dNbpy catalytic system to synthesize P*n*BA-PDMAEMA star block copolymer, where the PDMAEMA block segment worked as a base exterior. For the arm chain consisted of an acid exterior block segment, the *n*BA star polymer macroinitiator was polymerized with *tert*-butyl acrylate (*t*BA) in the CuBr/dNbpy catalytic system to synthesize the P*n*BA-*t*BA star block copolymer followed by a treatment with strong acid for deprotecting the *tert*-butyl groups in the *t*BA block segment to give P*n*BA-poly(acrylic acid) (PAA) star block copolymer. Both amphiphilic photosensitive star block copolymers showed well defined molecular weights with narrow polydispersities (PDI < 1.23).

Keywords: star polymers, amphiphilic block copolymers, photosensitizer, atom transfer radical polymerization (ATRP).

Introduction

Well defined 3-dimensional polymers such as dendrimers and star polymers have been known to show unexpected physical properties in comparison to corresponding 2-dimensional polymers due to its compact shapes with small gyration.¹ In addition, a variety of functions derived from chemical property can be added to such physical property by precise introduction of functional groups to a specific position in the 3-dimensional structure to give interesting synergetic properties. Such functionalizations to the 3-dimensional structure have often carried out with dendrimers due to its well defined structures, which shows the superior properties in various applications for catalyst, drug delivery system, display etc.² However, synthesis of dendrimer has usually required cumbersome multiple condensation reactions to increase the generation (molecular weight), which was even more complicated when a functional group was introduced into the structure. As a similar 3-dimensional macromolecule, a star polymer is an attracting alternative material, because the synthesis is by simple addition polymerization, which is easy to prepare high molecular weight with various functionalities through copolymeriza-

tions of functional monomers.³ Notably, controlled radical polymerization (CRP) is one of the best methods to synthesize such well defined functionalized star polymers with controlled molecular weight and chemical composition.^{4,5} For example, various functionalized star polymers were synthesized by selective functionalization to the arm chain, the end of the arm chain, and the core using functionalized initiators and monomers through the CRP method.⁶⁻⁹ Among these star polymers, functionalized star block copolymer was especially interesting, because it gave different core/shell structures such as hydrophilic shell and hydrophobic core or vice versa as a single molecule, which for example, was used as a catalyst to accelerate a catalytic reaction and showed interesting selective host-guest interaction with a specific molecule.^{10,11}

In this paper, syntheses of novel amphiphilic star block copolymers with a photosensitive core were examined for photodynamic therapy (PDT) application. PDT has been known a promising method for treatment of solid tumors, which usually composed of a photosensitizer to generate cytotoxic singlet oxygen (¹O₂) during light irradiation in the presence of triplet oxygen (³O₂).¹² To increase the cytotoxic ¹O₂, design of the photosensitizer is important, because the self quenching of the excited species by aggregation of the photosensitizers through their π - π stacking often occurred

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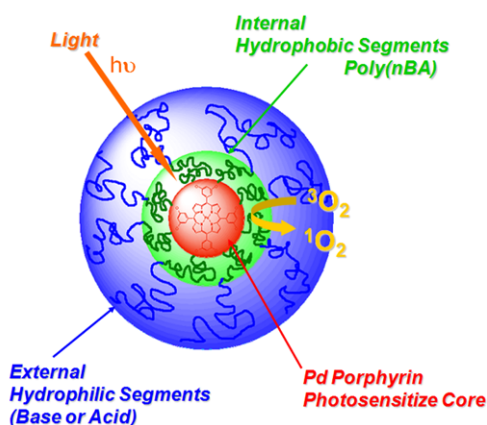


Figure 1. Amphiphilic star block copolymer photosensitizers for photooxidation reactions.

before generating $^1\text{O}_2$. Kataoka *et al.* designed a dendrimer typed photosensitizer, which consisted of a metal complexed porphyrin core surrounded by hydrophobic poly(benzyl ether) dendrons with ionic peripheral groups.¹³ This functionalized dendrimer effectively isolated the photosensitive dye in the core by the dendron shell to increase the efficiency in the PDT application. The functionalized star block copolymer examined in this paper mimicked this functionalized dendrimer, thus it composed of a metal complexed photosensitizer in the core surrounded by hydrophobic inner and ionic outer polymer block segments, where the hydrophobic inner block segment would effectively concentrated the hydrophobic oxygen into the photosensitizer core. For this, a photosensitive multi-functionalized initiator was first synthesized and polymerized with a hydrophobic monomer such as *n*-butyl acrylate (*n*BA) by Cu based living radical polymerization to synthesize a hydrophobic star polymer with a photosensitive core. This photosensitive *Pn*BA star polymer used as a macroinitiator to copolymerize a hydrophilic monomer such as acrylic acid (AA) or *N,N'*-dimethyl ethyl methacrylate (DMAEMA) by Cu based living radical polymerization,¹⁴ which could generate ionic groups by acid or base treatments in the shell in addition to hydrophobic photosensitive core (Figure 1).

Experimental

Materials. *n*-Butyl acrylate (*n*BA), *N,N'*-dimethylamino ethyl methacrylate (DMAEMA) and *tert*-butyl acrylate (*t*BA) were of commercial source (Aldrich, >99%), dried overnight over calcium chloride, and purified by distillation from calcium hydride before use. The photosensitive multi-functionalized initiator, palladium 5,10,15,20-tetrakis-(3,5-bis-[2-(2-bromo-propionyloxy)-ethoxy]-phenyl)-21H,23H-porphyrin complex was prepared according to the previous reports.¹¹ CuBr (Aldrich, 99.999%), CuCl (Aldrich, 99.995+ %), CuCl₂ (Aldrich, 99.999%) and 4,4'-dinonyl-2,2'-dipyridyl

(dNbpy, Aldrich, 97%) were used as received. *N,N,N',N'*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%) was distilled from calcium hydride before use. Anisole (Aldrich, 99.7%) was dried overnight over calcium chloride and purified by distillation from calcium hydride before use. Trifluoroacetic acid (TFA) (Aldrich, 99%) and dichloromethane (Aldrich, 99.8%) for the hydrolysis reaction were used as received.

General Polymerization Procedure for Poly(*n*BA) Star Polymer with Pd-Porphyrin Core. A typical polymerization procedure with *n*BA/Pd-porphyrin initiator/CuBr/dNbpy (400/1/8/16) is as follows: Pd-porphyrin initiator (0.395 mmol, 90.1 mg), CuBr (0.316 mmol, 45.4 mg), dNbpy (0.632 mmol, 258.4 mg), degassed anisole (36.3 mmol, 3.95 mL) and degassed *n*-butyl acrylate (15.8 mmol, 2.27 mL) were added sequentially to a 50-mL flame-dried round-bottom flask equipped with a three-way stopcock under a nitrogen atmosphere. The solution was stirred for 10 min at 25 °C and was then placed in an oil bath at 90 °C. In predetermined intervals, the polymerization was terminated by cooling to -78 °C. The conversion was determined by ¹H NMR. The reaction mixture was diluted with THF and filtrated through a neutral aluminum column to remove the catalyst. The solution was condensed and then poured into cold hexane. Precipitated viscous polymer was then filtered and dried overnight under vacuum at room temperature. The molecular weights and the chemical structures were characterized by SEC and ¹H NMR (see Table I).

General Polymerization Procedure for PDMAEMA-block-*Pn*BA Star Block Copolymer with Pd-Porphyrin Core. A typical polymerization procedure with DMAEMA/*Pn*BA star polymer with Pd-porphyrin/CuCl/CuCl₂/dNbpy (3200/1/10/2.5/25) is as follows: *Pn*BA star polymer with Pd-porphyrin ($M_w=35,900$, 0.013 mmol, 450.3 mg), CuCl (0.125 mmol, 12.4 mg), CuCl₂ (0.031 mmol, 4.2 mg), dNbpy (0.314 mmol, 128.3 mg), and degassed DMAEMA (40.1 mmol, 6.76 mL) were added sequentially to a flame-dried 50-mL round-bottom flask equipped with a three-way stopcock under a nitrogen atmosphere. The solution was stirred for 10 min at 25 °C and was then placed in an oil bath at 90 °C. After the polymerization in 100 min, the reaction was

Table I. Polymerization of *n*BA from the Multi-Functionalized Pd-Porphyrin Initiator (1) by CuBr Catalyzed Living Radical Polymerization in Anisole at 90 °C under Argon

run	Reaction Time (hr)	Conversion (%)	M_n (SEC)	M_w (SEC)	M_w/M_n (SEC)
1	0.5	13	6,000	6,500	1.09
2	4	24	13,300	14,200	1.07
3	18	42	22,800	24,800	1.09
4	48	62	30,000	36,400	1.21
5	98	78	42,400	59,200	1.40

terminated by cooling to $-78\text{ }^{\circ}\text{C}$. The reaction mixture was diluted with THF and filtrated through a neutral alumina column to remove the catalyst. The solution was condensed and then poured into cold hexane. Precipitated viscous polymer was then filtered and dried overnight under vacuum at room temperature. The molecular weights and the chemical structures were characterized by SEC and ^1H NMR.

General Polymerization Procedure for PAA-*block*-P*n*BA Star Block Copolymer with Pd-Porphyrin Core. A typical polymerization procedure with *t*BA/P*n*BA star polymer with Pd-porphyrin/CuBr/dNBpy (3110/1/8/16) is as follows: P*n*BA star polymer with Pd-porphyrin ($M_w=43,100$, 0.01 mmol, 452.1 mg), CuBr (0.084 mmol, 12.0 mg), dNBpy (0.168 mmol, 68.7 mg), and degassed *t*BA (32.6 mmol, 5.68 mL) were added sequentially to a flame-dried 50-mL round-bottom flask equipped with a three-way stopcock under a nitrogen atmosphere. The solution was stirred for 10 min at $25\text{ }^{\circ}\text{C}$ and was then placed in an oil bath at $90\text{ }^{\circ}\text{C}$. After the polymerization in 100 min, the reaction was terminated by cooling to $-78\text{ }^{\circ}\text{C}$. The reaction mixture was diluted with THF and filtrated through a neutral alumina column to remove the catalyst. The solution was condensed and then poured into cold hexane. Precipitated viscous polymer was then filtered and dried overnight under vacuum at room temperature. Obtained white powder was then acidified with small amount of TFA in dichloromethane and then extracted poured into cold hexane. Precipitated viscous polymer was then filtered and dried overnight under vacuum at room temperature. The molecular weights and the chemical structures were characterized by SEC and ^1H NMR.

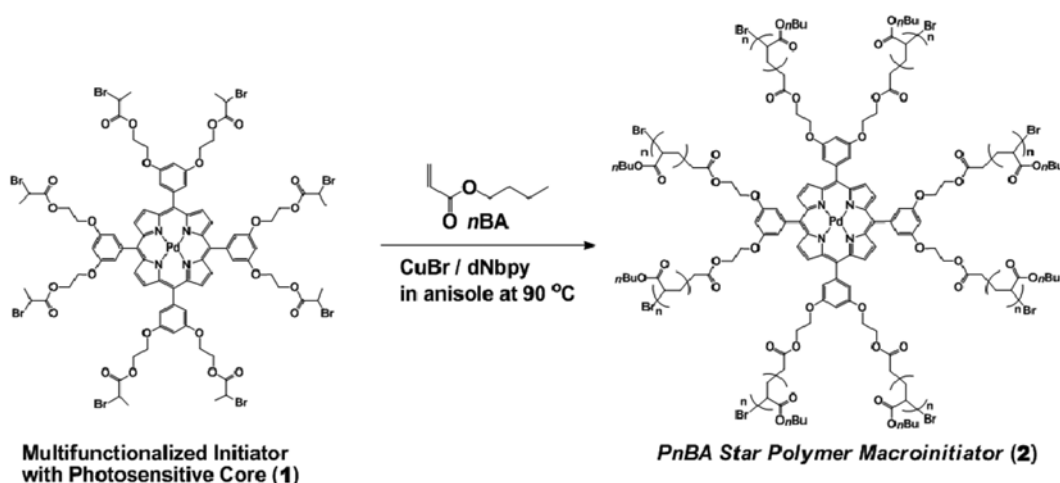
Polymer Characterization. The number average molecular weight (M_n) and molecular weight distributions (M_w/M_n) of the polymers were measured by JASCO PU-2080 plus SEC system equipped with RI-2031 plus refractive index detector and a UV-2075 plus UV detector (254 nm detection wavelength) using THF as the mobile phase at $40\text{ }^{\circ}\text{C}$ and a

flow rate of 1 mL/min. The samples were separated through four columns (Shodex-GPC KF-802, KF-803, KF-804, and KF-805). ^1H spectra were recorded in CDCl_3 at $25\text{ }^{\circ}\text{C}$ on a Varian Unity INOVA (^1H : 300 MHz). Fourier transform infrared (FTIR) spectra were measured with a Perkin-Elmer FTIR system Spectrum-GX using solvent cast films on KBr pellets.

Results and Discussion

P*n*BA Star Polymer with Photosensitive Core as a Macroinitiator. To synthesize the hydrophobic block core part with the photosensitizer, a multi-functionalized ATRP initiator with a porphyrin photosensitizer (**1**), palladium 5,10,15,20 - tetrakis-(3,5-bis-[2-(2-bromo-propionyloxy)-ethoxy]-phenyl)-21H,23H-porphyrin complex (Pd-porphyrin) was synthesized and polymerized with *n*-butyl acrylate (*n*BA) in the presence of CuBr catalyst with 4,4'-dinonyl-2,2'-bipyridyl (dNBpy) in anisole at $80\text{ }^{\circ}\text{C}$, where the bromopropionylethoxy group was worked as a ATRP initiator (Scheme I).

The polymerization smoothly proceeded with reaction time and the molecular weight of the obtained product increased in proportion to the conversion (Table I). Obtained P*n*BA star polymer (**2**) showed well controlled molecular weight with narrow polydispersity ($M_w/M_n < 1.04$ in the conversion $< 42\%$). However, the molecular weight distribution became a little broader when the conversion was over 50%. This was probably due to star-star coupling reactions, which was occurred when in syntheses of branched polymers by ATRP such as graft polymers and star polymers.¹⁵ Thus, stopping the polymerization at lower conversions was proper to achieve well-defined P*n*BA star polymer with Pd-porphyrin core, which is an important factor in preparing well-defined star block copolymers, because it would work as a macroinitiator in next block copolymerization. ^1H NMR



Scheme I. Synthesis of P*n*BA star polymer (**2**) from the multi-functionalized Pd-porphyrin initiator (**1**) by CuBr catalyzed living radical polymerization in anisole at $90\text{ }^{\circ}\text{C}$ under argon.

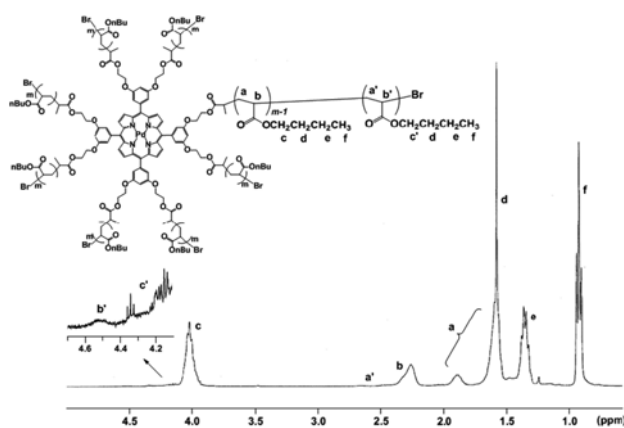
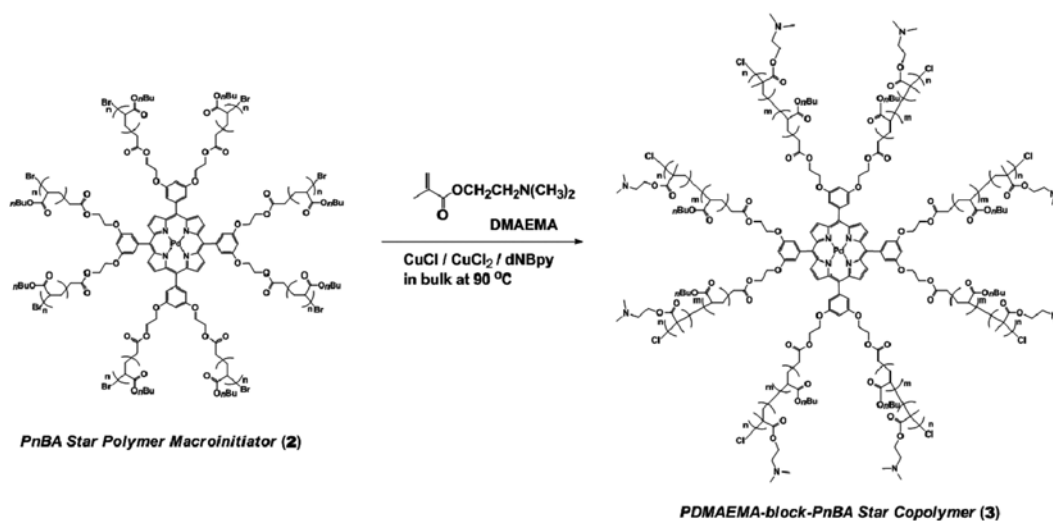


Figure 2. ^1H NMR spectrum of *PnBA* star polymer (macroinitiator) at room temperature in CDCl_3 .

spectrum of the obtained product, which was stopped at 20% conversion, showed the specific broadened peaks (*a-f*) originated from the protons in the *PnBA* star polymer (Figure 2). In addition to this, a small absorption peaks (*b'* and *c'*) of the ω -end repeating unit of *PnBA* adjacent to the bromide atom was observed at 4.5 and 4.2 ppm, respectively. When assuming the initiation was perfect, the number averaged molecular weight by ^1H NMR spectrum could be calculated from integration of the end group peak (*b'*) to the main polymer peak (*f*), which was 53,600 (M_n). This value was a little larger than that by SEC ($M_n=42,600$), which was probably due to smaller hydrodynamic volume of the star polymer in comparison to the corresponding linear polymer, because a linear polystyrene standard was used in SEC analysis. These results indicated that well-defined *PnBA* star polymer was successfully synthesized from the multi-functionalized initiator with Pd-porphyrin photosensitizer by ATRP.



Scheme II. Synthesis of PDMAEMA-*block-PnBA* star copolymers (**3**) from *PnBA* star polymer macroinitiator (**2**) by $\text{CuCl}/\text{CuCl}_2$ catalyzed living radical polymerization in bulk at 90°C under argon.

Base Exterior Amphiphilic Star Block Copolymer with Photosensitive Core. Obtained *PnBA* star polymer with Pd-porphyrin core (**2**) was then used as a macroinitiator for polymerization of *N,N'*-dimethyl ethyl methacrylate (DMAEMA) to synthesize base exterior amphiphilic star block copolymer with photosensitive core, PDMAEMA-*block-PnBA* star copolymer with Pd-porphyrin core (**3**) in the presence of CuCl and CuCl_2 mixture catalysts with dNBpy ligand in bulk at 90°C (Scheme II).

Obtained product after 100 min (conversion=57%) showed well defined unimodal SEC curve with narrow polydispersity ($M_n=143,400$; $M_w/M_n=1.23$), which clearly shifted to higher molecular weight in comparison to the *PnBA* star polymer precursor ($M_n=29,200$; $M_w/M_n=1.23$) (Figure 3). ^1H NMR analyses of the obtained PDMAEMA-*block-PnBA* star copolymer with Pd-porphyrin core showed characteristic absorption peaks (*a'* and *g-j*) from the PDMAEMA block segment in addition to those from the *PnBA* block segment (*a-f*) (Figure 4). Integration ratio of the peak (*i*) from the PDMAEMA to that (*c*) from the *PnBA* gave a relative unit ratio of each monomer, which gave the number averaged molecular weight, $M_n=352,900$. This molecular weight calculated by ^1H NMR spectrum was much larger

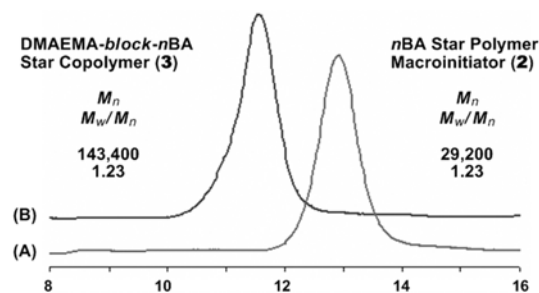


Figure 3. SEC curves of (A) *PnBA* star polymer (macroinitiator) and (B) PDMAEMA-*block-PnBA* star copolymer.

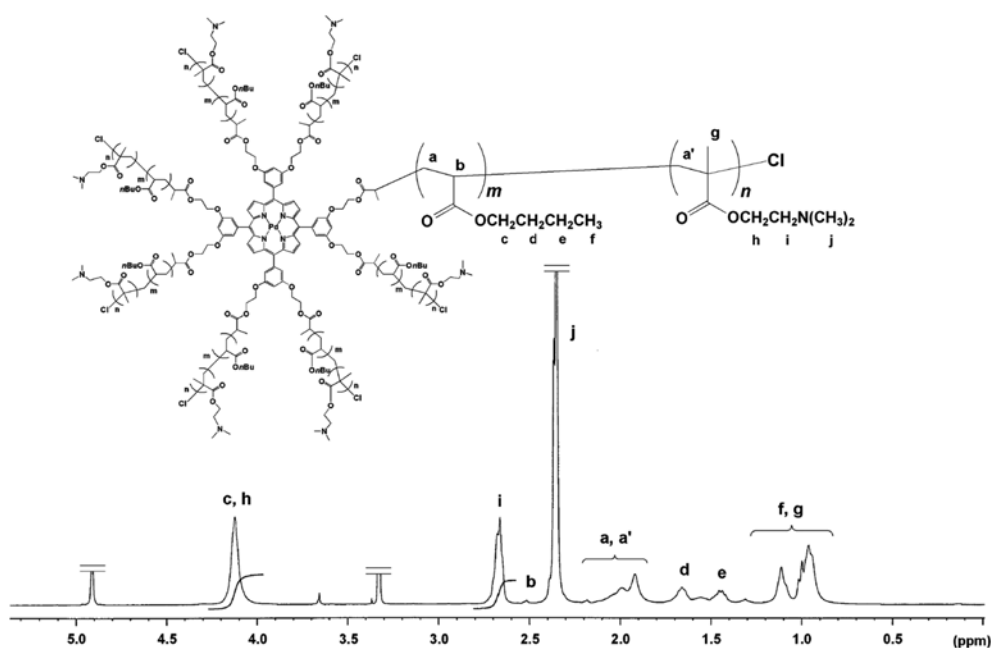


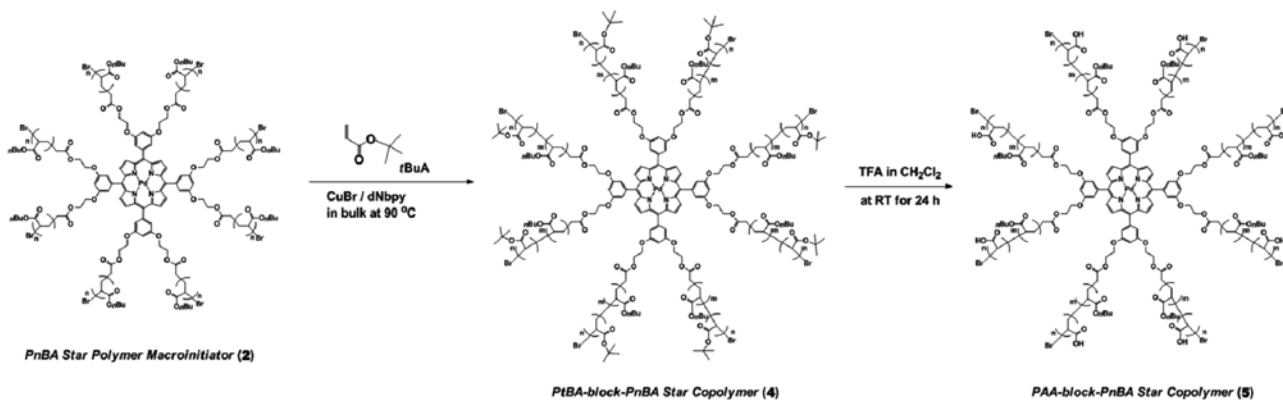
Figure 4. ^1H NMR spectra of PDMAEMA-*block*-PnBA star copolymer at room temperature in CDCl_3 .

than that by SEC ($M_n=143,400$), which was due to hydrodynamic volume change as described above and solubility change by the PDMAEMA exterior block segment. These results indicated that well-defined PDMAEMA-*block*-PnBA star copolymer with Pd-porphyrin core was successfully synthesized by block copolymerization of DMAEMA from PnBA star polymer macroinitiator by ATRP.

Acid Exterior Amphiphilic Star Block Copolymer with Photosensitive Core. In addition to the base exterior amphiphilic star block copolymer, an acid exterior amphiphilic star block copolymer with the photosensitive core (**5**) was examined by block copolymerization of *tert*-butyl acrylate (*t*BA) from PnBA star polymer macroinitiator (**2**) by CuBr catalyst with dNbpy ligand in bulk at 90°C , followed by acidification for deprotecting the *tert*-butyl group of the

poly(*t*BA) to give poly(acrylic acid) block segment (PAA) (Scheme III).

Obtained product after 2 h showed a well defined unimodal SEC curve with narrow polydispersity ($M_n=135,000$; $M_w/M_n=1.17$), which clearly shifted to higher molecular weight in comparison to the PnBA star polymer precursor ($M_n=43,100$; $M_w/M_n=1.13$) (Figure 5). Figure 6(A) showed ^1H NMR spectrum of the obtained PtBA-*block*-PnBA star copolymer with Pd-porphyrin (**4**). The absorption peaks (*a'*-*b'* and *g*) from the PtBA block segment in addition to those from the PnBA block segment (*a*-*f*). Integration ratio of the peak (*g*) from the PtBA to that (*c*) from the PnBA gave the number averaged molecular weight by ^1H NMR analysis ($M_n=141,700$). This well-defined PtBA-*block*-PnBA star copolymer with Pd-porphyrin was then acidified with trifluoro acid



Scheme III. Synthesis of PAA-*block*-PnBA star copolymers (**5**) by deprotection of *tert*-butyl group in PtBA-*block*-PnBA star copolymers (**4**), which was synthesized PnBA star polymer macroinitiator (**2**) by CuBr catalyzed living radical polymerization in bulk at 90°C under argon.

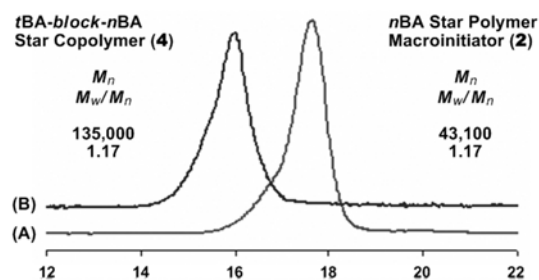


Figure 5. SEC curves of (A) *PnBA* star polymer (macroinitiator) and (B) *PtBA-block-PnBA* star copolymer.

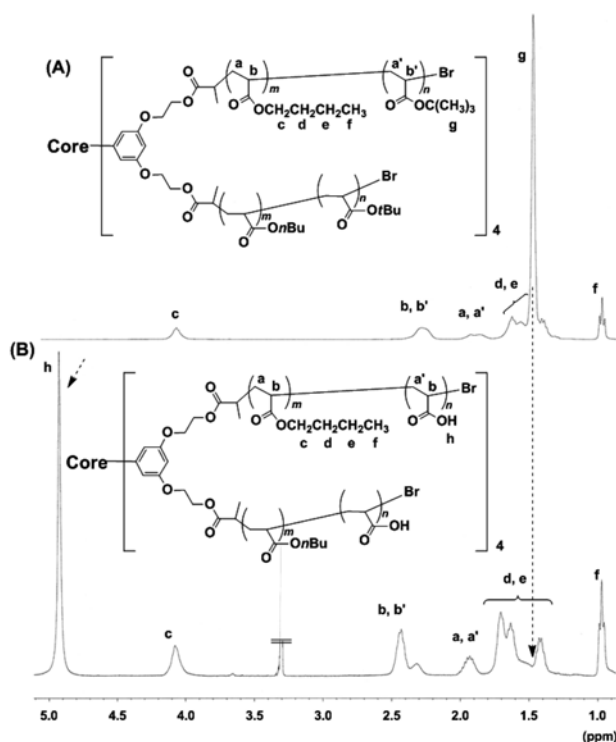


Figure 6. ^1H NMR spectra at room temperature: (A) *PtBA-block-PnBA* star copolymer in CDCl_3 and (B) *PAA-block-PnBA* star copolymer after acidification in CD_3OD .

(TFA) in methylene chloride. Figure 6(B) showed ^1H NMR spectrum of the obtained product after acidification. The characteristic absorption peak (g) of the methyl protons of the *tert*-butyl ester group in the *PtBA* was completely disappeared. Figure 7(A) and (B) showed FTIR absorption spectra of the products before and after acidification, respectively. After acidification, the characteristic absorption peaks originated from the carboxylic acid group in the PAA were observed at 1700 cm^{-1} (C=O stretch) and $2400\text{--}3500\text{ cm}^{-1}$ (O-H stretch). These results indicated that the acidification of the *PtBA-block-PnBA* star copolymer completely deprotected the *tert*-butyl group to give the acid exterior *PAA-block-PnBA* star copolymer with Pd-porphyrin quantitatively.

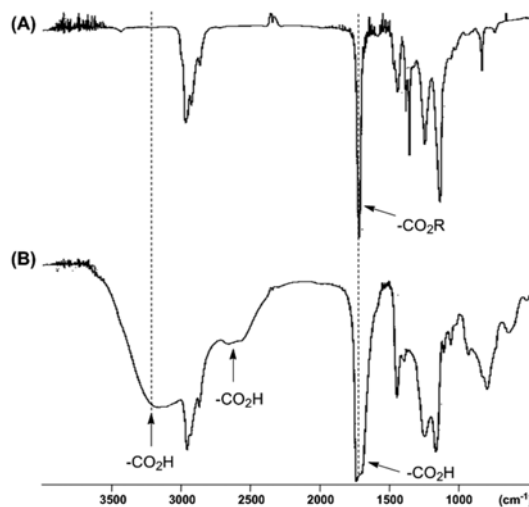


Figure 7. FTIR spectra (A) *PtBA-block-PnBA* star copolymer and (B) *PAA-block-PnBA* star copolymer after acidification.

Conclusions

This study successfully demonstrated that the ATRP method was useful to prepare well-defined photo and pH-sensitive amphiphilic star block copolymers with the photosensitive core. Thus, two series of the amphiphilic star block copolymers were synthesized, which consisted of hydrophilic and hydrophobic core shell structure with Pd-porphyrin core: PDMAEMA-*block-PnBA* star copolymer as a base exterior and PAA-*block-PnBA* star copolymer as an acid exterior with Pd-porphyrin cores, of which exteriors and the core would be sensitive by pH and photo stimuli, respectively. Detail physical studies with these amphiphilic star block copolymers as pH sensitive photosensitizers will be discussed in the forthcoming paper.

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