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Self-assembly and morphology transition of amphipathic spiropyran-based random copolymers to control drug release

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ABSTRACT
An amphipathic spiropyran-based random copolymer P(SPMA-co-DMAEMA) was synthesized by atom transfer radical polymerization, and the resulting copolymer was characterized by means of $^1$H nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, and gel permeation chromatography. The self-assembly behaviors and morphology transition were systematically investigated under single and combined external environmental stimuli by transmission electron microscopy. With coumarin 102 as the model drug molecule, the self-assembly micelles were used to control drug loading, release, and re-encapsulation to some extent. The characterization results indicated the successful preparation of the spiropyran-based random copolymer P(SPMA-co-DMAEMA). The external stimuli had some influences on the morphology of the self-assembly aggregate, and the 'schizophrenic' behavior was interestingly found in this work. The drug release experiments showed the reversible loading and release process up to a point, which might expand the potential application domain of the amphiphilic spiropyran-based random copolymer in drug delivery.

1. Introduction
In recent years, a great deal of stimuli-responsive amphipathic polymer micelles that respond to internal or external stimuli including pH,[1,2] temperature,[3] redox,[4] light,[5], and magnetic field [6] have been abundantly investigated due to their broad range of potential applications as nanocarriers,[7] biosensors,[8,9], and biochemical gates.[10] Among the various stimuli, light is one of the most attractive external stimuli because of the superiority in spatial and temporal control. The common photochromic monomers include azobenzenes, spiropyrans (SPs), spirooxazines, diarylethenes, and fulgides.[11–13] We choose SP as the photo-sensitive monomer due to the rapid response, large color difference, and good fatigue resistance.[14] In addition, pH and temperature dual-sensitive copolymers based on the monomer 2-(dimethylamino) ethyl methacrylate (DMAEMA) have been reported for many times due to the high polymerization activity.

The reports of self-assembly of amphiphatic copolymers can be found elsewhere. Chang’s team has synthesized polystyrene-block-polysoprene diblock copolymers (PS-b-PI), and studied the aggregation morphology as well as the essential property of the diblock copolymer.[18] As one of the pioneers of exploring the self-assembly process, this work establishes the theoretical foundation of self-assembly. Wang’s group has reported the preparation and self-assembly of the well-defined amphiphilic diblock copolymer poly(2-nitrobenzyl methacrylate)-b-poly(dimethylaminoethyl methacrylate) (PNBM-b-PDMAEMA).[4] It is attractive that the micelles are quadruple-stimuli-sensitive and the controlled release of a model molecule Nile Red (NR) in combination with two stimulations is investigated. Liu’s group has synthesized amphipathic random copolymers containing hydrophobic dodecyl (C12) chain and hydrophilic L-glutamic acid, and their self-assembly in solution as well as on the solid surfaces have been investigated.[19] They have obtained several kinds of morphologies such as giant vesicle, vesicle, honeycomb film, and sphere, and revealed that the self-assembly behavior is dependent on the hydrophilic and hydrophobic balances, which is useful in comprehending the self-assembly process.

According to the above discussions, we can find that most of attentions have been paid to the self-assembly of the block copolymers, and there are, however, little reports about self-assembly of the random copolymers. The reason may be explained by the different molecular structure between block and random copolymers: block...
copolymers with specific and regular structure are usually prone to self-assembly to typical morphology, while it is challenging for the self-assembling of random copolymers without definite structure. Among the reports about self-assembly behaviors and morphologies, there are, to our best knowledge, rare comprehensive works focusing on the controllable conditions such as the initial concentration, structure unit ratio of random copolymers, and the external conditions. Moreover, most of the sensitive micelles reported up to now are responsive to the single stimulus such as light, pH, and ions, etc. At the same time, dual or multiple stimuli are increasingly attracting more and more attentions, which may be easily adapted to the complex environment of controlled drug release.

In the present work, we report the synthesis of a triple stimuli-responsive random copolymer composed of photo-responsive SPMA unit and temperature/pH-responsive DMAEMA unit by atom transfer radical polymerization (ATRP).\[20–22\] The structure and composition of the resulting copolymer are studied in detail, and the self-assembly process and morphology transition are also discussed. To enhance the application of the polymeric micelles, the controlled release of coumarin 102 under single and combined stimulation is investigated to some extent.

2. Experimental

2.1. Materials

The monomer 2-(dimethylamino) ethyl methacrylate (DMAEMA, 99%, Aladdin) was passed through a column of basic alumina to remove inhibitors before use. The photo-sensitive monomer 1′-\(\text{O}^{\text{CH}}\)-3′,3′-dimethyl-6-nitrospiro\((2\text{H}-1\text{-benzopyran},2,2′\text{-indoline})\) (SPMA) was synthesized according to methods described in the literatures [14,23–25] (see Supplementary data). \(N,N,N,N′,N″\text{-Pentamethyl diethylenetriamine}(\text{PMDETA, 98%, TCI})\) as the ligand, ethyl 2-bromoisobutyrate (EBiB, 98%, TCI) as the initiator, copper(I) bromide (CuBr, 99%) as the catalyst, methanol (99.5%), tetrahydrofuran (THF, 99%), hexane (97%), dichloromethane (DCM, 99.5%), and coumarin 102 (97%, Heowns) were all used as received.

2.2. Synthesis of triple responsive random copolymer P(SPMA-co-DMAEMA)

The similar synthesis procedure of the target product P(SPMA-co-DMAEMA) was described in our previous work.[26,27] The synthetic route was shown in Scheme 1 and the detailed operation procedure was described in Supplementary data.

2.3. Self-assembly of the random copolymer P(SPMA-co-DMAEMA)

In a typical protocol, the self-assembly aggregates were prepared by adding water into a solution of the copolymer in THF at some special conditions. To be specific, 1 mg copolymer P(SPMA-co-DMAEMA) was dissolved in 1 mL THF, and then 10 mL deionized water was added dropwise into the solution by an injection pump at the flow rate of 2 mL h\(^{-1}\). The whole self-assembly process was carried out under the visible light irradiation with magnetic stirring. After about 700 μL deionized water was injected, the solution turned turbid and yellow indicating aggregation of the copolymer. The self-assembly conditions, such as the initial concentration, the solvent, and the irradiation, were changed to get various morphologies.

2.4. The loading and release of coumarin 102 for the self-assembly aggregate

For a typical loading of coumarin 102, 1 mg copolymer P(SPMA-co-DMAEMA) and 0.2 mg coumarin 102 were dissolved in 1 mL THF, and then 10 mL deionized water was added dropwise into the solution at the flow rate of 2 mL h\(^{-1}\). The whole self-assembly process was carried out under the visible light irradiation with magnetic stirring.

With regard to the release of coumarin 102 from the aggregates, the fluorescence intensity of the hydrophobic dye was monitored and the subtraction before and after external stimuli was regarded as the release percentage of the loading model molecule. The fluorescence intensity of coumarin 102 receded after the releasing from the micelle because the hydrophobic model molecule released from the micelle was insoluble and precipitated in water.

\[\text{Scheme 1. The synthetic process of P(SPMA-co-DMAEMA) by ATRP.}\]
2.5. Characterization

The structure was determined by \(^1\)H nuclear magnetic resonance (\(^1\)H NMR) spectroscopy using a 500 MHz Bruker AVANCE III NMR spectrometer in CDCl\(_3\) as well as composition of the resulting copolymer.

Fourier transform infrared spectroscopy (FT-IR) measurement was recorded on a Nicolet model 6700, in which the spectral region ranged from 450 to 4000 cm\(^{-1}\).

The molecular weights (MWs) and the molecular weight distributions of the random copolymer were determined by gel permeation chromatography (GPC, PL-gPC 120). The commercially available polystyrene sample was used as the standard to generate a calibration curve, and DMF as the mobile phase was delivered at a flow rate of 1 mL min\(^{-1}\).

Transmission electron microscopy (TEM) observations were conducted on Titan G2 60-300 at an acceleration voltage of 300 kV. The morphologies of the self-assembly nanoparticle were observed by TEM. The sample was prepared by placing 10 μL self-assembly nanoparticle solution on copper grids successively coated with thin films of formvar and carbon and was detected after the volatilization of the solution.

Fluorescence measurements were performed on F-4600 Fluorescence Spectrophotometer with a slit width of 10 nm for both excitation and emission. The test voltage was 700 V.

3. Results and discussion

3.1. Synthesis of P(SPMA-co-DMAEMA) at different rate of comonomer

The schematic preparation of the amphipathic random copolymer P(SPMA-co-DMAEMA) is shown in Scheme 1. In our previous work,[26] we have synthesized the copolymer whose feed molar ratio is 1:20 (SPMA:DMAEMA) and the actual molar ratio is 1:30.4. A series of copolymers with different feed molar ratios are prepared using the same procedure in this work. Three P(SPMA-co-DMAEMA) copolymers are obtained by varying the comonomer ratio and the resulting samples are named with C1 (P(SPMA\(_1\)-co-DMAEMA\(_{9.3}\))), C2 (P(SPMA\(_1\)-co-DMAEMA\(_{14.6}\))), and C3 (P(SPMA\(_1\)-co-DMAEMA\(_{30}\))), respectively. All the characterization data are shown using the sample C1.

The successful synthesis of the random copolymer is confirmed by \(^1\)H NMR spectroscopy (see Figure 1) due to the presence of the characteristic peak at 2.23 and 8.01 ppm. The actual structure unit ratio is estimated from the integral area. The peak integral at 8.01 ppm attributed to the two proton of benzopyran phenyl group is 2 (as a benchmark), and the peak integral at 2.23 ppm due to the six methoxy protons of the DMAEMA unit is about 55.83, so the molar ratio of SPMA and DMAEMA unit is 1:9.3. The same calculation is carried out for the samples C2 and C3.

Figure 1. \(^1\)H NMR spectrum of amphiphilic random copolymer P(SPMA-co-DMAEMA). (Sample: C1).

The analyses of FT-IR spectrum ascertain the molecular structure of copolymer P(SPMA-co-DMAEMA) further and the result is demonstrated in Figure 2. The strong absorption peak of N–H bond of tertiary amine group in DMAEMA unit is around 3431 cm\(^{-1}\). The bands around 2950 and 2860 cm\(^{-1}\) are due to C–H bond of CH\(_3\). The existence of SPMA unit is verified by the appearance of the peaks around 1610, 1579, 1482, and 1459 cm\(^{-1}\). Meanwhile, the bending vibration peaks of NO\(_2\), C–N, and Ar–H are also observed at 1521, 1338, and 1272 cm\(^{-1}\), respectively. Moreover, the absorption peaks at 1153, 1729, 1020, and 956 cm\(^{-1}\) are attributed to the C–O, C=O, C–C–N, and O–C–N bending vibration, respectively.

The number-average molecular weight (M\(_n\)) and the polydispersities index (PDI) of the as-prepared copolymer P(SPMA-co-DMAEMA) (C1) are about 17,300 and 1.73, respectively (see Figure 3). The number of repeat
usually includes nucleation and gradual growth process, and the result is generally that hydrophobic chain is as the core and the hydrophilic one is as the shell in aqueous solution. The schematic micellization (SPMA-core, DMAEMA-shell) of the amphipathic random copolymer P(SPMA-co-DMAEMA) is shown in Scheme 2.

### 3.2.1. Self-assembly morphology of P(SPMA-co-DMAEMA) with different structure unit ratios

Inspired by sphere formation mechanism which has been studied by Wang [28], we have investigated the morphologies of the samples with different unit ratios. One-milligram copolymer C3 is dissolved in 1 mL THF, and 10 mL deionized water is added into the solution to complete the self-assembly under the visible light irradiation. The aggregation morphology of P(SPMA1-co-DMAEMA30) (C3) is shown in Figure 4(a). From the figure, it is obvious that there is no structured micelle. As can be seen from Figure 4(b), the self-assembly aggregation of P(SPMA1-co-DMAEMA14.6) (C2) at the same condition presents apparent globular micelle, but the globular aggregation is not structured enough, especially existing dissociative and non-assembled polymer segments at the periphery. Compared with Figure 4(a) and (b), it is evident that more clear and structured sphere aggregate is observed in the image of P(SPMA1-co-DMAEMA9.3) (C1) as shown in Figure 4(c).

The self-assembly aggregation of random copolymer in selective solution is an enthalpy-driven process.[29] The micellization of the copolymers occurs through phase separation caused by the hydrophobic interaction.[30] The difference of morphology among the three samples may be arose by the hydrophobic interaction. Since the percentage of hydrophobic SPMA segment is increased from C3 to C1, sphere aggregate with core–shell structure is obtained after the achievement of balance between hydrophilic and hydrophobic unit.

### 3.2.2. The influence of the initial concentration on self-assembly morphology

To explore the influence of the initial concentration of the random copolymer P(SPMA-co-DMAEMA) on the unit is calculated to be nine according to the molar ratio between SPMA and DMAEMA unit (1:9.3) and the molecular weight.

Three different copolymers are synthesized by changing monomer ratios, and the details of the random copolymers are listed in Table 1. In this work, the ratio between SPMA and DMAEMA can be also employed to reflect the ratio of hydrophobic and hydrophilic unit. The obtained samples are different in the percentage of hydrophobic SPMA unit. The higher the percentage of SPMA unit is, the more hydrophobic the copolymer is.

### 3.2. Self-assembly morphology of P(SPMA-co-DMAEMA)

The obtained random copolymers can self-assembly into micellar nanoparticles or other morphologies because of their amphipathic essence. The self-assembly process

![Scheme 2. The schematic self-assembly of P(SPMA-co-DMAEMA).](image)

**Table 1.** GPC details of the amphipathic random copolymers P(SPMA-co-DMAEMA).

| Copolymers | $M_n$ | $M_w$ | $M_w/M_n$ (PDI) | mol% SPMA |
|------------|-------|-------|-----------------|-----------|
| C1         | 17300 | 30000 | 1.73            | 9.7       |
| C2         | 16900 | 25000 | 1.48            | 6.4       |
| C3         | 13000 | 22800 | 1.75            | 3.2       |
aggregation morphology, sample C1 dissolved in THF with three different initial contents is chosen. The initial concentration is 0.2, 1, and 3 mg mL\(^{-1}\), corresponding to the morphologies in Figure 5(a)–(c), respectively. As can be seen from Figure 5(a), the aggregation is semitransparent and thin because the random copolymer solution with low concentration (0.2 mg mL\(^{-1}\)) cannot provide enough hydrophobic and hydrophilic chains to achieve self-assembly. Increasing the initial concentration to 1 mg mL\(^{-1}\), the shape is structured and smooth spherical micelle as shown in Figure 5(b). The aggregation morphology in Figure 5(c) is a kind of obvious vesicle which has evident inner and outer layers. We may choose appropriate shape for drug release carrier according to the diversity of morphology caused by the initial concentration. It has been reported that the vesicular assembly is suitable for delivery vehicles owing to the structure of as-biological membrane.\(^{[31]}\)

### 3.2.3. Self-assembly morphology of P(SPMA-co-DMAEMA) in different solvents

Three different selective solvents (THF, DCM, and methanol) are used to dissolve the random copolymer P(SPMA-co-DMAEMA) (C1), and the diverse shapes are exhibited in Figure 6(a)–(c). Obvious shell–core structure with a thin layer of shell in the periphery can be observed in THF as shown in Figure 6(a), and its formation is due to the aggregation of SPMA in core and DMAEMA in shell. Inspired with the honeycomb pattern of Liu \(^{[19]}\), we have studied the self-assembly of the copolymer in DCM. It is interesting that the aggregation morphology is petal-like structure and the holistic profile is spherical unexpectedly, as shown in Figure 6(b). There is no self-assembly aggregation, but dispersive, inhomogeneous, and dissociative random copolymer nanoparticles are found when methanol is used as the selective solvent (see Figure 6(c)). The average particle diameter is about 8 nm and the reason of inhomogeneity is that the copolymer is random.

### 3.2.4. The influence of the external condition on self-assembly morphology

All the previous experiments are carried out in the same external condition: visible light as the irradiation source and the neutral deionized water as the precipitator. The
The reason of the micellar pocket is that DMAEMA unit becomes hydrophobic in alkaline water, and SP isomer transfers to MC segment under the irradiation of UV light. The transformations among these conditions are conformed to ‘schizophrenic’ behaviors.[32–34] Meanwhile, partial ring-opened MC unit reversibly isomerizes to SP under alkaline condition, so there may be counteraction of hydrophilic–hydrophobic balance, leading to the formation of the dissociative copolymer nanoparticles inside and outside the pocket.

The above systematic discussion on the four kinds of aggregation morphologies verifies the possibility of self-assembly of the random copolymer. The obtained vesicular assembly can be used in drug release and the controlled release processes under different stimulations are discussed as follows.

### 3.3. Encapsulation, controlled release, and re-encapsulation of coumarin 102 under single and combined stimulation

SPMA unit is hydrophobic under the irradiation with visible light and hydrophilic under the irradiation with UV light due to the reversible isomerization between SP and MC. In alkaline solution, the DMAEMA chains become shrinking and SPMA unit is hydrophobic. The various self-assembly conditions are listed as follows: visible light irradiation and the neutral deionized water (pH 7) as precipitator in Figure 7(a), UV light irradiation and neutral deionized water (pH 7) as precipitator in Figure 7(b), visible light irradiation and the alkaline water solution (pH 13) as precipitator in Figure 7(c), and UV light irradiation and the alkaline water solution (pH 13) as precipitator in Figure 7(d).

The shape with a typical shell–core micelle in Figure 7(a) has been discussed particularly in Section 3.2.3. The morphology in Figure 7(b) is not a kind of structured spherical micelle, but there is an obvious aggregating tendency. The phenomenon may be caused by the isomerization from SP to MC leading to the transition of micellization. On the condition of Figure 7(c) (visible light, pH 13), both SPMA and DMAEMA segments are hydrophobic and become shrinking. The shape is indefinite, unstructured, and dissociative because the double hydrophobic chains cannot form a specific self-assembly morphology. The interesting appearance in Figure 7(d) is just like a big pocket that loads dissociative copolymer nanoparticles. We guess the reason of the micellar pocket is that DMAEMA unit becomes hydrophobic in alkaline water, and SP isomer transfers to MC segment under the irradiation of UV light. The transformations among these conditions are conformed to ‘schizophrenic’ behaviors.[32–34] Meanwhile, partial ring-opened MC unit reversibly isomerizes to SP under alkaline condition, so there may be counteraction of hydrophilic–hydrophobic balance, leading to the formation of the dissociative copolymer nanoparticles inside and outside the pocket.

The above systematic discussion on the four kinds of aggregation morphologies verifies the possibility of self-assembly of the random copolymer. The obtained vesicular assembly can be used in drug release and the controlled release processes under different stimulations are discussed as follows.

The hydrophobic fluorochrome coumarin 102 is loaded in the core of the micelle in the self-assembly process as illustrated in Section 2.4. The schematic diagram of self-assembly loading, pH/photo-controlled release, and...
loaded coumarin 102 changes from bright yellow to clear pink after adding pH 3 aqueous solution. The color change and the release kinetic curve [35] are shown in the inset of Figure 8(b). The isomerization from MC to MCH in acid condition and the protonation of nitrogen atom in tertiary amine group result in the color change and decrease in the fluorescence.

Figure 8(c) shows no obvious decrease in the fluorescence at pH 10, indicating little release of coumarin 102. The release process is recorded by fluorescence measurements when heating the solution to 60 °C as shown in Figure 8(d). The release percentage of coumarin 102 is 17.2% in 8 h and the reason is the shrinking of micelle at the relatively high temperature.

After the disruption of micellar solution and releasing coumarin 102 under the irradiation of UV light, the visible light is used to realize the regeneration of polymeric micelles. With vigorous stirring, the released coumarin 102 is re-encapsulated into the micelle as demonstrated by the increase in its emission intensity (see Figure 9). It points to about 68.1% recovery of emission intensity on regeneration of the micelles in 40 min from Figure 9, meaning the reversible loading and release process to some extent. It may expand the potential application domain of the amphiphilic spiropyran-based random copolymer in drug delivery.

The research of controlled drug release under single stimulation is appropriate for fundamental and theoretical study. In consideration of the complex external environment, the combined stimulation is necessary for exploring the potential application of drug release.

3.3.2. Controlled release under combined stimulation

Figure 10(a)–(c) show the release results of coumarin 102 under the combined stimulation. The release profile of coumarin 102 under the combined stimulation of pH 3 and
UV light irradiation is shown in Figure 10(a), from which it can be seen that the release percentage (51.2%) under the combined stimulation is significantly higher than that under single pH 3 stimulation (21.4%, 5 min). Under the combined stimulation of pH 10 and UV light irradiation for 5 min, the release percentage reaches 58.4%, which is much higher than that under pH 10 stimulation (0.34%, 8 h) (see Figure 10(b)). The combination of pH stimulation and UV light irradiation can enhance the release of the loaded molecules, which obviates the need for harsh conditions such as UV light irradiation for a longer time or extreme pH stimulation, increasing the possibility of applying as nanocarriers under relatively mild conditions. The effect of combined stimulation of temperature ($T = 60^\circ C$) and UV light irradiation on the release of loaded coumarin 102 is shown in Figure 10(c). It can be seen that there are slight more molecules being released upon the combined stimulation (26.0%, 5 min) compared with that under single stimulation of temperature (17.2%, 8 h).

Figure 8. Controlled release of coumarin 102 under stimulation: (a) UV light irradiation, (b) pH 3 aqueous solution, (c) pH 10 aqueous solution, (d) $T = 60^\circ C$. (Sample: C1).

Figure 9. Emission spectra of encapsulated coumarin 102, coumarin 102 released from disrupted micellar solution after UV irradiation, and regenerated micellar solution with coumarin 102 partially re-encapsulated after irradiation with visible light. (Sample: C1).
Disclosure statement
No potential conflict of interest was reported by the authors.

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References
[1] Lundberg P, Lynd NA, Zhang Y, et al. pH-triggered self-assembly of biocompatible histamine-functionalized triblock copolymers. Soft Matter. 2013;9:82–89.
[2] Zhou P, Liu Y-Y, Niu L-Y, et al. Self-assemblies of the six-armed star triblock ABC copolymer: pH-tunable morphologies and drug release. Polym. Chem. 2015;6:2934–2944.

Figure 10. Controlled release of coumarin 102 under combined stimulation: (a) pH 3 and UV light irradiation, (b) pH 10 and UV light irradiation, and (c) temperature ($T = 60\,\degree C$) and UV light irradiation. (Sample: C1).

4. Conclusions
In summary, we report the successful synthesis of triple responsive spiropyran-based random copolymer P(SPMA-co-DMAEMA). The characterizations $^1$H NMR, FT-IR, and GPC are used to verify the structures and compositions. The TEM investigation reveals various morphologies at different conditions such as the structure unit ratio, the initial concentration, the external self-assembly condition, and the selective solvent. By contrasting the various morphologies, the system 3 mg C1 sample dissolving in 1 mL THF with the irradiation of visible light and the deionized water (pH 7) as the precipitator is suitable to accomplish the loading of coumarin 102. The controlled release processes with single and combined stimulation are recorded by fluorescence measurements. It is noted that the enhanced release of the model molecule coumarin 102 from the copolymer micelle nanocarriers can be achieved in combination of two stimuli (pH/light, $T$/light) compared with those under single stimulation, which can increase the possibility of applying in nanoreactors and drug delivery under relatively mild conditions.  \[36,37\]
Cui H, Liu H, Chen S, et al. Synthesis of amphiphilic block-copolymers: from micelles to vesicles. Macromolecules 2012;47:8777–8783.

Lee H, Wu W, Oh JK, et al. Light-induced reversible formation of polymeric micelles. Angew. Chem. 2007;119:2505–2509.

Hickey RJ, Haynes AS, Kikkawa JM, et al. Controlling the self-assembly structure of magnetic nanoparticles and amphiphilic block-copolymers: from micelles to vesicles. J. Am. Chem. Soc. 2011;133:1517–1525.

Fomina N, Sankaranarayanan J, Almutairi A. Photochemical mechanisms of light-triggered release from nanocarriers. Adv. Drug Deliv. Rev. 2012;64:1005–1020.

Wang G, Zhang J. Photoresponsive molecular switches for biotechnology. J. Photochem. Photobiol. C: Photochem. Rev. 2012;13:299–309.

Gracia R, Mecerreyes D. Polymers with redox properties: materials for batteries, biosensors and more. Polym. Chem. 2013;4:2206–2214.

Tokarev I, Minko S. Multiresponsive, hierarchically structured membranes: new, challenging, biomimetic materials for biosensors, controlled release, biochemical gates, and nanoreactors. Adv. Mater. 2009;21:241–247.

Gohy JF, Zhao Y. Photo-responsive block copolymer micelles: design and behavior. Chem. Soc. Rev. 2013;42:7117–7129.

Jochum FD, Theato P. Temperature- and light-responsive smart polymer materials. Chem. Soc. Rev. 2013;42:7468–7483.

Stuart MAC, Huck WT, Genzer J, et al. Emerging applications of stimuli-responsive polymer materials. Nat. Mater. 2010;9:101–113.

Cui H, Liu H, Chen S, et al. Synthesis of amphiphilic spiropyran-based random copolymer by atom transfer radical polymerization for Co(II) recognition. Dyes Pigments. 2015;115:50–57.

Cho SH, Jhon MS, Yuk SH. Temperature-sensitive swelling behavior of polymer gel composed of poly (N, N-dimethylaminoethyl methacrylate) and its copolymers. Eur. Polym. J. 1999;35:1841–1845.

Zhang J, Xie R, Zhang S-B, et al. Rapid pH/temperature-responsive cationic hydrogels with dual stimuli-sensitive grafted side chains. Polymer 2009;50:2516–2525.

Zhou W, Liu H, Ye H, et al. Synthesis and adsorption behaviors of poly(2-(dimethylamino)ethyl methacrylate) brushes on silica particles by surface-initiated atom transfer radical polymerization. Powder Technol. 2013;249:1–6.

Park S, Cho D, Ryu J, et al. Fractionation of block copolymers prepared by anionic polymerization into fractions exhibiting three different morphologies. Macromolecules 2002;35:5974–5979.

Zhu X, Liu M. Self-assembly and morphology control of new L-glutamic acid-based amphiphilic random copolymers: giant vesicles, vesicles, spheres, and honeycomb film. Langmuir 2011;27:12844–12850.

Liu H, Cui H, Wang R, et al. Synthesis and characterization of poly (methyl methacrylate) brushes on silica particles by surface-initiated atom transfer radical polymerization. Asian J. Chem. 2014;26:2987–2991.

Liu H, Zhou W, Ye H, et al. Effect of catalyst on formation of poly(methyl methacrylate) brushes by surface initiated atom transfer radical polymerization. J. Cent. South Univ. 2014;21:3049–3056.

Liu H, O’Mahony CT, Audouin F, et al. Random poly(methyl methacrylate-co-styrene) brushes by ATRP to create neutral surfaces for block copolymer self-assembly. Macromol. Chem. Phys. 2012;213:108–115.

Raymo FM, Giordani S. Signal processing at the molecular level. J. Am. Chem. Soc. 2001;123:4651–4652.

Wu T, Zou G, Hu J, et al. Fabrication of photoswitchable and thermotunable multicolor fluorescent hybrid silica nanoparticles coated with dye-labeled poly(N-isopropylacrylamide) brushes. Chem. Mater. 2009;21:3788–3798.

Wang Y, Hong CY, Pan CY. Spiropyran-based hyperbranched star copolymer: synthesis, phototropy, FRET, and bioapplication. Macromolecules 2012;13:2585–2593.

Chen S, Liu H, Cui H, et al. Synthesis of spiropyran-containing random copolymer by atom transfer radical polymerization and its complexation with metal ions. Des. Monomers Polym. 2015;18:574–582.

Liu H, Chen S, Cui H, et al. Fabrication of triple responsive polymer brushes and their catalytic performance after loading palladium. RSC Adv. 2015;5:72444–72452.

Li Y, Deng Y, Tong X, et al. Fabrication of photoresponsive uniform colloidal spheres from an amphiphilic azobenzene-containing random copolymer. Macromolecules 2006;39:1108–1115.

Price C. Micelle formation by block copolymers in organic solvents. Pure Appl. Chem. 1983;55:1563–1572.

Zhang L, Shen H, Eisenberg A. Phase separation behavior and crew-cut micelle formation of polystyrene-b-poly(acrylic acid) copolymers in solutions. Macromolecules 1997;30:1001–1011.

Dan K, Bose N, Ghosh S. Vesicular assembly and thermo-responsive vesicle-to-micelle transition from an amphiphilic random copolymer. Chem. Commun. 2011;47:12491–12493.

Zhou YN, Zhang Q, Luo ZH. A light and pH dual-stimuli-responsive block copolymer synthesized by copper(0)-mediated living radical polymerization: solvatochromic, isomerization, and “schizophrenic” behaviors. Langmuir 2014;30:1489–1499.

Liu S, Armes SP. Polymeric surfactants for the new millennium: a pH-responsive, zwitterionic, schizophrenic diblock copolymer. Angew. Chem. Int. Ed. 2002;41:1413–1416.

Liu S, Billingham NC, Armes SP. A schizophrenic water-soluble diblock copolymer. Angew. Chem. Int. Ed. 2001;40:2328–2331.

Liu H, Sun R, Yi J, et al. Kinetics of methyl methacrylate grafting polymerization onto flaky aluminum powder. J. Appl. Polym. Sci. 2010;115:3040–3044.

Tokarev I, Minko S. Stimuli-responsive porous hydrogels at interfaces for molecular filtration, separation, controlled release, and gating in capsules and membranes. Adv. Mater. 2010;22:3446–3462.
