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pH-Regulated Controlled Swelling and Sustained Release from the Core Functionalized Amphiphilic Block Copolymer Micelle

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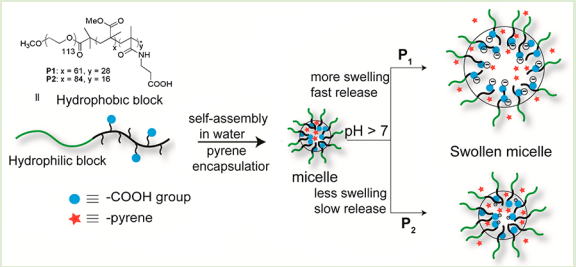
Supporting Information

ABSTRACT: pH-responsive amphiphilic block copolymers based on poly(ethylene glycol)monomethyl ether-*b*-poly(methyl methacrylate-*co*-methacrylamidepropanoic acid) (PEO-*b*-PMMA-*co*-PMAPA) with different MMA/MAPA ratios were synthesized from respective amine-reactive prepolymers based on poly(ethylene glycol)-monomethyl ether-*b*-poly(methyl methacrylate-*co*-methacryloxysuccinimide) (PEO-*b*-PMMA-*co*-PMASI) in such a way that the pH-responsive carboxylic acid groups were randomly distributed in the hydrophobic (PMMA) block. In aqueous medium, they formed micellar aggregates. Control experiments showed stability and critical aggregation concentration and dye encapsulation properties were better for carboxylic acid functionalized micelles at acidic pH compared to a structurally similar block copolymer micelle that lacked any carboxylic acid group. This was attributed to H-bonding among the carboxylic acid groups. In basic pH upon deprotonation, controlled swelling of the aggregates was observed due to repulsion among the negatively charged carboxylate groups. The extent of swelling/deswelling was well controlled by simply changing the percentage of the pH-responsive units in the hydrophobic block and could be probed quantitatively by pH-dependent dynamic light scattering (DLS) and fluorescence resonance energy transfer (FRET) studies. The aggregates were able to encapsulate a hydrophobic guest such as pyrene at the interior of the micelle, and sustained release of this hydrophobic probe was achieved selectively at basic pH due to swelling of the micelles instead of complete disassembly that generally leads to burst release.



Amphiphilic block copolymers self-assemble into various well-organized nanoarchitectures including micelle, vesicle, multimicellar clusters, etc.[1] Study of such self-assemblies has attracted considerable attention in the last two decades not only from the aspect of fundamental understanding but also due to their potential applications in diverse fields including biomaterials, biomedicines, and catalysis.[2] In this context, placement of a desired functional group in the appropriate location is highly important to control the self-assembly, stimuli-responsive disassembly, and sending the cargo to a specific target site.[3] Functionalization of an amphiphilic block copolymer can be carried out either at the hydrophilic block or hydrophobic block. Also there is a significant interest in incorporating a functional group at the chain end. Various strategies have been adopted successfully to decorate the outer surface of the hydrophilic block with different functionalities including sugars,[4] polypeptides,[5] folates,[6] and others[7] with the purpose of utilizing those assemblies in biomimetics[8] or targeted delivery[9] applications. While selective functionalization of the shell domain has drawn major attention, the functionalization of the core of the micelle is less explored.[10] We envisaged developing a general strategy that enables us to covalently attach diverse groups at the hydrophobic core would have credential at its own right to explore structural diversity for functional utilities of the polymeric nanoaggregate such as selective dye encapsulation, covalent cross-linking, fluorescent labeling, and stimuli-responsiveness. With these aims, we prepared a reactive prepolymer based on poly(ethylene glycol)monomethyl ether-*block*-poly(methylmethacrylate-*co*-methacryloxysuccinimide) (PEO-*b*-PMMA-*co*-PMASI) where the amine reactive MASI unit was randomly distributed in the hydrophobic PMMA block (Scheme 1). Post polymerization modification of the reactive MASI unit[11,12] was carried out with *β*-alanine to obtain the desired core functionalized amphiphilic polymer poly(ethylene glycol)monomethyl ether-*b*-poly-(methylmethacrylaye-*co*-methacrylamidepropanoic acid) (PEO-*b*-PMMA-*co*-PMAPA) with a free $-CO_2H$ group as the pH-responsive unit.

In this communication, we show micellar aggregation of these polymers, pH-regulated tunable swelling of the aggregates, and implications in stimuli-responsive sustained release of encapsulated dye. PEO-*b*-PMMA-*co*-PMASI (**4**) was synthesized using an atom transfer radial polymerization (ATRP) technique. A PEO-Br macroinitiator (**1**) was reacted with MMA (**2**)/MASI (**3**) using Cu(I)Br/PMDETA in anisole at 90 °C using the molar ratio of MI/MMA/MASI/Cu(I)Br/PMDETA = 0.02/1.6/0.4/0.02/0.04 (see Supporting Information for the detailed experimental procedure). GPC analysis of **4a** revealed (Figure S1, Supporting Information) the number

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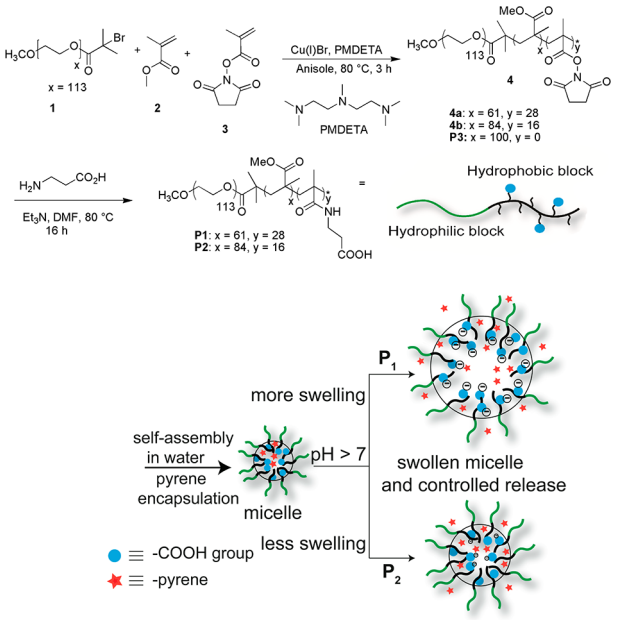
Scheme 1. (Top) Synthesis of Various Amphiphilic Polymers and (Bottom) Schematic Presentation of Micellization and pH-Dependent Tunable Swelling of the Aggregates



average molecular weight (M_n) to be 9900 g/mol (PDI = 1.2). Post polymerization modification of the reactive MASI unit with β-alanine furnished the final amphiphilic polymer (**P1**) with a free $-CO_2H$ group as the pH-responsive unit. The peak corresponding to the methylene protons in MASI (**4a**) at δ = 2.8 ppm was absent in **P1**, suggesting complete substitution of the MASI functional group with β-alanine (Figure 1). The

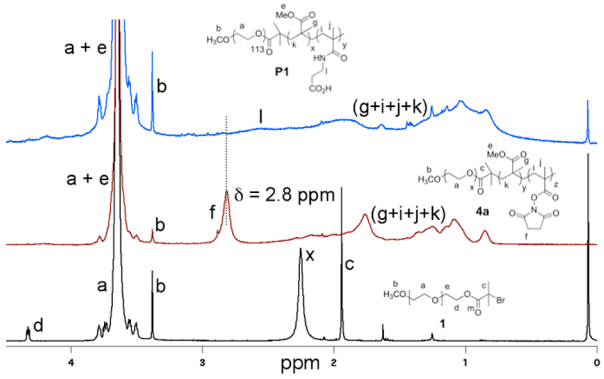


Figure 1. ^{1}H NMR of PEO-based macroinitiator (black), prepolymer **4a** (brown), and **P1** (blue). x denotes water peak.

substitution was further probed by FT-IR study in which the peaks at 1809, 1782, and 1740 cm^{-1} were absent in **P1**, whereas new peaks appeared at 1730 and 1670 cm^{-1}, corresponding to the ester and amide functionalities, respectively (Figure S2, Supporting Information).[13]

Aggregation of **P1** was investigated by high-resolution transmission electron microscopy (HR-TEM), which revealed the presence of uniform spherical particles with an average diameter of 25−30 nm (Figure 2a) suggesting micelle formation. Dynamic light scattering (DLS) studies showed a single peak corresponding to average hydrodynamic diameter (D_h) of 20 ± 5 nm (Figure 2b), which corroborated very well with the dimension of the particles found from TEM images.

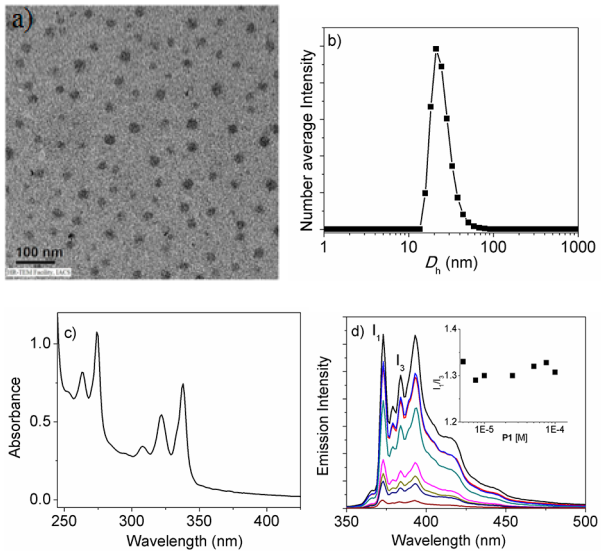


Figure 2. (a) TEM image of **P1** aggregates. (b) Distribution D_h of **P1** aggregates in water (c = 0.1 mM, pH = 5.4) by DLS study. (c) Absorption spectrum of pyrene in the presence of **P1** aqueous solution ($c = 1 \times 10^{-4}$ M). (d) Emission spectra of pyrene dissolved in aqueous solution of **P1** at varying concentrations. (Inset) Variation of I_1/I_3 in pyrene emission spectra as a function of concentration of **P1**. Pyrene concentration was 1×10^{-6} M in all the cases.

The encapsulation ability of these micellar aggregates was tested using a hydrophobic spectroscopic probe pyrene. Figure 2c shows the absorption spectrum of pyrene in aqueous solution of **P1**. Sharp and intense absorption bands confirm pyrene encapsulation inside the micellar aggregates. Note that pyrene on its own has negligible solubility in water, and thus no absorption band could be noticed in the absence of **P1** (data not shown). Further emission spectra of pyrene showed intense bands with vibronic fine structure (Figure 2d). The ratio of the emission intensities of the first (I_1) and the third (I_3) vibronic bands was found to be 1.32, which indicates the dielectric of the micellar core ($8.93\varepsilon_0$ at 20 °C) is comparable to that of dichloromethane (I_1/I_3 = 1.37).[14] The extinction coefficient of pyrene in dichloromethane was estimated to be 5.68×10^4 M^{-1} cm^{-1} at λ = 337 nm (Figure S3, Supporting Information). Using these data, concentration of the encapsulated pyrene was estimated to be 1.3×10^{-5} M which corresponds to an encapsulation efficiency of 0.02 mg/1.0 mg of **P1**. To estimate the critical aggregation concentration (CAC), concentration-dependent pyrene emission spectra were recorded, and it was noticed that even in the presence of ~10^{-6} M **P1** the I_1/I_3 value remained unchanged (inset, Figure 2d) suggesting the CAC to be less than 10^{-6} M. To examine whether the presence of the $-CO_2H$ group is playing any role to impose such low CAC, a control polymer **P3** (Scheme 1) that is devoid of any carboxylic acid group was synthesized.

In this case, the CAC was found to be 1×10^{-5} M (Figure S4, Supporting Information), which was at least 1 order of magnitude higher when compared to that of **P1**. Pyrene encapsulation efficiency of **P3** was determined to be 6.8×10^{-3} mg/1.0 mg of **P3** (Figure S5, Supporting Information), which was almost one-third compared to that of **P1**. Furthermore, the hydrodynamic diameter of **P3** aggregates was found to be 142 nm by DLS (Figure S6, Supporting Information), which was seven times higher compared to that of **P1**. On the basis of these observations, it is evident that the presence of $-CO_2H$

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groups indeed helped in achieving superior aggregation properties such as compact morphology, low CAC, and high encapsulation efficiency possibly due to the additional stability that is gained by H-bonding among the carboxylic acid groups inside the micellar core.

To investigate the response of such micellar nanoassembly to pH stimuli, change in the D_h was monitored by a DLS study in a window of pH 5.4 to 10.0 (Figure 3a). Untill pH 6.0, the D_h was ~20 nm, but with further increase in pH it increased drastically to 142 nm (~7-fold). No significant change was observed when pH was increased further until 10.0. The sharp increase in the size of the aggregates can be attributed to swelling of the micellar particles due to electrostatic repulsion among the negatively charged carboxylate groups generated in basic pH.[15] TEM study of the polymer solution at pH 8.0 also exhibited swollen assembly with an average size of 130 nm (Figure S7, Supporting Information), matching very well with the size found in DLS. To check the reversibility of the swelling behavior, the pH of the solution was further brought back to 4.0 (indicated as pH:4.0* in Figure 3a), and it was found that the size of the aggregates had shrunk to 19 nm, clearly indicating the reappearance of the original compact micellar particle. Notably, the control polymer **P3** did not show any change (Figure S6, Supporting Information) in aggregate size with varying pH in a similar window, confirming the observed change in the case of **P1** is indeed due to the presence of a carboxylic acid group.

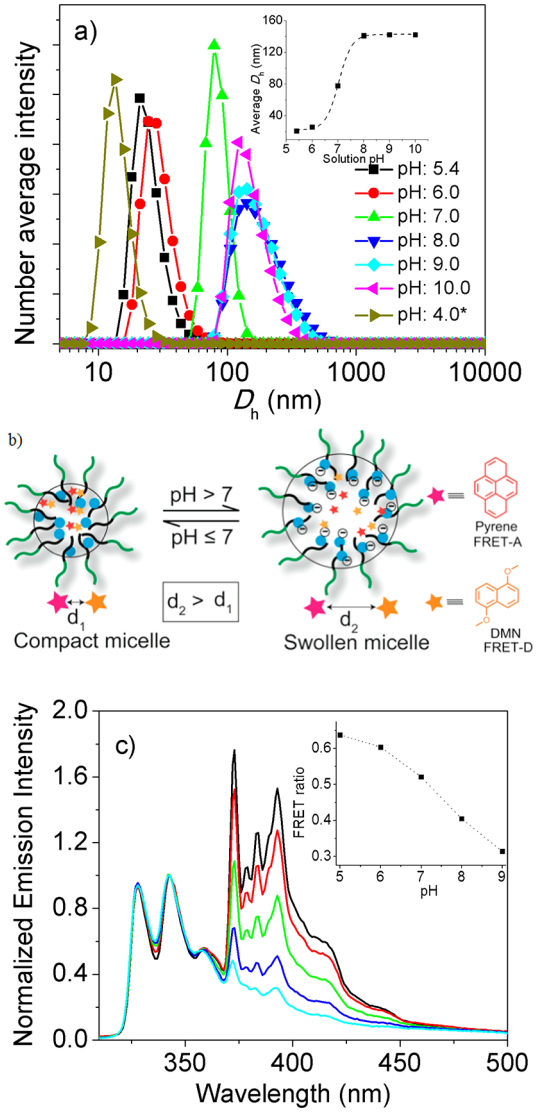

Figure 3. (a) pH-dependent particle size distribution of **P1** micelles (c = 1 × 10^{-4} M). * indicates solution pH was readjusted to 4.0 for checking reversibility. Inset: Plot of average D_h vs pH. (b) Schematic showing the working principal of a FRET experiment to probe swelling of the micellar aggregate. (c) Change in the emission spectra of coencapsulated DMN and pyrene (normalized at DMN emission at 342 nm) at different pH. λ_{ex}: 295 nm. Inset: change in the FRET ratio as a function of pH.

To gain more insight into micellar swelling, we carried out photoluminescence experiments where the FRET between the 1,8-dimethoxynapthalene (DMN) donor and pyrene acceptor,[16] coencapsulated in the micelle, was monitored (Figure 3c) as a function of pH.[17a] At pH = 5.0, excitation corresponding to the absorption of the donor chromophore (λ_{ex} = 290 nm) resulted in very week emission in the range of 310−350 nm for DMN, and rather intense emission bands were noticed in the range of 370−395 nm due to pyrene. A solution of these chromophores in THF in the absence of **P1** (Figure S8, Supporting Information) showed no such behavior. This confirms effective FRET between DMN and pyrene when they were encapsulated together within the micelle. With increasing pH, the pyrene emission intensity, when compared with respect to normalized DMN emission intensity, gradually (Figure 3c) decreased suggesting diminishing of the FRET efficiency at higher pH. FRET ratio ($I_a/(I_a + I_d)$, where I_a and I_d are emission intensities of the acceptor and donor at 373 and 342 nm, respectively) when plotted as a function of pH (inset, Figure 3c) showed only minor change until pH 6.0 beyond which it decreased sharply with increasing pH. FRET efficiency depends on several parameters among which one is the distance between the donor and the acceptor. In the swollen micelle, the donor and the acceptor molecules are allowed to distribute themselves over relatively larger volume compare to that in the compact micelle, and thus their average distance increases with increasing pH (Figure 3b) resulting in less efficient FRET. It is also noteworthy that I_1/I_3 of pyrene emission (Figure 3c) changed from 1.34 to 1.45 by increasing the pH from 5.0 to 9.0, indicating a relatively more polar microenvironment for pyrene inside the micellar core at basic pH. Although the FRET technique has been used to probe amphiphilic polymeric aggregates in a few occasions,[17] to the best of our knowledge this is the first report where micellar swelling could be probed by such an elegant spectroscopic technique.

In an attempt to examine whether the extent of pH-regulated swelling of micellar particles can be tuned by varying the amount of $-CO_2H$ groups, the aggregation property of **P2** (Scheme 1) was compared with that of **P1**. At pH 4.0, morphology and particle size obtained by TEM (Figure 4a) and DLS (Figure 4c) were found to be almost identical to those observed for **P1** suggesting similar micellar aggregation.

However, the CAC of **P2** (0.8 × 10^{-5} M) was found to be (Figure S9, Supporting Information) significantly higher compared to **P1** possibly due to less stability in the presence of fewer amounts of COOH groups. More interestingly, when pH was increased from 4.0 to pH 8.0, particle size (D_h) increased (Figure 4c) by only ~2-fold (from 28 to 60 nm) in sharp contrast to **P1** for which almost a 7-fold increase was noticed (Figure 3a) upon similar pH variation. This could also be supported by TEM images of the aggregates at pH 8.0

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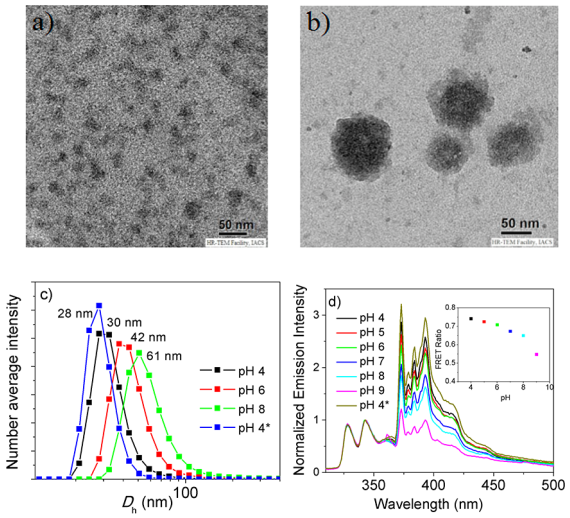

Figure 4. TEM images of the **P2** aggregate at (a) pH 4.0 and (b) pH 8.0. (c) Particle size distribution obtained from DLS of **P2** micelles at different pH. (d) Change in the emission spectra of coencapsulated DMN and pyrene (normalized at DMN emission at 342 nm) at different pH. λ_{ex}: 295 nm. Inset: change in the FRET ratio as a function of pH. pH 4* in the legend (c and d) represents data when solution pH was readjusted to 4.0 for checking reversibility.

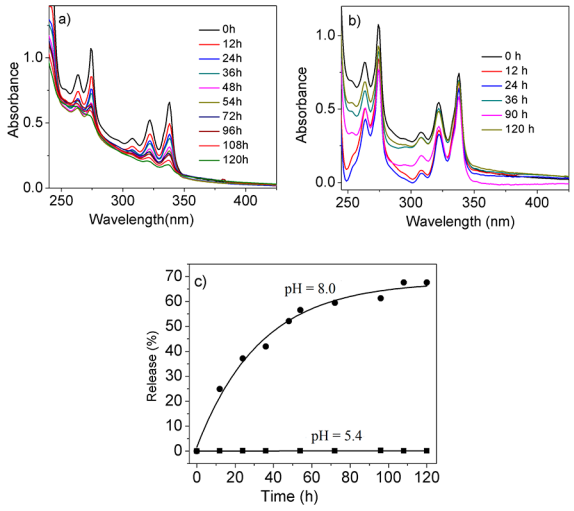

Figure 5. Variation of the absorption spectra of pyrene with time encapsulated in **P1** aggregates at (a) pH 8.0 and (b) pH 5.4. (c) Percentage release of pyrene with time at two different pHs; % release was calculated by $(A_0 - A_t)/A_0 \times 100$, where A_0 and A_t represent the absorbance (λ = 337 nm) at t = 0 and at any given time t, respectively.

(Figure 4b) where swollen particles were observed. Furthermore, in this case photoluminscent experiments (Figure 4d) revealed only 27% decrease in the FRET ratio by changing the pH from acidic to basic in contrast to a 51% decrease in the case of the **P1** micelle (Figure 3c). When the solution pH was reduced to 4.0, the spectrum (dark yellow line in Figure 4d) almost resembled the initial one (black line in Figure 4d) at the same pH suggesting reversibility of the process. This also eliminates the possibility of any notable loss of donor/acceptor guest molecules during swelling. These results clearly indicate that tunable swelling of micellar particles could be achieved just by variation of the amount of pH-responsible functionality incorporated in the hydrophobic block.

We further examined pH-triggered release of encapsulated pyrene from the micellar aggregates in a swelled state. Pyrene was encapsulated as a hydrophobic probe inside the core of the **P1** micelle, and the absorption spectra were monitored as a function of time (Figure 5a) at pH 8.0. With increasing time, the absorbance of pyrene decreased slowly suggesting release from the micellar core to bulk water where it is insoluble.

To check whether release was indeed facilitated due to swelling, a control experiment was carried out separately at pH 5.4 where the micelle is supposedly in more compact form compared to that at pH 8.0. In this case, no significant change in the absorption spectra of the encapsulated pyrene was noticed (Figure 5b) over the same period of time. The percentage release was calculated in both cases by monitoring the change in the absorbance at 338 nm. Figure 5c shows at pH 8.0 almost 70% pyrene was released in sustained manner over the period of 120 h, whereas no dye was released at pH 5.4, strongly suggesting that the swelling of the micellar aggregates promoted sustained release selectively at basic pH by diffusion of the dye molecules from the core of the micelle to the bulk water. To check the possibility of any ester hydrolysis under such conditions, **P3** was treated with aqueous solution of NaOH (pH 9.0), and ^{1}H NMR was examined before and after the basic treatment. No change in integration of the peak corresponding to the −OMe group of the PMMA block was observed (Figure S10, Supporting Information) even after 5 days, ruling out any probability of ester hydrolysis during the course of the dye release experiment. While relevant reports on pH-responsive micelles that include either a carboxylic acid or amine group in each repeat unit of the polymeric chain[18] exhibit spontaneous pH-induced disassembly or morphology transition of the aggregates resulting in burst release of the encapsulated drugs, our design provides a unique route for achieving controlled release[19] by pH-sensitive swelling of micelle instead of complete disassembly.

In conclusion, we have demonstrated a general synthetic protocol to functionalize the hydrophobic domain of an amphiphilic block copolymer by incorporating a certain percentage of a highly reactive unit, which can be quantitatively substituted with the desired functionality (Table S1, Supporting Information) through simple chemical transformation. As an example, we incorporated a pH-responsive unit in the hydrophobic block and varied the percentage of the pH-responsive unit by changing the feed ratio of the reactive monomer. Consequently, we were able to control the extent of swelling/deswelling upon deprotonation/protonation of the pH-responsive functionality. We have also shown as a consequence of swelling instead of complete disassembly that a hydrophobic guest such as pyrene could be released from the micelle in sustained manner instead of burst release. Further structural variation of the amphiphilic block copolymer using this strategy and its implications in aggregation is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis, experimental detail, detailed description of various equipments used in this study, and additional spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(12) The amount of incorporation of MASI, calculated using NMR spectroscopy, was found a little higher than the feed used. To understand the reason, the reactivity ratio of the two monomers was determined by the extended K−T method (see Figure S11, Table S2, and related text in the Supporting Information for details) which revealed $r_{MMA} = 0.41$ and $r_{MASI} = 2.04$. This ($r_{MMA} < 1$, $r_{MASI} > 1$, and ($r_{MMA} \times r_{MASI}$) < 1) is indicative of the random nature (nonideal) of the copolymer with relatively higher incorporation of the more reactive monomer and thus corroborates well with experimental observation.

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(15) pK_a of propionic acid ∼ 5.0 in water. However, we observed the onset of transition from compact to swelled state above pH 6.0 (Figure 3a, 4c). This can be attributed to an apparent higher pK_a of the carboxylic acid in this particular case due to its residence inside the micellar core where the microenvironment is considerably nonpolar (I_1/I_3 suggests it is comparable to dichloromethane) compared to water.

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