

Well-Defined Star-Shaped Rod–Coil Diblock Copolymers as a New Class of Unimolecular Micelles: Encapsulation of Guests and Thermoresponsive Phase Transition

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ABSTRACT: A series of star-shaped rod-coil diblock copolymers composed of poly(arylene ether sulfone) (PAES) as a core, and poly[2-(2-methoxyethoxy)ethyl methacrylate-co-oligo(ethylene glycol) methacrylate] [poly(MEO₂MA-co-OEGMA)] as a shell was synthesized by combination of chain-growth condensation polymerization (CGCP) and atom transfer radical polymerization (ATRP). In the presence of 4-arm initiator (1), CGCP of 4-fluoro-4'-hydroxydiphenyl sulfone potassium salt (2) via nucleophilic aromatic substitution (S_NAr) reaction yielded a well-defined star-shaped polymer with four fluorine end groups (C5-F and C8-F). Transformation of the fluorine groups into ATRP initiating sites produced a macroinitiator having four bromine groups (C5-Br and C8-Br). In the presence of the macroinitiator, random copolymerization of MEO₂MA and OEGMA via ATRP formed thermoresponsive shell blocks to produce a desired star-shaped PAES-b-poly(MEO₂MA-co-OEGMA) block copolymer with various block lengths. Dynamic light scattering (DLS) of the star-shaped diblock copolymers in aqueous solutions revealed that hydrodynamic diameters $(D_{\rm h})$ of the polymers decreases significantly by addition of Nile Red due to the transition from polymeric aggregates to unimolecular micelles. Fluorescence spectroscopy confirmed that the polymers behave as unimolecular micelles in the encapsulation of Nile Red, but another transition into multimolecular polymer micelles was observed by UV/vis spectroscopy when the excess amount of Nile Red was used. Turbidity measurements of the polymer solutions indicated that unimolecular micellar state was necessary to exhibit lower critical solution temperature (LCST) if the shell length was relatively short compared to the core size. Macroscopic aggregation was observed above LCST, and removal of encapsulated guests from water was demonstrated by simple filtration.

Introduction

Unimolecular micelles are covalently constructed macromolecules that consist of hydrophobic inner cores and hydrophilic outer shells.^{1–3} In contrast to conventional micelles, which are weak physical aggregates of low molecular weight surfactants or amphiphilic block copolymers,^{4–6} unimolecular micelles maintain the intrinsic micellar structure and encapsulation abilities under abrupt changes of environments such as dilution.⁷ The structural robustness of unimolecular micelles attracts many applications including drug and gene delivery,^{8–11} dispersion of dyes and fragrances,^{12–18} and removal of organic molecules in water.^{19–21} Combination of hydrophobic cores and stimuli-responsive shell polymers such as poly(*N*-isopropylacrylamide) (PNIPAM)²² is expected to produce smart materials which changes the physical state and actively releases encapsulated guest molecules when external stimuli such as temperature,^{22–25} pH,^{26–31} redox,³² light,^{33,34} or catalyst³⁵ are applied.

Most of unimolecular micelles have been obtained by surface modification of dendrimers^{36–38} or hyperbranched polymers^{39,40} and stable encapsulation of guests has been demonstrated without the existence of critical micellar concentration (cmc).^{9,12,17–20,30} However, dendrimers suffer from the tedious step by step synthesis and limitation in size while inherently polydisperse hyper-branched polymers are not suitable for the synthesis of well-defined unimolecular micelles. One of potential alternatives to surface-

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modified amphiphilic dendrimers and hyperbranched polymers is a star-shaped block copolymer that consists of a hydrophobic multiarm core block and a hydrophilic shell block tethered at each arm of the core.^{7,24,41–43} The development of controlled polymerization techniques such as atom transfer radical polymerization (ATRP)⁴⁴ and ring-opening polymerization (ROP)⁴⁵ makes it possible to synthesize a variety of star-shaped block copolymers with controlled molecular weight of each arm and narrow molecular weight distributions.^{7,24,41–43} Encapsulation abilities toward hydrophobic dyes have been demonstrated for star-shaped diblock copolymers with core blocks composed of aliphatic polyesters or vinylic polymers.^{24,42,43}

Hydrophobic and rigid condensation aromatic polymers such as poly(arylene ether)s⁴⁶ have not been used in the construction of star-shaped block copolymers because of difficulties in syntheses of precisely defined condensation polymers. However, a recent development of chain-growth condensation polymerization (CGCP) has opened an easy access for well-defined condensation polymers.^{47–51} The block copolymers containing rigid rod blocks are expected to show differences compared to the block copolymers, consisting of two coils. Indeed, linear block copolymers containing condensation and addition blocks have been synthesized using CGCP and self-assembly driven by incompatibility between rod and coil blocks was reported.^{49,50}

Herein, we describe the synthesis of well-defined star-shaped, rod-coil diblock copolymers that consist of poly(arylene ether sulfone) (PAES) as a core. Using a 4-arm initiator, well-defined 4-arm PAESs were synthesized by CGCP, and then initiating sites Scheme 1. Synthetic Route for (a) 4-Arm PAES Core Block with Fluorine Ends (C5–F and C8–F), (b) ATRP Macroinitiator (C5–Br and C8–Br), and (c) Star-Shaped Diblock Copolymers, PAES-*b*-poly(MEO₂MA-*co*-OEGMA) (C5–S68, C5–S83, C5–S97, and C8–S79, C8–S87, C8–S110)



for ATRP were introduced at each chain end. To take an advantage of thermoresponsiveness, poly[2-(2-methoxyethoxy)ethyl methacrylate-*co*-oligo(ethylene glycol) methacrylate] [poly(MEO₂-MA-*co*-OEGMA)],^{52,53} which becomes hydrophobic and aggregates above lower critical solution temperature (LCST), was selected as a shell block. Poly(MEO₂MA-co-OEGMA) is hydrophilic at room temperature so the unimolecular micelle readily goes into water and LCST can be adjusted by the incorporation ratio of OEGMA. By ATRP in the presence of the macroinitiator, a series of 4-arm PAES-b-P(MEO₂MA-co-OEGMA)s with various block lengths and composition was synthesized, and the unimolecular nature of the star-shaped diblock copolymers were investigated. Dye encapsulation measurements based on the fluorescence and UV/vis spectroscopy revealed that the stability of unimolecular micelles is strongly affected by the chain length ratio between core and shell block and the amount of dyes in the solution.

Results and Discussion

Synthesis of Star-Shaped PAESs as a Core. The synthetic route for 4-arm star-shaped PAES-b-poly(MEO₂MA-co-OEGMA) is shown in Scheme 1. The composition of starshaped core-shell PAES-b-poly(MEO₂MA-co-OEGMA) was expressed in form of Cn-Sm, where *n* and *m* indicate molecular weights in kDa of PAES core block and poly-(MEO₂MA-co-OEGMA) shell block, respectively. For the synthesis of 4-arm PAES as a hydrophobic core, the 4-arm initiator for CGCP, 1,2,4,5-tetrakis(4-fluoro-3-trifluoromethylbenzamido)benzene (1) was prepared by amidation of 1,2,4,5-benzenetetramine tetrahydrochloride with 4-fluoro-3-trifluoromethylbenzoyl chloride. The fluorine leaving groups (B) of initiator 1 was activated by the trifluoromethyl group at the ortho position as well as the amide group at the para position. In the presence of 1 and 18-crown-6, 4-fluoro-4'-hydroxydiphenyl sulfone potassium salt (2), a AB' type monomer, was polymerized at 120 °C in sulfolane (Scheme 1a). A previous study indicated that the polymerization of the monomer 2 did not occur without appropriate initiators, because the fluorine leaving group (B') of the monomer 2 is deactivated by the phenoxide group (A). However, the polymerization was initiated by the substitution of the more reactive fluorine group of the appropriate initiator by the monomer, and then proceeded in a chain-growth manner without self-polymerization.⁴⁷

The ¹H NMR spectrum of the polymer (C5–F) obtained by CGCP of the monomer 2 does not show any peaks corresponding to the aromatic protons at ortho position to the hydroxyl end group which appears at 6.9 ppm (Figure 1a), suggesting that the self-polymerization or transetherifications did not occur during the polymerization. The ratio of the integral values of the protons in the initiator moiety to the protons in the chain end was 1.03, also indicating the absence of side reactions. Molecular weights of the polymers obtained by NMR analysis (end-group analysis) were in good agreement with the theoretical values $(M_n \text{ (theor)})$ (see Table 1). A representative GPC trace of C5-F (Figure 2a) shows a narrow molecular weight distribution with polydispersity (PDI) of 1.16. Molecular weights of C5-F based on the linear polystyrene standards are within $\pm 15\%$ range compared to the molecular weight based on the NMR end-group analysis. By changing the feed ratio of monomer to initiator, it was possible to control the molecular weight of polymers up to 10 kg/mol. However, GPC analysis revealed that the molecular weight distribution became broaden as the molecular weight increased more than 5 kg/mol presumably due to the transetherification. It seems that the transetherification at the ethereal oxygen next to the initiating site cleaves the chains from the star-shaped polymers and the detached linear chains react further with the monomer, producing low-molecular weight polymers. In the case of C8-F with $M_{\rm n}$ (NMR) of 7.4 kg/mol, the proton integration ratio of the initiator moiety to the chain ends became higher than 1 (1.16), supporting that the transetherification reaction occurred



Figure 1. ¹H NMR spectra of (a) **C5–F**, (b) **C5–OH** (DMSO-*d*₆, 400 MHz), and (c) **C5–Br** (CDCl₃, 400 MHz).

Table 1. Molecular Weights of the PAES Core Block

	$M_{\rm n}({\rm theor})^a$	$M_{\rm n}({\rm NMR})^b$	$M_{\rm n}({ m GPC})^c$	PDI^{c}
C5-F	4030	3770	4340	1.16
С5-ОН	4450	4190	4940	1.18
C5–Br	5050	4790	5110	1.17
C8-F	7380	7440	6430	1.48
C8-OH	7800	7860	6840	1.48
C8-Br	8390	8450	6820	1.51

^{*a*}On the basis of the feed ratio of monomer to initiator. ^{*b*} Determined by ¹H NMR end-group analysis. ^{*c*} Determined by THF-GPC using polystyrene standards (RI detector, PLgel columns).

at the ethereal oxygen next to the initiating site but a slight extent.

To introduce initiating sites for ATRP, the fluorine end groups of C5-F were transformed to benzylic hydroxyl groups (C5–OH) via S_NAr reaction with 4-hydroxybenzyl alcohol, and then to sec-bromide groups (C5-Br) via esterification reaction with 2-bromoisobutyryl bromide (Scheme 1b). The S_NAr reaction of C5–F with 4-hydroxybenzyl alcohol was carried out in DMSO at 50 °C using K₂CO₃ as a base. The reaction was complete after 48 h to yield C5-OH where the less reactive benzylic hydroxyl groups remained intact. As shown in the ¹H NMR spectrum of C5–OH (Figure 1b), disappearance of the triplet at 7.45 ppm which corresponds to the aromatic protons *ortho* to the fluorine group confirms that the fluorine end groups were converted to the benzylic hydroxyl groups. Accurate control of reaction temperature as well as reaction time was important not only for the quantitative substitution of the fluorine end groups, but also to avoid the cleavage of the chains. A slightly shifted but unimodal GPC trace was observed after the reaction, suggesting no side reaction such as transetherification occurred (Figure 2b). Then C5–OH was transformed into C5–Br by esterification with 2-bromoisobutyryl bromide. ¹H NMR spectrum of C5–Br shows no trace of the benzylic protons next to the hydroxyl group at 4.49 ppm, indicating the quantitative introduction of sec-bromide groups. The GPC trace of C5-Br was almost identical to that of C5-OH (Figure 2c).



Figure 2. THF–GPC profiles of (a) C5–F, (b) C5–OH, (c) C5–Br, (d) C8–F, (e) C8–OH, and (f) C8–Br (RI detector, PLgel columns).

The end modification protocol was also applied to **C8–F** to yield **C8–OH** and **C8–Br**. The GPC traces of **C8–OH** and **C8–Br** in Figure 2d-f show that the molecular weight distributions were preserved during the end group modification even though a weak shoulder peak corresponding to low molecular weight polymer was noticed. After the introduction of *sec*-bromide groups, the molecular weights of **C5–Br** and **C8–Br** were determined as 4.8 kg/mol and 8.5 kg/mol by the NMR end-group analysis, respectively. Characterization details of the synthesized PAESs are summarized in Table 1. Figure S1 and S2 in the Supporting Information describes the method for the determination of molecular weights of 4-arm star-shaped PAES by ¹H NMR spectroscopy in detail.

Synthesis of Star-Shaped PAES-b-poly(MEO₂MA-co-OEGMA)s. Synthesis of poly(MEO₂MA-co-OEGMA)s via ATRP technique and their LCST properties were reported by J.-F. Lutz et al.^{52,53} Modifying the established condition found in the literature, random copolymerization of MEO₂₋ MA and OEGMA in the presence of the macroinitiator C5–Br or C8–Br were conducted using CuCl, CuCl₂ and 2,2'-bipyridine in anisole as a solvent (Scheme 1c). The molecular weight of poly(MEO2MA-co-OEGMA)s was controlled by varying the polymerization time. The feed ratio of MEO₂ MA to OEGMA was set to 9:1 to have the polymers with LCST transition at 38.4 °C.53 Molecular weights of the synthesized 4-arm star-shaped PAES-b-poly(MEO₂MA-co-OEGMA)s are listed in Table 2. Linear poly(MEO₂MA-co-OEGMA) with a similar molecular weight was also synthesized as an analogue (S23, M_n (theor) = 22.5 kg/mol).

Incorporation of poly(MEO₂MA-*co*-OEGMA) as a shell block was confirmed by the ¹H NMR spectroscopy measured in DMSO- d_6 , where both the core and the shell blocks are readily dissolved. In Figure 3, the peaks corresponding to the aromatic protons of the PAES core block as well as the aliphatic protons of the poly(MEO₂MA-*co*-OEGMA) shell block were clearly visible in the range of 7–8 and 0.5–4.5 ppm, respectively. Using the molecular weight of the PAES core block obtained by ¹H NMR end-group analysis, the molecular weight of the poly(MEO₂MA-*co*-OEGMA) shell block was determined from the integral values of aromatic

Table 2. Molecular Weight and PDI of the 4-Arm Star-Shaped PAES-b-poly(MEO₂MA-co-OEGMA)s

entry	PAES-Br	$\frac{\text{poly(MEO_2MA-co-OEGMA) (each arm)}}{M_n(\text{theor})^b}$	4-arm PAES- <i>b</i> -poly(MEO ₂ MA- <i>co</i> -OEGMA)			
	$M_{\rm n}{}^a$		$M_{\rm n}({\rm theor})^c$	$M_{\rm n}({\rm NMR})^d$	M_n^{e}	PDI ^e
C5-S68	4790	15900	68 400	77 800	28 700	1.26
C5-S83	4790	19 600	83 200	87 600	28 800	1.21
C5-S97	4790	23 100	97100	105 000	36200	1.24
C8-S79	8450	17 600	78 700	108 000	31 500	1.37
C8-S87	8450	19 600	86700	110 000	31 700	1.39
C8-S110	8450	24 600	107 000	135 000	38 000	1.31
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^{*a*} Determined by ¹H NMR end-group analysis. ^{*b*} On the basis of the conversion from the ¹H NMR analysis. ^{*c*} Obtained by summation of M_n^a and $4M_n^{b}$. ^{*b*} On the basis of the integration of the core and the shell blocks from ¹H NMR spectra measured in DMSO- d_6 . ^{*e*} Determined by THF-GPC using polystyrene standards (UV detector, GF-HQ columns).



Figure 3. ¹H NMR spectrum of C5–S83 in DMSO- d_6 (400 MHz).

protons (A) for PAES and aliphatic protons next to the estereal oxygen (1) for poly(MEO₂MA-*co*-OEGMA) (see Figure S3, S4 and Table S1 in the Supporting Information for the detail). The molecular weights of poly(MEO₂MA-*co*-OEGMA) were in good agreement with theoretical ones based on the conversion. Incorporation ratio of OEGMA to MEO₂MA was also obtained from the integration of protons next to the estereal oxygen (1) and protons between ethereal oxygens (2) from the ¹H NMR spectra in DMSO-*d*₆. Consistent with the literature, ^{52,53} the incorporation ratio turned out to be very close to the feed ratios indicating that OEGMA with MEO₂MA monomers were randomly copolymerized.

Polymers with unimolecular micellar properties have been reported to have different conformations depending on the polarity of the solvent.^{7,54-56} When measured in more hydrophilic NMR solvents such as methanol- d_4 and D₂O, the peaks corresponding to the aromatic protons in PAES were suppressed or even disappeared (Figure S5, Supporting Information). The lowered intensity of the protons in PAES suggests that the hydrophobic PAES surrounded by poly-(MEO₂MA-co-OEGMA) in hydrophilic media has reduced mobility as expected. Optimization of columns and eluents for the GPC analysis of 4-arm star-shaped PAES-b-poly-(MEO₂MA-co-OEGMA)s was challenging because the polymer consists of drastically different chemical functionalities within the architecture. Figure 4 depicts the GPC traces of PAESs and 4-arm star-shaped PAES-b-poly-(MEO₂MA-co-OEGMA)s with different molecular weights. Though the chromatograms were not in perfectly symmetric shape presumably due to the complicated interaction with the columns, it was found that 4-arm star-shaped PAES-bpoly(MEO₂MA-co-OEGMA)s with narrow polydispersities



Figure 4. THF-GPC profiles of C5-S68, C5-S83, and C5-S97 from the macroinitiator C5-Br. GPC traces of C5-F and C5-OH under the identical condition were also shown (UV detector, GF-HQ columns).

below 1.3 were obtained when the C5-Br macroinitiator with M_n (NMR) of 4.8 kg/mol was used. It seems that the monomers consumed during the polymerization were entirely transformed to the polymer chains which grow from the 4-arm macroinitiator, and the homopolymer, poly-(MEO₂MA-co-OEGMA), was not produced. The presence of CuCl₂ was essential to avoid coupling between growing arm-chains by decreasing the polymerization rate, hence keeping narrow molecular weight distributions of the polymers. Molecular weights determined by GPC based on the linear polystyrene calibration standards were smaller than those obtained by ¹H NMR analysis presumably because of the compact nature of the star-shaped polymers compared to their linear analogues. ${}^{57-60}$ When the macroinitiator C8–Br was used for the synthesis of star-shaped PAES-b-poly-(MEO₂MA-co-OEGMA), GPC chromatograms showed a shoulder peak at lower molecular weight region, and the polydispersities broadened up to 1.39. This low molecular weight fraction might originate from the polymers obtained by transetherification as discussed above. Though the broad nature of the macroinitiator, it was found that the ATRP process proceeded in a controlled fashion as in the case of C5–Br, evidenced by a decrease in the PDI of the resulting 4-arm star-shaped PAES-b-poly(MEO₂MA-co-OEGMA)s while the shape of the molecular weight distribution was preserved.

Hydrodynamic Size of the Polymers in Aqueous Solutions: Effect of Dyes. Hydrodynamic diameters $(D_{\rm h})$ of the synthesized 4-arm star-shaped PAES-b-poly(MEO₂MA-co-OEGMA)s in aqueous solutions were investigated by dynamic light scattering (DLS) study. Polymer solutions with 0.5 wt % concentration were subjected to the scattering measurements and their D_hs were determined as numberaverage diameters of lognomial distributions. The DLS study revealed that the D_h values were not proportional to the molecular weights of polymers determined by GPC analysis and surprisingly large in the cases of C8-S79 and C8-S87 (Figure 5, white column). The DLS results suggested that the polymers may exist as polymeric aggregates rather than unimolecular micelles in aqueous solution, especially when they had a short hydrophilic shell. In such a situation, aggregation of the core blocks may be driven by the



Figure 5. $D_{\rm h}$ (nm) of polymers at 0.5 wt % concentration without Nile Red (white column, left) and with Nile Red (filled column, right). $D_{\rm h}$ was determined as number-average lognomial mean diameter values.

interaction between the hydrophobic PAES-segments in the core blocks. Surprisingly, $D_{\rm h}$ s of the polymers were dramatically changed when Nile Red, a hydrophobic dye, was loaded into the solutions at the concentration of 16 mg/L. $D_{\rm h}$ s of all the polymer were reduced down from 60% to 32% of the $D_{\rm h}$ s without dyes (Figure 5, filled column). It seems that the decrease of $D_{\rm h}$ by addition of Nile Red occurred due to the dissociation of the polymeric aggregates to unimolecular micelles. This phenomenon has been reported recently,⁵ although in general the incorporation of hydrophobic molecules has been thought to enhance the association of unimolecular micelles to multimolecular polymer micelles.^{61,62} Here, the encapsulation of hydrophobic dyes into the hydrophobic core of the polymers seems to interrupt the interaction between the core blocks and fill the core space. Other hydrophobic dyes such as fat brown RR and pyrene showed a similar effect on $D_{\rm h}$ of the polymers (Figure S6, Supporting Information).

By using an atomic force microscope (AFM), it was possible to directly observe the difference between the polymeric aggregates and the unimolecular micelles. The 0.5 wt % polymer solutions were diluted to 10^{-15} mM, casted on a piranha-washed silicon wafer and investigated with AFM. Figure 6 shows images of **C5–S83** with Nile Red (Figure 6a) and without the dye (Figure 6b). It is apparent that the polymers with Nile Red appeared as uniform particles with the diameter of 20–40 nm while the polymers without the dye formed large irregular particles ranged from 50–100 nm in diameter, which is consistent with the DLS analysis. It is noticed that the diameter of particles observed on the AFM was larger than the D_h value of polymers, presumably because of aggregation of particles during the evaporation of water and flattening of the particles on the surface.

Spectroscopic Analysis on the Encapsulation of Dyes. The reduction in D_h s of the polymers on the encapsulation of Nile Red does not confirm that the polymers behave as a unimolecular micelle in aqueous solutions. Thus, fluorescence spectroscopy was applied to aqueous solutions of the polymers to investigate further the encapsulation of Nile Red by the star-shaped PAES-*b*-poly(MEO₂MA-*co*-OEGMA). Because Nile Red becomes fluorescent only in hydrophobic environments, it is possible to trace the Nile Red encapsulated in the inner hydrophobic pocket of micelles by measuring the fluorescence intensities using a spectrofluorophotometer with excitation wavelength of 570 nm.^{63–65} Figure 7a represents a change of fluorescence intensities of Nile Red



Figure 6. AFM images of C5–S83 containing (a) Nile Red, and (b) no dyes.



Figure 7. (a) Fluorescence spectra of Nile Red (16 mg/L) in aqueous solutions at different concentrations of **C5–S83** ($\lambda_{ex} = 570$ nm). (b) Fluorescence intensity at λ_{max} plotted with different polymer concentrations.

depending on the concentration of C5-S83. A gradual increase in the fluorescence intensity of Nile Red with increase of the polymer concentration indicates that C5-S83 is encapsulating Nile Red in the hydrophobic PAES core. A similar tendency was also observed for other star-shaped diblock copolymers as summarized in Figure 7b, where the maximum fluorescence intensities were plotted against the concentration of the polymers. Sodium dodecyl sulfate (SDS), which has a critical micelle concentration (cmc) at concentration of 2.3 mg/L, was also shown for comparison. SDS showed a typical S-shaped curve having an inflection point at cmc and indicated no encapsulation of dyes below cmc due to the absence of micelle. Compared to that, all the polymers investigated in this study revealed a steady increase of the amount of encapsulated Nile Red even at very low concentration without the presence of cmc. The above results support that the 4-arm star-shaped PAES-b-poly(MEO₂MAb-OEGMA)s having a covalently linked core-shell architecture



Figure 8. UV/vis spectra of Nile Red in polymer solutions of (a) C5–S97 and (b) C8–S110. (c) Absorption intensity at $\lambda = 559$ nm plotted against the number of dye molecules per polymer molecules.

behave as unimolecular micelles in aqueous media even at very low concentrations. At high concentrations, the fluorescence intensities became saturated because most of the Nile Red molecules were encapsulated. Interestingly, the increase of the fluorescence intensities was more rapid in the case of polymers with the shorter shell (C5-S68 and C8-S79). When they had a similar shell length, the polymer with the larger core exhibited higher fluorescence. Some Nile Red molecules might be encapsulated in the shell of the polymers but they did not contribute much to the fluorescence intensities because they resided in the hydrophilic environments.⁶⁶ When the concentration of polymer increased, they appeared to gradually repartition to hydrophobic cores and increase the fluorescence intensities. Interestingly, the fluorescence intensities of C5-S68 and C8-S79 went down in high polymer concentrations, implying that the polymers with short shell are not stable in high concentrations and lose their unimolecular nature.67,68

It should be also noted that the wavelength at which fluorescence intensity is maximum (λ_{max}) was shifted to a shorter wavelength with **C8** series ($\lambda_{max} = 608 \text{ nm}$) compared to **C5** series ($\lambda_{max} = 611 \text{ nm}$), and SDS ($\lambda_{max} = 635 \text{ nm}$)



Figure 9. AFM images of C5-S97 with (a) 5 and (b) 70 Nile Red molecules loaded per one polymer molecule.

presumably because the micellar core in **C8** series provides more hydrophobic environment than the others and more effective in stabilizing the dye in the excited state.

The encapsulation capacity of the 4-arm star-shaped PAES-b-poly(MEO₂MA-b-OEGMA)s was also measured with Nile Red by UV/vis titration experiments. Parts a and b of Figure 8 show UV/vis spectra of C5-S97 and C8-S110 aqueous solutions (0.01 mM) with different amounts of Nile Red loaded in the solution. The spectra showed a gradual increase in absorbance due to the increased amount of Nile Red dispersed in the solution, but the absorbance abruptly increased between 30 to 50 equiv of Nile Red per one polymer molecule, along with the hypsochromic shift of maximum absorption wavelength from 559 to 512 nm for C5-S97 and 559 to 515 nm for C8-S110, respectively. It was even possible to load 70 equiv of dye molecules. The AFM image of C5-S97 with 70 equiv of Nile Red showed that large and irregular particles were formed (Figure 9). It seems that 4-arm star-shaped PAES-b-poly(MEO₂MA-b-OEGMA)s adopted a conformational change on heavy loading of Nile Red into polymeric aggregate similar to the reported amphiphilic dendritic systems, where the solubility of dyes was greatly enhanced above a certain concentration.62

Compared to the previous study about star-shaped diblock copolymers with the aliphatic ester core and the OEGMA shell that indicated the unimolecular micelle was saturated after loading of a few (<30) dye molecules,⁴³ it is interesting to observe that the star-shaped diblock copolymers synthesized in this study shows much higher dye loading capacity in the unimolecular micellar state even with the smaller core block. The PAES core block appears to provide a rigid hydrophobic compartment inside the micelle which is favored by hydrophobic dyes. Also, the PAES core block seems to be essential in the transition into polymeric aggregates because aggregation of the polymers seems to be driven by aggregation of the PAES core block mediated by hydrophobic dyes, and more dyes can be extracted from water by the transition.

Thermoresponsive Properties. Temperature-dependent phase transition of the polymers was investigated by UV/vis spectroscopy to determine LCST of the solution. Figure 10 depicts the temperature-dependent transmittance change of the polymer aqueous solutions (0.5 wt %) with and without Nile Red. In the cases of the polymer solutions without Nile Red, significant cloudiness was observed only for the polymers with the longer shell, i.e., C8–S110. C8–S79 and C8–S87 did not show a distinct LCST while the linear analogue S23 clearly showed a LCST. It seems that aggregation of the core blocks may hamper the phase transition of poly(MEO₂MA-*b*-OEGMA)s by restricting the movement of the chains. However, all the polymer solutions with Nile Red showed a LCST presumably because the encapsulation



Figure 10. Transmittance ($\lambda = 700$ nm) plotted with temperature of 0.5 wt % polymer aqueous solutions (a) without and (b) with Nile Red (16 mg/L).





of dyes dissociated the polymeric aggregates into unimolecular micelles as discussed in the previous section, even though the transmittance change was relatively small with **C8–S79** (80%) and **C8–S87** (55%). It appears that the short shell chains tethered from a large core prefer to interact with the core block and fill the core space over LCST, not to aggregate with other shell polymers. Similar LCST behavior induced by a guest molecule has been reported recently.⁶⁹

Scheme 2 summarizes the phase transition of the 4-arm star-shaped PAES-*b*-poly(MEO₂MA-*b*-OEGMA)s. They exist as aggregates in aqueous solutions, but become unimolecular micelles upon addition of hydrophobic guests and show clear LCST. When an excess amount of the guest is loaded, a transition to multimolecular polymer micelles occurs. Also, the thermoresponsiveness of the poly(MEO₂MA-*b*-OEGMA) in the shell of unimolecular micelles allows a controlled phase transition into aggregates above LCST.



Figure 11. UV/vis spectra of 1 wt % aqueous solution of C5-S97 containing Nile Red (16 mg/L) and NaCl (50 g/L) before heating (black line), and after filtration above LCST (red line). The inset indicates the visual change during the process.

To take an advantage of thermo-responsiveness of unimolecular micelles in removal of hydrophobic contaminants in water, we performed a dye extraction experiment of **C5–S97** with Nile Red. A brine solution of 1 wt % polymer concentration was prepared and Nile Red was loaded (16 mg/L). By simply heating the polymer aqueous solution above LCST and filtering it, Nile Red in the solution was completely removed as the UV/vis spectrum showed no absorbance at all (Figure 11). It demonstrates the utility of thermoresponsive unimolecular micelles which encapsulate hydrophobic contaminants in water, aggregate above LCST, and are readily separated from the solution by simple filtration.

Conclusion

Amphiphilic star-shaped diblock copolymers containing rigid PAES units in the core and thermoresponsive poly(MEO₂MA*co*-OEGMA) units in the shell were prepared by combination of CGCP and ATRP. Investigation of micellar properties of the polymers in aqueous solution indicated that they behaved as unimolecular micelles capable of thermoresponsive phase transition. The length of shell block was important to maintain the stability of the unimolecular micelles in a wide range of concentration. This type of unimolecular micelles is expected to find applications in removal of organic residues in water.

Experimental Section

General Data. All chemicals were purchased from Sigma-Aldrich. 1,2,4,5-Benzenetetramine tetrahydrochloride, 4-fluoro-3-trifluoromethylbenzoyl chloride, 4,4'-difluorodiphenyl sulfone, 18-crown-6, 4-hydroxybenzyl alcohol, 2-bromoisobutyryl bromide, copper(I) chloride (CuCl), copper(II) chloride (CuCl₂), 2,2'-bipyridine, Nile Red, pyrene, and fat brown RR were used without further purification. Triethylamine (TEA), N-methyl-2pyrrolidone (NMP), sulfolane, toluene, dimethyl sulfoxide (DMSO), methylene chloride (MC), and anisole were distilled under reduced pressure before use. Di(ethylene glycol) methyl ether methacrylate (MEO2MA), and poly(ethylene glycol) methyl ether methacrylate (OEGMA) were passed through a column filled with neutral alumina before use. ¹H and ¹³C NMR spectra of synthesized materials were recorded on Bruker Fourier transform AC 300 (300 MHz) or Bruker Fourier transform AC 400 (400 MHz) spectrometers. Molecular weights and molecular weight distributions of polymers were measured by the means of gel permeation chromatography (GPC). The GPC diagrams were obtained with Viscotek T60A equipped with RI

detector and packing column (PLgel 10 µm MIXED-B) using THF as an eluent at 35 °C, or Younglin 9200 equipped with UV detector (set at 270 nm) and packing column (Shodex, GF-HQ columns) using THF an eluent at 40 °C. The number and weightaverage molecular weights of the polymers were calculated relative to linear polystyrene standards. DLS measurements were performed on a 90Plus/BI-MAS particle size analyzer (Brookhaven Instruments Corp.) at wavelength of 658 nm. The scattering angle used for the measurements was 90°. The CONTIN approximation was used to convert the diffusion coefficient into the hydrodynamic diameter $(D_{\rm h})$. Fluorescence spectra were recorded on a SHIMADZU RF-5301pc. UV/vis absorption and transmittance experiments were performed on a JASCO V-530 spectrometer equipped with a ETC-505T temperature controller. For the preparation of each polymer aqueous solution with constant Nile Red concentration, specific amounts of polymer loaded on containers were stirred for 24 h with aqueous dispersion of Nile Red (16 mg/L) which was prepared by sonication. And samples of different amounts of Nile Red with constant polymer concentration were prepared similar to the previously reported procedures.⁷⁰ Aliquots of Nile Red in acetone solution were added to containers and the acetone was left to evaporate. Loaded amounts of Nile Red were exactly controlled by the amounts of injected acetone. Polymer aqueous solutions (0.01 mM) were added into the containers and left to equilibrate for 24 h. All samples were filtered through a 0.45 μ m syringe filter before characterization. AFM study was conducted using a Park system XE-100 in a tapping mode.

1,2,4,5-Tetrakis(4-fluoro-3-trifluoromethylbenzamido)benzene (1). 1,2,4,5-Benzenetetramine tetrahydrochloride (0.50 g, 1.77 mmol) and TEA (2.05 mL, 14.7 mmol) in NMP (20 mL) were stirred in one-neck round bottomed flask. 4-Fluoro-3-trifluoromethylbenzoyl chloride (1.72 g, 7.59 mmol) was dissolved in NMP (30 mL) and slowly added to the flask at room temperature. Then the temperature was raised to 80 °C and the reaction mixture was stirred for 24 h, cooled to room temperature, and then poured into distilled water. The solid was filtered off and recrystallized in N,N-dimethylformamide (DMF) and toluene to yield yellowish white solid (0.836 g, 48%). MALDI-TOF-MS: 897.48 for $[M - H]^-$ (calcd: 897.10). ¹H NMR (DMSO- d_6 , 400 MHz, ppm): 10.33 (s, 4H), 8.33 (m, 8H), 8.02 (s, 4H), 7.67 (t, 4H, J = 9.5 Hz). ¹³C NMR (DMSO- d_6 , 100 MHz, ppm): 163.34, 160.63 (d, J = 257.0 Hz), 135.16 (d, J = 9.5 Hz), 131.35 (d, J = 3.1 Hz), 128.82, 127.08 (br), 123.07, 122.29 (q, J = 270.3 Hz), $117.52 (d, J = 20.7 Hz), 116.43 (dq, J_1 = 32.8 Hz, J_2 = 12.9 Hz).$ Anal. Calcd for C₃₈H₁₈F₁₆N₄O₄: C, 50.79; H, 2.02; F, 33.83; N, 6.24; O, 7.12. Found: C, 50.87; H, 2.01; N, 6.23.

4-Fluoro-4'-hydroxydiphenyl Sulfone Potassium Salt (2). To a mixture of 4,4'-difluorodiphenyl sulfone (12.9 g, 50.7 mmol) and DMSO (35 mL) was added slowly with stirring aqueous solution (15 mL) of potassium hydroxide (11.3 g, 201 mmol). Then the solution was heated to 40 °C and stirred for 10 h under N₂. The reaction mixture was cooled to room temperature and then poured into water. Unreacted 4,4'-difluorodiphenyl sulfone was removed by filtration and the solution was acidified with concentrated hydrochloric acid to precipitate a white powder. This solid, 4-fluoro-4'-hydroxydiphenyl sulfone, was filtered off and dried. Then it was dissolved in methanol, and potassium hydroxide (0.99 eq to 4-fluoro-4'-hydroxydiphenyl sulfone) in aqueous solution was added. The mixture was stirred at room temperature until it became homogeneous. After evaporation of methanol, plate-like product was filtered and dried in vacuo at 60 °C for overnight. The solid was purified by recrystallization from methanol and toluene to yield white needle-like crystals (4.30 g, 53.6%). mp of acidified product: 156 °C. ESI-MS of acidified product: 275.02 for $[M + Na]^+$ (Calcd: 275.02). ¹H NMR (DMSO-d₆, 400 MHz, ppm): 7.78 (m, 2H), 7.31(t, 2H, J = 8.9 Hz), 7.20 (d, 2H, J = 7.2 Hz), 6.00 (d, 2H, J = 7.1 Hz). ¹³C NMR (DMSO-*d*₆, 100 MHz, ppm): 177.10, 163.37 (d,

J = 248.0 Hz), 142.26 (d, J = 3.0 Hz), 129.64, 128.60 (d, J = 9.2 Hz), 119.43, 116.03 (d, J = 22.2 Hz), 112.77. Anal. Calcd for C₁₂H₈FKO₃S: C, 49.64; H, 2.78; F, 6.54; K, 13.47; O, 16.53; S, 11.04. Found: C, 47.86; H, 3.48; S, 10.84.

Synthesis of 4-Arm PAES Core Block with Fluorine End Groups. CGCP of 2 with 1 were conducted according to the literature procedures.⁴⁷ The procedure for the synthesis of C5–F is as follow: a dried Schlenk flask was charged with 1 (0.228 g, 0.254 mmol), 2 (0.996 g, 3.43 mmol), and 18-crown-6 (0.907 g, 3.43 mmol), and then dried *in vacuo* for 6 h at 50 °C. Sulfolane (24.5 mL) was refluxed at 120 °C to remove water by azeotropric distillation with toluene, and then added to the reaction flask via gastight syringe under dry nitrogen atmosphere. The mixture was degassed three times by "freeze–pump–thaw" cycles and placed in an oil bath preset to 120 °C and stirred for 24 h. Then the reaction mixture was cooled to room temperature and poured into methanol (900 mL) containing acetic acid (9 mL). The solid was filtered off and dried *in vacuo* to give C5–F (0.961 g, 93%). $M_n 4.34 \times 10^3$ g/mol. PDI: 1.16. ¹H NMR (DMSO-*d*₆, 400 MHz, ppm): 10.38, 8.41, 8.27, 8.05, 7.99, 7.45, 7.38, 7.27.

Using the above procedure, **C8**–**F** was synthesized from **1** (0.120 g, 0.134 mmol), **2** (1.082 g, 3.73 mmol), and 18-crown-6 (0.985 g 3.73 mmol). After 60 h of polymerization, 0.926 g of polymer was obtained (94% yield). M_n 6.43 × 10³ g/mol. PDI: 1.48. ¹H NMR (DMSO- d_6 , 400 MHz, ppm): 10.37, 8.41, 8.27, 8.03, 7.98, 7.45, 7.37, 7.27.

Introduction of Benzylic Hydroxyl End Group to 4-Arm PAES. C5–OH was synthesized as follows. A 50 mL three-necked round bottomed flask was charged with C5–F (0.91 g, 0.241 mmol), 4-hydroxybenzyl alcohol (0.479 g, 3.86 mmol), potassium carbonate (0.800 g, 5.79 mmol), and DMSO (27.5 mL). The reaction mixture was heated to 50 °C for 48 h under nitrogen atmosphere. After cooling to room temperature, the solution was poured into the mixture of 0.1 M HCl (aq) (800 mL) and methanol (100 mL) and stirred. The crude product was collected by filtration, dissolved in DMF (5 mL), and reprecipitated into methanol (900 mL). The precipitate was collected by filtration and washed with distilled water and methanol. The polymer was dried *in vacuo* at 60 °C for overnight (0.838 g, 83%). M_n 4.94 × 10³ g/mol. PDI: 1.18. ¹H NMR (DMSO- d_6 , 400 MHz, ppm): 10.35, 8.40, 8.26, 8.02, 7.98, 7.92, 7.38, 7.27, 7.07, 5.22, 4.49.

Using the above procedure, **C8–OH** was synthesized from **C8–F** (0.895 g, 0.120 mmol), 4-hydroxybenzyl alcohol (0.239 g, 1.90 mmol), potassium carbonate (0.399 g, 2.89 mmol). 0.832 g of polymer was obtained (88% yield). $M_{\rm n}$ 6.84 × 10³ g/mol. PDI: 1.48. ¹H NMR (DMSO- d_6 , 400 MHz, ppm): 10.37, 8.41, 8.27, 8.03, 7.98, 7.94, 7.38, 7.27, 7.07, 4.49.

Introduction of Initiating Sites for ATRP. The synthesis of C5–Br is illustrated. To a mixture of C5–OH (0.750 g, 0.179 mmol), TEA (0.6 mL, 4.30 mmol), and MC (30 mL) in ice bath, 2-bromoisobutyryl bromide (0.53 mL, 4.30 mmol) in MC (7 mL) was added slowly with vigorous stirring. The mixture was stirred for 48 h at room temperature under N₂. Then the mixture was concentrated by evaporating approximately a half of the solvent under reduced pressure and poured into methanol (900 mL) containing acetic acid (9 mL). The crude product was collected by filtration, dissolved in MC (5 mL), and reprecipitated into methanol (900 mL). The precipitate was collected by filtration and redissolved in MC (50 mL). The solution was dried over MgSO₄, filtered, and evaporated to give a brownish product (0.784 g, 91%). M_n 5.11 × 10³ g/mol. PDI: 1.17. ¹H NMR (CDCl₃, 400 MHz, ppm): 7.92, 7.86, 7.39, 7.08, 7.02, 5.18, 1.93.

Using the above procedure, **C8–Br** was synthesized from **C8–OH** (0.800 g, 0.102 mmol), 2-bromoisobutyryl bromide (0.45 mL, 3.64 mmol), TEA (0.51 mL, 3.66 mmol). 0.664 g of polymer was obtained (77% yield). M_n 6.82 × 10³ g/mol. PDI: 1.51. ¹H NMR (CDCl₃, 400 MHz, ppm): 7.91, 7.85, 7.39, 7.08, 7.01, 5.18, 1.93.

Synthesis of 4-Arm Star-Shaped PAES-*b*-poly(MEO₂MA*co*-OEGMA)s. The synthesis of C5–S83 using C5–Br as a macroinitiator is described. A dried Schlenk flask was charged with CuCl (8.02 mg, 0.0810 mmol), CuCl₂ (2.18 mg, 0.0162 mmol), 2,2'-bipyridine (30.4 mg, 0.194 mmol), MEO₂MA (915 mg, 4.86 mmol), and OEGMA (257 mg, 0.540 mmol) under dry nitrogen atmosphere. After degassed anisole solution of C5-Br (43 mg, 0.00899 mmol) was added to the flask via gastight syringe, three cycles of "freeze-pump-thaw" were performed to remove any oxygen from the polymerization mixture. Then, the flask was heated at 90 °C. The reaction mixture was carefully extracted via gastight syringe under dry nitrogen atmosphere at a certain time interval to investigate the polymerization kinetics. Conversion of the monomer was determined from the ¹H NMR spectra of the reaction mixture by comparing integration of protons next to the estereal oxygen at 4.3 ppm corresponding to both monomers and 4.0 ppm corresponding to the polymer, respectively. At a proper monomer conversion around 60%, the polymerization mixture was quenched by cooling in dry ice/ acetone bath and diluted with ethanol. The solution was passed through a small column of alumina, filtered through a $0.2 \,\mu m$ syringe filter, and evaporated. The crude product was purified by dialysis in deionized water for 2 days (Spectra/Por 3 Dialysis Membrane, cutoff: 3500 g/mol). The purified polymer was obtained in a form of yellowish oil after azeotropic distillation of water with ethanol (0.391 g, 52%). $M_n 2.88 \times 10^4$ g/mol. PDI: 1.21. ¹H NMR (DMSO-d₆, 400 MHz, ppm): 7.98, 7.27, 4.20, 3.59, 3.50, 3.45, 3.30, 3.26, 1.83, 1.73, 0.95, 0.79.

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Supporting Information Available: Figures showing ¹H NMR spectra of the polymers used in the determination of molecular weights of the polymers, ¹H NMR spectra of **C5–S83** in protic solvents, and size distributions of the polymer aqueous solutions on loading of various dyes, and a table giving incorporation ratios of OEGMA to MEO₂MA. This material is available free of charge via the Internet at http://pubs.acs.org.

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