Polymer 51 (2010) 3068–3074

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Phenylboronic acid as a sugar- and pH-responsive trigger to tune the multiple micellization of thermo-responsive block copolymer

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ARTICLE INFO

Article history:
Received 27 February 2010
Received in revised form
13 April 2010
Accepted 26 April 2010
Available online 20 May 2010

Keywords:
Phenylboronic acid
CMT
Micelle

ABSTRACT

Phenylboronic acid-containing thermo-responsive block copolymer, poly(ethylene oxide)-b-poly (methoxydi(ethylene glycol) methacrylate-co- aminophenylboronic acid ethyl methacrylate) (PEO-b-P (DEGMMA-co-PBAMA)), was employed to investigate the multiple micellization and dissociation transitions. The unique sugar- and pH-responsive properties of phenylboronic acid were interesting to provide two parallel approaches to tune the critical micellization temperature (CMT) and multiple micellization of thermo-responsive block copolymer. The block copolymers were molecularly soluble below 21 °C and underwent micellization above 21 °C at pH 8.7. After glucose was added at 24 °C, hydrophobic phenylboronic acid was changed to hydrophilic boronate–glucose complex and the CMT of the thermo-sensitive block was increased which caused the dissociation of micelles. In parallel, if the solution pH was increased from 8.7 to 11 at 25 °C, micelles were disrupted because of the formation of hydrophilic phenylboronate anion, which elevated the CMT of the thermo-sensitive block polymer. The introduction of phenylboronic acid groups into the thermo-responsive block copolymers provides a novel approach to tune the multiple micellization and dissociation transitions that might have great potentials in biomedical applications.

1. Introduction

During the past decade, stimuli-responsive block copolymers have attracted much interest because of their ability to undergo micellization or dissolution in response to external stimulus. Thus, they are particularly suitable in areas such as drug and gene delivery, tissue engineering, biosensors and separation processes [1–7]. A common principle for dissociation of micelles involves the change of the polymeric polarity and break of the hydrophobicity/hydrophilicity balance of the core-forming component by the use of an external trigger. A lot of chemical and physical stimuli including temperature [8,9], pH [10], redox [11], photo [12,13], host–guest interaction [14], biomolecules [15] have been employed to induce the micellization and dissociation of stimuli-responsive block copolymers.

Thermo-responsive polymers can become hydrophobic from hydrophilic when the temperature is above a critical point, known as lower critical solution temperature (LCST). A lot of thermo-responsive polymers have been reported, such as poly(N-isopropyl acrylamide), poly(propylene oxide) and poly(N,N-diethylacrylamide). Poly(methoxydi(ethylene glycol) methacrylate) (PDEGMMA) is a new class of thermo-responsive polymer with excellent anti-fouling/stealth behavior since it is mainly composed of biocompatible oligo(ethylene glycol) segments. How to control the LCST of a polymer is an important issue. In general, LCST can be adjusted by incorporation of hydrophobic or hydrophilic units in the thermo-responsive polymer. The LCST will be increased if it is copolymerized with a hydrophilic monomer. In contrast, the LCST will be decreased if it is copolymerized with a hydrophobic monomer. This phenomenon is utilized to design block copolymer micelles with controlled instability. Hennink et al. reported a novel type of thermo-responsive polymers whose LCST increased from below to above 37 °C with the hydrolysis of the hydrophobic lactate side groups [16–19]. Zhao et al. copolymerized thermo-responsive monomers with the photo or pH-responsive monomers. The LCST could be controlled by UV irradiation or adjustment of solution pH and the assembly and disassembly can be realized by combining temperature and photo/pH triggers [20,21].

Boronic acid-containing polymers are a unique class of stimuli-responsive polymers with potential applications as self-healing materials, therapeutic agents, self-regulated drug delivery systems, and sensors for sugars and glycoproteins [22–29]. Boron-containing bioengineering polymers, including various copolymers of p-vinylphenylboronic acid and phenylbornic acid-containing

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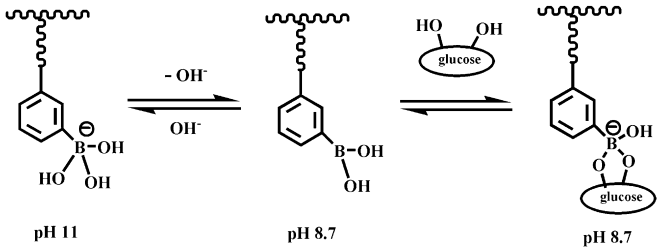
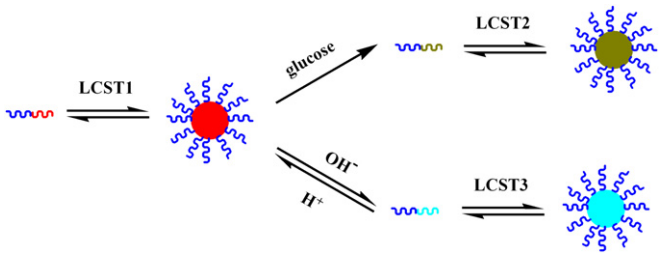
doi:10.1016/j.polymer.2010.04.061



Scheme 1. Glucose concentration and pH-induced hydrophilicity–hydrophobicity transition of phenylboronic acids.



Scheme 3. Schematic illustration of multiple micellization and dissociation transitions of thermo-, glucose- and pH-responsive block copolymer PEO-b-P(DEGMMA-co-PBAMA).

copolymers with sugar (e.g. glucose) and DNA (or RNA) sensitivities are a subject of many researchers [30,31]. Boronic acids are uniquely stimuli-responsive because their water solubility is tunable by pH and solution diol concentration (Scheme 1) [32]. Above the pK_a of boronic acid, boronic acid exists as a hydrophilic boronate anion form. But the boronate anions can be converted to neutral/hydrophobic boronic acid and subsequent chain dehydration if the solution pH is adjusted to below the pK_a of boronic acid. In the presence of sufficient concentration of diol, neutral boronic acids can form ionized cyclic boronate esters with 1,2- and 1,3-diols, which makes the hydrophobic boronic acids hydrophilic. As more diol is added, the driving force for boronic acid-diol complexation is increased to generate more boronate–glucose complex. As a result, a lot of boronic acid-containing polymers were employed as saccharide (especially glucose) receptors [33–39]. Very recently, phenylboronic acid-containing block copolymers were synthesized to design glucose-responsive micelles [15,23,40].

In our research, phenylboronic acid was specially designed as a sugar- and pH-responsive trigger to tune the multiple micellization of thermo-responsive block copolymer. Poly(ethylene oxide)-b-poly(methoxydi(ethylene glycol) methacrylate-co-glycidyl methacrylate) (PEO-b-P(DEGMMA-co-GMA)) was synthesized via atom transfer radical polymerization (ATRP). GMA was then partly converted to phenylboronic acid-containing methacrylate PBAMA by the reaction between epoxy group and amino group to form thermo-, glucose- and pH-responsive block copolymer PEO-b-P (DEGMMA-co-PBAMA) (Scheme 2). Because the glucose- and pH-responsive phenylboronic acid-containing PBAMA was copolymerized with thermo-responsive DEGMMA, the LCST of PDEGMMA could be adjusted by pH and glucose concentration. The multiple micellization and dissociation transitions of PEO-b-P(DEGMMA-co-PBAMA) were investigated under combinations of glucose concentration and temperature or pH and temperature in detail (Scheme 3).

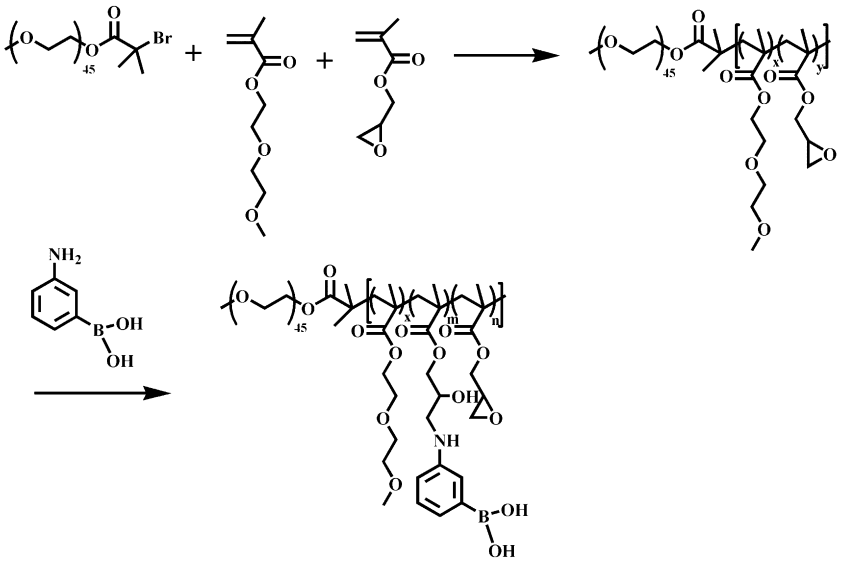
2. Experimental section

2.1. Materials

Poly(ethylene oxide) methyl ether (Aldrich, PEO-OH, $M_n \sim 2000$ g/mol), 2-bromoisobutyryl bromide (Aldrich), Nile red (TCI), glucose (Sinopharm Chemical Reagent Co., Ltd.), 3-aminophenylboronic acid monohydrate (Alfa) were used as received without further purification. Glycidyl methacrylate (Alfa, GMA) was purified by distillation under vacuum prior to use. Methoxydi (ethylene glycol) methacrylate (DEGMMA, Aldrich) was passed through a basic alumina column to remove inhibitor and then stored in a refrigerator before use. PEO Macroinitiator PEO-Br was synthesized by the reaction of PEO-OH and 2-bromoisobutyryl bromide [41].

2.2. Synthesis of PEO-b-P(DEGMMA-co-GMA)

CuBr (14.4 mg, 0.1 mmol), PEO-Br (0.21 g, 0.1 mmol), PMDETA (21 μL, 0.1 mmol), DEGMMA (2.78 g, 15 mmol), and GMA (0.43 g, 1.5 mmol) were dissolved in 5 mL of anisole in a 10 mL flask under N_2 atmosphere. Then, the mixture was degassed three times using



Scheme 2. Schematic illustration of the synthesis of PEO-b-P(DEGMMA-co-PBAMA).

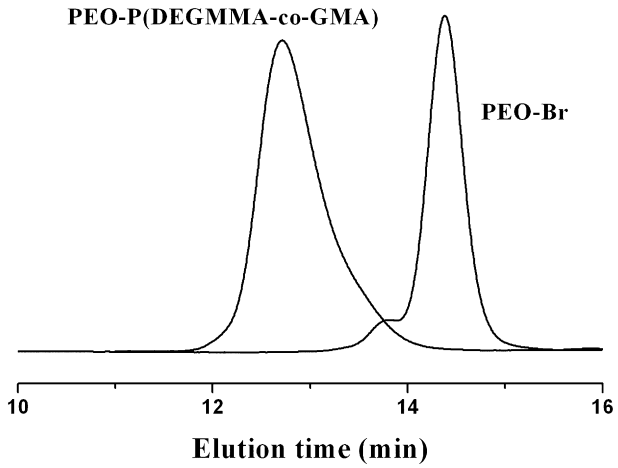


Fig. 1. Gel permeation chromatography curves of macroinitiator PEO-Br and PEO_{45}-b-P($DEGMMA_{82}$-co-GMA_9) ($M_{n,GPC}$ = 21,100 g/mol, PD = 1.21).

the freeze-pump-thaw procedure and sealed under vacuum. Then the ampoule was placed in a preheated oil bath (60 °C) for 3 h. The solution was passed through a neutral Al_2O_3 column with chloroform as eluent to remove the catalyst. The block polymer was collected by reprecipitation twice into hexane. The polymer was then dried in high vacuum.

2.3. Synthesis of PEO-b-P(DEGMMA-co-PBAMA)

In a 100 mL round-bottomed flask, 0.5 g of PEO-b-P(DEGMMA-co-GMA) and 68 mg of 3-aminophenylboronic acid monohydrate were dissolved in 15 mL of dioxane and 5 mL of water (pH 8) under stirring. The reaction was allowed to proceed at 75 °C for 48 h. After that, the solvent was removed under vacuum, and the copolymer was precipitated into diethyl ether for 3 times. The copolymer was dried under vacuum.

2.4. Preparation of polymer solutions

0.5 mg/mL of PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$) aqueous solution was prepared by the following procedure. 5 mg of polymer and 10 mL of water was directly added into a small vial. The polymer solution was sonicated in an ultrasonic ice/water bath for 30 min to ensure complete dissolution. The solution pH was then adjusted to 8.7.

The polymer solution loaded with Nile Red was prepared as described below. 21 μL of 0.1 mg/mL Nile Red solution in acetone was added into an empty vial, which was then placed in vacuum for 2 h to remove the solvent. Then, 10 mL of 0.5 mg/mL polymer solution was added into the vial. The solution was stirred overnight in dark.

2.5. Determination of critical micellization temperature (CMT)

The fluorescence emission spectra of Nile Red in a 0.5 mg/mL aqueous polymer solution at various temperatures were recorded. At each temperature, the solution was equilibrated for 10 min. The maximum fluorescence intensities were plotted against temperatures for the determination of CMT.

2.6. Characterization

The ^1H NMR spectra of the polymers were recorded on a Bruker DMX500 spectrometer. Molecular weights and molecular weight distributions were determined using a Gel Permeation Chromatography (GPC) using THF as eluent. Calibration was carried out using a series of near-monodisperse polystyrene standards. DLS measurements were performed on the samples using a Brookhaven 90Plus size analyzer at the 90° scattering angle. Intensity-average hydrodynamic diameter was adopted in this research. Fluorescence emission spectra were recorded from Perkin–Elmer LS 55 fluorescence spectrometer. The excitation wavelength was 550 nm, and the fluorescence emission spectra were recorded from 570 to 720 nm. The slit width was 7.5 nm.

3. Results and discussion

3.1. Synthesis of block copolymers

The synthetic route of the thermo-, sugar- and pH-responsive block copolymer PEO-b-P(DEGMMA-co-PBAMA) was shown in Scheme 2. First, PEO-b-P(DEGMMA-co-GMA) was synthesized via

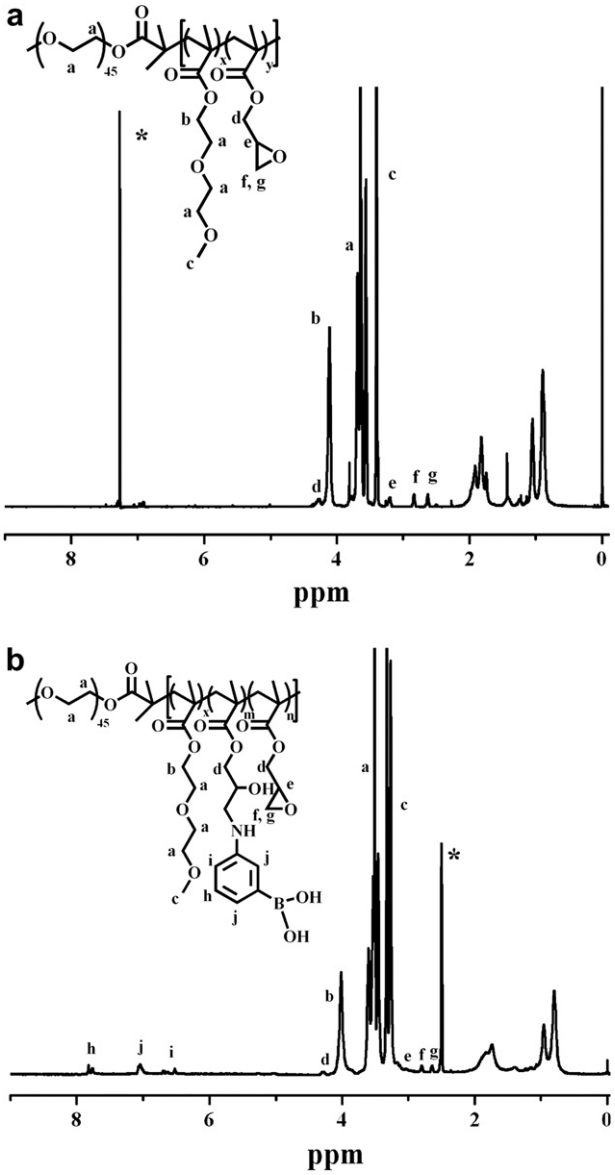


Fig. 2. ^1H NMR spectra of (a) PEO_{45}-b-P($DEGMMA_{82}$-co-GMA_9) in $CDCl_3$; (b) PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) in DMSO-d_6. * indicates residual NMR solvent.

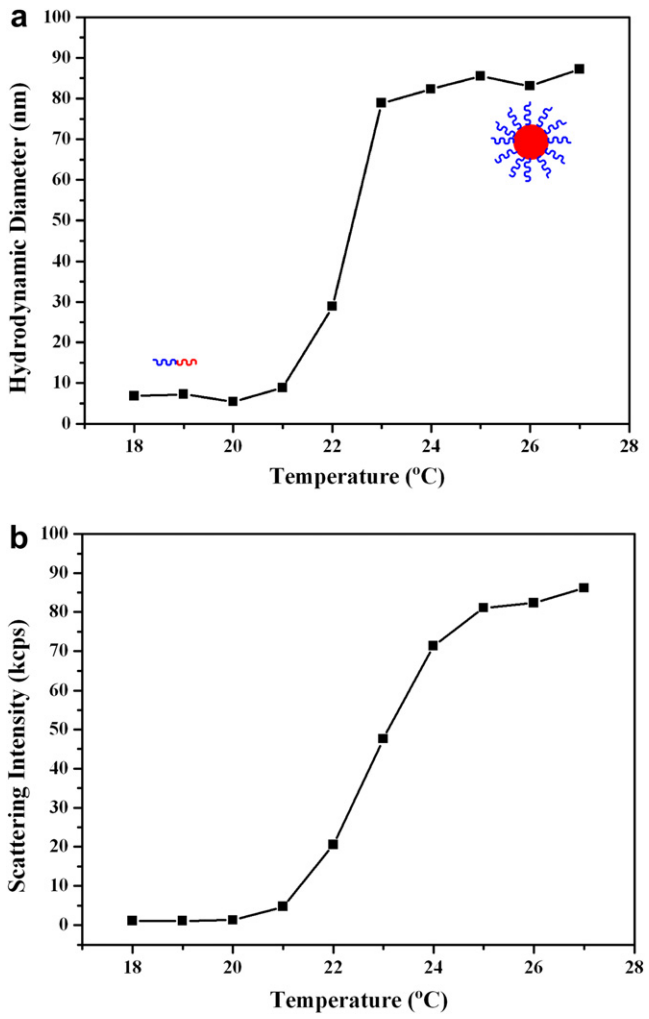


Fig. 3. Light scattering Intensity (a) and the hydrodynamic diameter (b) as a function of temperature in a DLS study of 0.5 mg/mL PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) solution at pH 8.7.

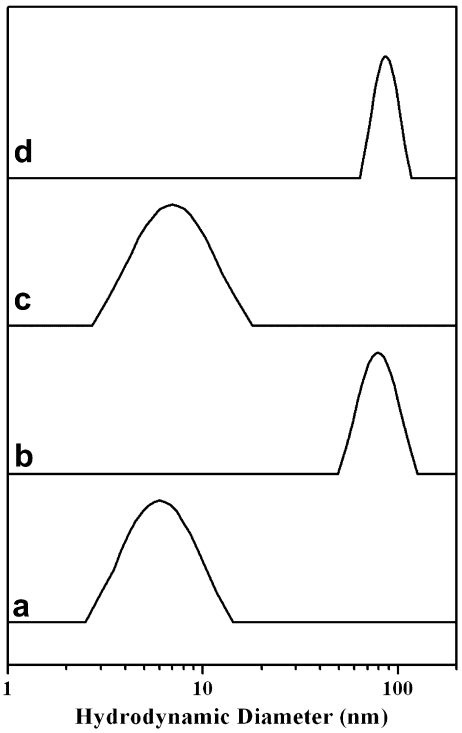


Fig. 4. Intensity-average hydrodynamic diameter obtained with an aqueous solution of PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) (a) unimers at 18 °C before glucose was added; (b) micelles at 24 °C before glucose was added; (c) unimers at 24 °C after glucose was added; (d) micelles at 30 °C after glucose was added.

atom transfer radical polymerization (ATRP) using PEO_{45}-Br as macroinitiator. GMA units were then partly converted to phenylboronic acid-containing methacrylate PBAMA by the reaction between epoxy group and amino group. The successful synthesis of block copolymers PEO-b-P(DEGMMA-co-GMA) was characterized by GPC and ^{1}H NMR. The number-average molecular weight (M_n) and molecular weight distributions (PD) of PEO-Br and PEO-b-P (DEGMMA-co-GMA) were determined by GPC using THF as shown in Fig. 1. As GPC indicated, the resulting PEO-b-P(DEGMMA-co-GMA) had relatively low polydispersity (PD = 1.21). Typical ^{1}H NMR spectra of each step in the synthesis was shown in Fig. 2 with the relevant signals labeled. We can see the characteristic peaks of DEGMMA (δ 3.34–3.48, 3.52–3.88, 4.02–4.21) and GMA (δ 2.56–2.70, 2.76–2.93, 3.15–3.32) in Fig. 2a. By comparing the well-defined peak integrals of PEO, DEGMMA units and GMA units, the degrees of polymerization, DP, of DEGMA and GMA blocks were calculated as 82 and 9 respectively. Thus, the obtained polymer was denoted as PEO_{45}-P($DEGMMA_{82}$-co-GMA_9). After PEO_{45}-P($DEGMMA_{82}$-co-GMA_9) was reacted with 3-aminophenylboronic acid, the characteristic peaks of phenylboronic acid (δ 6.45–6.79, 6.92–7.15, 7.61–7.88) appeared in Fig. 2b. But not all of the GMA units can be reacted with 3-aminophenylboronic acid. We could still see the characteristic peaks of GMA in Fig. 2b, although the peak integrals of GMA were greatly reduced compared to that of the PEO and DEGMMA units. The conversion ratio was about 60% from Fig. 2b and there were in average five PBAMA units in each polymer. The obtained targeted polymer was denoted as PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$).

3.2. Thermo- and glucose-responsive multiple micellization and dissociation transitions

0.5 mg/mL of PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$) at pH 8.7 was used for the demonstration of thermo- and glucose-triggered multiple micellization and dissociation transitions in water because of the LCST shift of PDEGMMA. We studied the self-assembly and disassembly of the micelles in response to temperature and glucose concentration changes by dynamic light scattering (DLS) and fluorescence spectroscopy. PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$) was first directly dissolved in water at 18 °C and the solution pH was then adjusted to 8.7. The intensity-average hydrodynamic diameter (D_h) was only 6.8 nm at 18 °C, indicating that the block copolymer was molecularly dissolved. Upon heating, the D_h started to increase dramatically at ~21 °C (Fig. 3). The D_h increased to ~90 nm and stabilized out above 24 °C. At the same time, the average count rate, a measurement of light scattering intensity with units of kilocounts per second (kcps), which varied directly with the production of particle size and concentration gradually increased. Surprisingly, the light scattering intensity continued to increase above 24 °C. Similar phenomena were also observed by other research groups [21,42]. The increase of light scattering intensity suggested that the thermo-sensitive P($DEGMMA_{82}$-co-$PBAMA_5$) block was undergoing a hydration-to-dehydration transition. P($DEGMMA_{82}$-co-$PBAMA_5$)-core micelles appeared. The critical micellization temperature (CMT1), which was determined from the plot of the light scattering intensity versus temperature (Fig. 3b) was 21.2 °C.

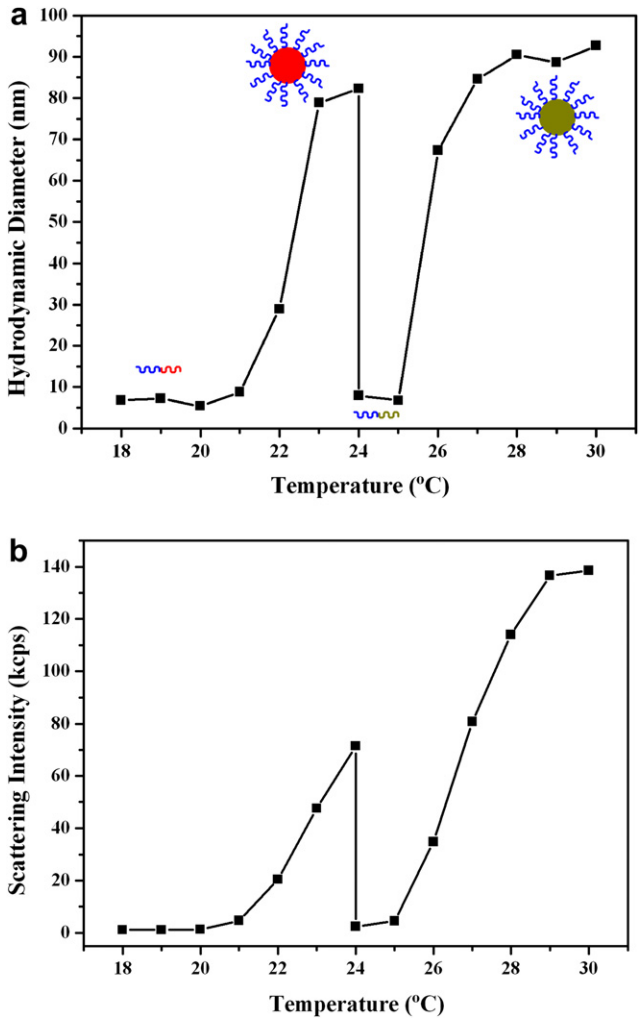


Fig. 5. Light scattering intensity (a) and the hydrodynamic diameter (b) as a function of temperature in a DLS study of multiple micellization and dissociation transitions of 0.5 mg/mL PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) solution at pH 8.7 in responsive to solution temperature and glucose concentration. Glucose was added at 24 °C.

Phenylboronic acids can act as excellent glucose receptors with high equilibrium association constant (Scheme 1) [43,44]. The formation of boronate–glucose complex can adjust the overall equilibrium from neutral/insoluble boronic acid moieties to anionic/hydrophilic boronates. Therefore, the extent of ionization (also the water solubility) of boronic acid-containing polymers increases with glucose concentration [37,45]. If phenylboronic acid was copolymerized with thermo-responsive monomer, such as N-isopropylacrylamide, the LCST would be influenced by glucose concentrations [36,37]. We expected that multiple micellization and dissociation transitions would be induced by the addition of glucose because of the LCST shift. At 24 °C and pH 8.7, glucose was added into the micellar solution to yield a final solution concentration of glucose = 50 mM. The solution was then stirred for 24 h at 24 °C. Before glucose was added, the D_h of the micellar solution was 82.3 nm and the polydispersity index (PDI) was 0.085 at 24 °C (Fig. 4b). But after glucose was added, the D_h was suddenly reduced to 8.2 nm accompanied with the dramatic reduction of the light scattering intensity from 71.4 kcps to 2.4 kcps (Figs. 4c and 5). Micelles were dissociated after glucose was added. It was because the cyclic boronate ester formation between glucose and the phenylboronic acid units led to hydrophobic PBAMA units water soluble which would increase the LCST of thermo-sensitive P

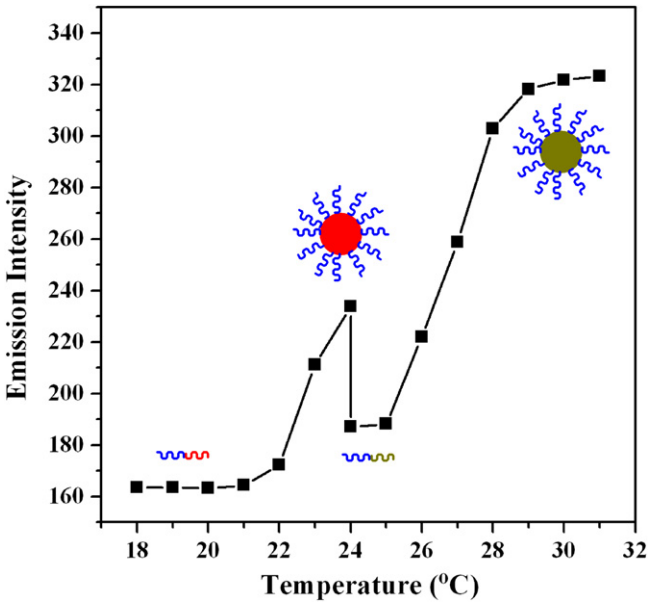


Fig. 6. Maximum fluorescence emission intensity of Nile Red in 0.5 mg/mL PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) solution at pH 8.7 in response to solution temperature and glucose concentration. Glucose was added at 24 °C.

(DEGMMA-co-PBAMA) block. The hydrophobic P(DEGMMA-co-PBAMA) block hence became hydrophilic after glucose was added and the micelles were disassembled. When the solution temperature was further increased from 24 °C to above 25 °C, the light scattering intensity began to increase significantly (Fig. 5b). The D_h was also increased and reached 92.1 nm at 30 °C (Fig. 4d). Micelles were organized again and the critical micellization temperature (CMT2) determined from Fig. 5b was 25.5 °C.

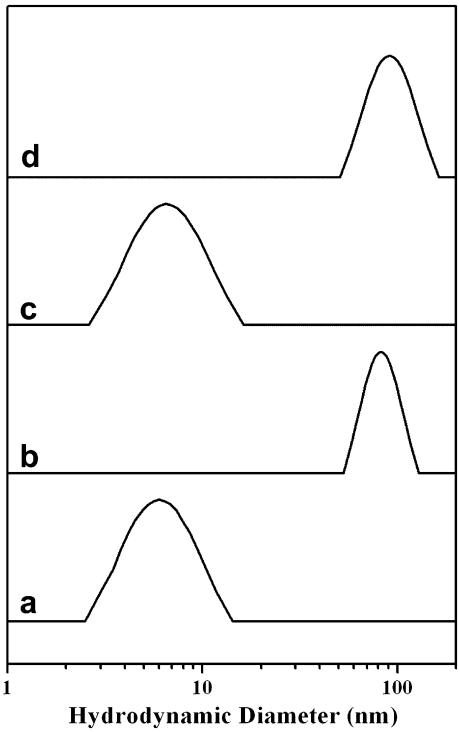


Fig. 7. Intensity-average hydrodynamic diameter obtained with an aqueous solution of PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) (a) unimers at 18 °C and pH 8.7; (b) micelles at 25 °C and pH 8.7; (c) unimers at 25 °C and pH 11; (d) micelles at 32 °C and pH 11.

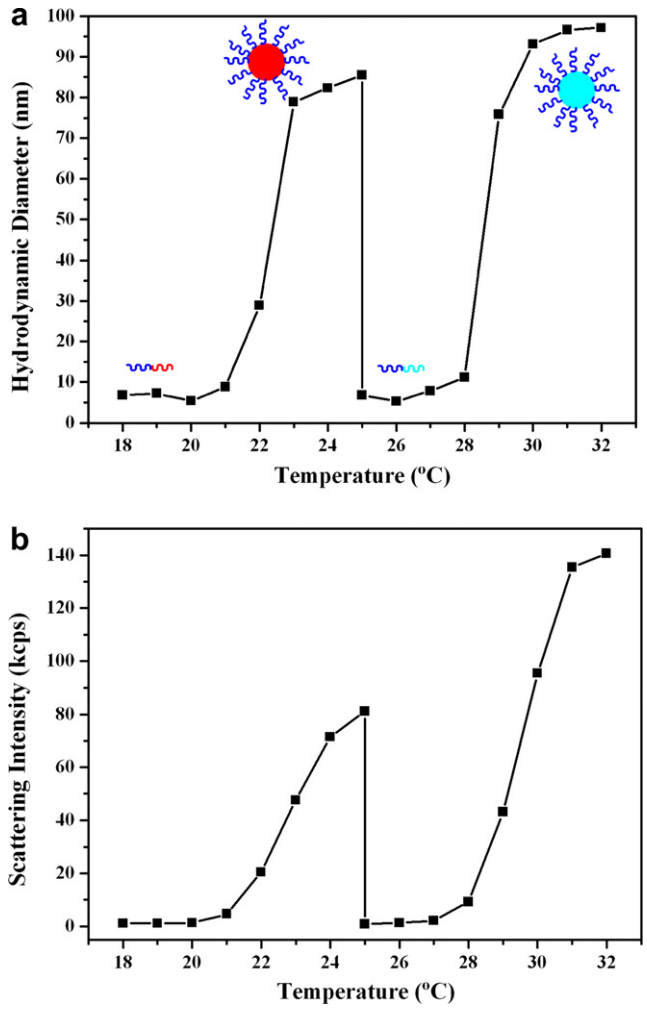


Fig. 8. Light scattering Intensity (a) and the hydrodynamic diameter (b) as a function of temperature in a DLS study of multiple micellization and dissociation transitions of 0.5 mg/mL PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) solution in responsive to solution temperature and pH. The solution pH was adjusted to 11 at 25 °C.

The thermo- and glucose-responsive multiple micellization and dissociation transitions of PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$) because of the LCST shift were further studied by fluorescence spectroscopy. Nile Red was used as the fluorescence probe since its fluorescence is known to increase substantially in a hydrophobic environment such as the core of micelles [46,47]. When the solution temperature was raised above 21 °C from 18 °C, the fluorescence emission intensity increased significantly, which indicated that the molecularly soluble polymer chains were associated into micelles and the Nile Red molecules were then encapsulated into the hydrophobic core (Fig. 6). At the same time, the maximum fluorescent emission peak underwent a blueshift during this procedure, from 635 nm at 18 °C to 630 nm at 24 °C, which further proved that the Nile Red molecules moved from a hydrophilic to a hydrophobic environment and thus the micelles were formed in the solution. The CMT1, detected from the plot of maximum fluorescent emission intensity versus temperature (Fig. 6), was 21.8 °C, which was very close to the DLS study (21.2 °C). After glucose was added, the fluorescence emission intensity was reduced dramatically as shown in Fig. 6 accompanied with a redshift of the maximum fluorescent emission peak from 630 nm to 633 nm. The micelles were disassembled into unimers after the addition of glucose. After the temperature was further raised, the fluorescence emission intensity increased again and the maximum fluorescent emission peak underwent a blueshift (from 633 nm at 24 °C to 627 nm at 30 °C), which indicated the reformation of micelles. The CMT2 was also detected as 25 °C (Fig. 6).

3.3. Thermo- and pH-responsive multiple micellization and dissociation transitions

As is shown in Scheme 1, phenylboronic acid is not only sugar-responsive, but also pH-responsive. Hydrophobic phenylboronic acid can become hydrophilic boronate anion after adjustment of the solution pH. We expected that the LCST of PDEGMMA would be increased after the solution pH was elevated which could induce the multiple micellization and dissociation transitions. From Fig. 3, PEO_{45}-P($DEGMMA_{82}$-co-$PBAMA_5$) block copolymer can self-assemble into micelles above 21 °C at pH 8.7. The D_h of the micellar solution was 85.5 nm and the PDI was 0.076 at 25 °C (Fig. 7b). After the solution pH was adjusted to 11 by the addition of NaOH, the D_h was reduced to 7.9 nm. Meanwhile, the light scattering intensity was greatly reduced, which indicated the pH-induced dissociation of micelles (Fig. 8). In this situation, hydrophobic phenylboronic acid units became hydrophilic boronate anion after the solution pH was changed from 8.7 to 11. As a result, the LCST of thermo-sensitive P(DEGMMA-co-PBAMA) block was increased. The hydrophobic P(DEGMMA-co-PBAMA) block hence became hydrophilic and the micelles were disassembled. Further increasing of the solution temperature from 25 °C to above 28 °C would result in the greatly increasing of the light scattering intensity (Fig. 8b). The D_h was also increased and reached 97.1 nm at 32 °C (Figs. 7d and 8a). Micelles were formed again and the critical micellization temperature (CMT3) determined from Fig. 8b was 27.8 °C.

Fluorescence spectroscopy was also used to track the thermo- and pH-responsive multiple micellization and dissociation transitions. After the solution pH was adjusted to 11 at 25 °C, the fluorescence emission intensity was reduced dramatically as shown in Fig. 9. Meanwhile, the maximum fluorescent emission peak underwent a redshift during this procedure, from 630 nm at pH 8.7 to 634 nm at pH 11, which showed the dissociation of the micelles. When the solution temperature was further raised, the

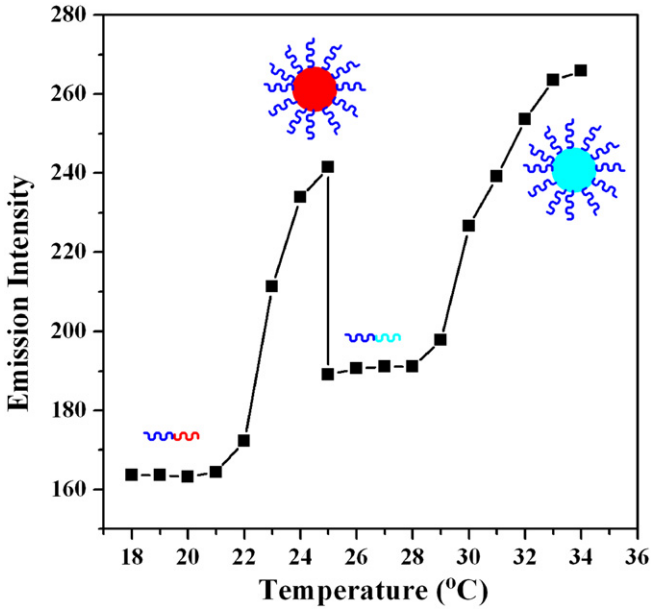


Fig. 9. Maximum fluorescence emission intensity of Nile Red in 0.5 mg/mL PEO_{45}-b-P($DEGMMA_{82}$-co-$PBAMA_5$) solution in responsive to solution temperature and pH. The solution pH was adjusted to 11 at 25 °C.

fluorescence emission intensity was increased again as expected and the maximum fluorescent emission peak underwent a blue-shift (from 634 nm at 25 °C to 626 nm at 32 °C), which indicated the reformation of micelles. By the plot of maximum fluorescent emission intensity versus temperature (Fig. 9), we found the critical micellization temperature (CMT3) was 28.5 °C which was very close to the DLS study.

4. Conclusions

In conclusion, thermo-, glucose- and pH-responsive block copolymer PEO-b-P(DEGMMA-co-PBAMA) was synthesized by ATRP and sequentially reaction between epoxy group and amino group. The multiple micellization and dissociation transitions of the block copolymer were induced because of the LCST shift after the addition of glucose or NaOH. The block copolymers can self-assemble into micelles above 21 °C at pH 8.7. When glucose was added at 24 °C, DLS and fluorescence spectroscopy showed the micelles were dissociated into unimers. Further increasing the temperature induced the formation of micelles again. On the other hand, adjustment of the solution pH from 8.7 to 11 at 25 °C can also result in the dissociation of the micelles. After the temperature was raised again, micelles were formed as expected. The multiple micellziation and dissociation transitions may find potential applications in controlled encapsulation, re-encapsulation and triggered release of substances.

Acknowledgements

Financial support from the Natural Science Foundation of China (NSFC- 20774082, 50830106), Programs Foundation of Ministry of Education of China (No. 20070335024), Science Fundation of Chinese University and Open Project of State Key Laboratory of Supramolecular Structure and Materials (SKLSSM200911) and Natural Science Foundation of China of Zhejiang Province (Y4080250) is gratefully acknowledged.

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