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Bisphenol A-responsive microgel comprising hydrophilic poly(acrylamide) network

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Bisphenol A-responsive microgel composed of hydrophilic poly(acrylamide) network

Stimuli-responsive microgels that exhibit rapid changes in size in response to external stimuli such as pH and temperature are of great interest for the development of smart sensors, drug delivery carriers, and separation materials. This paper describes the preparation of molecule-responsive microgels with molecular recognition sites comprising a hydrophilic network *via* inverse miniemulsion polymerization using a water-soluble emulsifier. The water-soluble emulsifier comprising hydrophilic poly(sulfobetaine) and hydrophilic/oleophilic poly[oligo(ethylene glycol)methacrylate-*co*-2-(2'-methoxyethoxy)ethyl methacrylate] blocks were synthesized *via* reversible addition fragmentation chain transfer (RAFT) polymerization. The resulting block copolymer, PSB-POEG, stabilized the water-chloroform interface in a water-in-oil (W/O) emulsion. Water droplets in a W/O emulsion stabilized with PSB-POEG allowed the inverse miniemulsion polymerization of acrylamide (AAm), acryloyl-modified β-cyclodextrin (CD), and *N,N'*-methylenebisacrylamide to obtain CD-conjugated PAAm microgels with a diameter of approximately 150 nm. The resulting CD-PAAm microgels were stably dispersed in an aqueous medium by the addition of water, followed by evaporation of chloroform. The CD-PAAm microgels exhibited rapid shrinkage in response to bisphenol A (BPA) owing to the formation of CD-BPA-CD complexes acting as dynamic cross-links. The proposed method for preparing hydrophilic microgels by inverse miniemulsion polymerization using a water-soluble emulsifier allows the preparation of molecularly imprinted and bioconjugated microgels, providing a useful platform for designing rapidly responsive soft nanomaterials for molecular sensors, separation substrates, and drug delivery carriers.

Keywords: Molecule-responsive microgel; Inverse miniemulsion polymerization; Water-soluble emulsifier; RAFT polymerization; Zwitterionic polymer; Inclusion complex; Cyclodextrin

Introduction

Stimuli-responsive microgels that undergo changes in size in response to external stimuli are of great interest because of their potential applications in drug delivery systems, smart separation substrates, and sensors [1-4]. The stimuli-responsiveness of such microgels is mainly based on changes in the hydrophilicity of the polymer networks or osmotic pressure by charged groups. In addition, bioconjugation onto stimuli-responsive microgels allows the formation of biomolecule-responsive microgels [5-9]. For example, glucose oxidase-immobilized poly(acrylic acid) microgels showed a glucose-triggered decrease in size owing to the protonation of carboxylates of microgels by a decrease in local pH, resulting from the enzymatic reaction of glucose oxidase [8].

In contrast to conventional stimuli-responsive hydrogels, we have developed molecularly stimuli-responsive hydrogels [10-13] and microgels [14-18] that change in size upon recognition of a target molecule. The recognition of a target molecule induces a change in the crosslinking density through the formation or dissociation of molecular complex cross-links. For example, a polyacrylamide (PAAm) hydrogel with β-cyclodextrin (CD) as a ligand shrank in response to the target bisphenol A (BPA) owing to the formation of sandwich-like CD-BPA-CD complexes acting as dynamic cross-links [13]. Moreover, molecular imprinting of BPA during the preparation of BPA-responsive hydrogels allows for greater shrinkage than that of non-imprinted hydrogels. We also revealed that a rapid responsive change in size was accomplished by decreasing the size of the molecule-responsive hydrogel [14-18]. Because surfactants that stabilize the interface of monomer droplets and the resulting microgels may affect the molecular complexes as dynamic cross-links, soap-free emulsion polymerization was applied to prepare molecule-responsive microgels. The glucose-responsive microgel prepared *via* soap-free emulsion copolymerization of diethylaminoethyl methacrylate, methacrylate

with a pendant glucose, acryloyl-conjugated lectin concanavalin A, and poly(ethylene glycol)dimethacrylate exhibited the target glucose-responsive swelling [15].

Microgels prepared *via* soap-free emulsion polymerization are composed of a relatively hydrophobic polymer network. Such hydrophobic polymer networks induce nonspecific adsorption of hydrophobic molecules onto microgels through hydrophobic interactions, resulting in undesirable shrinkage. Therefore, molecule-responsive microgels with hydrophilic polymer networks are required to recognize a hydrophobic target molecule without nonspecific adsorption. Inverse miniemulsion polymerization is a promising method for preparing microgels with hydrophilic networks [19]. For example, PAAm [20-24], poly[oligo(ethylene glycol)methacrylate] (POEGMA) [25,26], and zwitterionic polycarboxybetaine microgels [27] were prepared by inverse miniemulsion polymerization. As amphiphilic surfactants were used to stabilize the aqueous monomer solution droplets in the W/O emulsion, the surfaces of the resulting hydrophilic microgels were covered with surfactants. The dispersion of the resulting microgels in an aqueous medium requires the removal of adsorbed surfactants from the surface of the resulting microgels by thorough washing with polar solvents such as methanol and tetrahydrofuran. Therefore, there is a demand for a method for the facile preparation of water-dispersible microgels composed of a hydrophilic polymer network without removal of the surfactant by a thorough washing process.

Recently, we proposed a novel strategy for preparing nanocapsules [28,29] and core-shell microgels [30] comprising a completely hydrophilic polymer network *via* interfacial reaction in a W/O emulsion. We designed a water-soluble emulsifier composed of extremely hydrophilic poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) and hydrophilic/oleophilic POEGMA blocks. The water-soluble emulsifier PMPC-*b*-POEGMA stabilized the water-chloroform interface because the PMPC and

POEGMA blocks were distributed in the water and chloroform phases, respectively. Water droplets stabilized with a PMPC-*b*-POEGMA emulsifier in a W/O emulsion provide a useful interfacial reaction field for preparing soft nanomaterials. The copolymerization of poly(ethylene glycol)methacrylate with bis(2-methacryloyl)oxyethyl disulfide from the water-soluble PMPC-*b*-POEGMA emulsifier, which stabilized the water-chloroform interface in the W/O emulsion, provided reductively responsive nanocapsules [28]. Nanocapsules were also prepared by the interfacial cross-linking of a PMPC-*b*-POEGMA emulsifier using divinyl sulfone [29]. Moreover, the copolymerization of MPC with *N,N′*-methylenebisacrylamide (MBAA) from the water-soluble PMPC-*b*-POEGMA emulsifier in water droplets of the W/O emulsion allowed the preparation of a core-shell microgel with a hydrophilic PMPC core and LCST-type thermoresponsive POEGMA shell derived from the PMPC-*b*-POEGMA emulsifier [30]. The most fascinating advantage of the preparation method of soft nanomaterials using a W/O emulsion stabilized with a water-soluble PMPC-*b*-POEGMA emulsifier is that the resulting soft nanomaterials are easily dispersed in aqueous media without the need for thorough washing to remove the emulsifier. Therefore, this method is promising for preparing molecule-responsive microgels composed of hydrophilic networks with molecular complexes as dynamic cross-links.

   To address the challenges associated with nonspecific adsorption and complex surfactant removal in previous methods, this paper reports a novel method for preparing BPA-responsive microgels comprising a hydrophilic PAAm network *via* inverse miniemulsion polymerization using a water-soluble emulsifier. A water-soluble block copolymer comprising a hydrophilic poly(sulfobetaine) block and a hydrophilic/oleophilic poly[oligo(ethylene glycol)methacrylate-*co*-2-(2′-methoxyethoxy)ethyl methacrylate] (PSB-POEG) was synthesized *via* reversible

addition fragmentation chain transfer (RAFT) polymerization, and its interfacial

properties were investigated to prepare W/O emulsions. BPA-responsive microgels

were prepared *via* inverse miniemulsion polymerization of AAm, acryloyl-CD, and

MBAA using PSB-POEG as a water-soluble emulsifier. This study also describes the

BPA-responsive behavior of the resulting BPA-responsive microgels. Fundamental

research on the preparation of microgels with molecular recognition sites comprising a

hydrophilic network will contribute significantly to the development of molecular

sensors, separation materials, and carriers for drug delivery systems.

Materials and Methods

Materials

Acrylamide (AAm), *N,N*-diethylaminoethyl methacrylate, *N,N′*-methylenebisacrylamide

(MBAA), 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044), 4,4'-

azobis(4-cyanovaleric acid) (ACVA), bisphenol A (BPA), *p*-toluenesulfonyl chloride,

p-toluenesulfonic acid monohydrate, β-cyclodextrin (CD), sodium azide, triphenyl

phosphine, and acryloyl chloride were purchased from Fujifilm Wako Pure Chemical

Corporation (Osaka, Japan). 1,3-propanesultone, 2-(2'-methoxyethoxy)ethyl

methacrylate (MEO$_2$MA), poly(ethylene glycol)dimethacrylate, and 2,2,2-

trifluoroethanol (TFE) were purchased from Tokyo Chemical Industry Co., Ltd.

(Tokyo, Japan). Oligo(ethylene glycol)methacrylate (M_w: 300; OEGMA), and 4-cyano-

4-(phenylcarbonothioylthio)pentanoic acid (CTPA) were purchased from Millipore-

Sigma (St. Louis, MO, USA). [2-(Methacryloyloxy)ethyl]dimethyl-(3-

sulfopropyl)ammonium hydroxide (SB) [31] and monoacryloyl-β-cyclodextrin

(acryloyl-CD) [13] were prepared as previously reported. The detailed synthesis is

described in the Supporting Information. OEGMA and MEO$_2$MA were purified using a

basic alumina column to remove inhibitors. All the aqueous solutions were prepared using ultrapure water (Milli-Q, 18.2 MΩ·cm). Other solvents were obtained from commercial sources and used as received.

Synthesis of PSB macroRAFT agent

SB (1.00 g, 3.58 mmol), CTPA (20.4 mg, 0.073 mmol), and ACVA (4.0 mg, 0.014 mmol) were dissolved in 2.5 mL TFE. The solution was deoxygenated by three freeze–pump–thaw cycles, followed by stirring at 90 °C for 24 h. The product was precipitated in methanol (50 mL) to remove the unreacted monomers. The isolated product was dried under vacuum to obtain PSB macroRAFT agent (yield: 0.78 g).

Synthesis of PSB-b-P(OEGMA-co-MEO$_2$MA) (PSB-POEG)

OEGMA (370 mg, 1.24 mmol), MEO$_2$MA (237 mg, 1.26 mmol), PSB macroRAFT agent (200 mg, 12.6 μmol), and ACVA (706 μg, 2.52 μmol) were dissolved in 3.9 mL of TFE. The solution was deoxygenated by bubbling with Ar gas for 30 min and stirred at 90 °C for 8 h. The product was precipitated in a 78 mL diethyl ether/hexane mixture (diethyl ether/hexane = 2/1 (v/v)) to remove the unreacted monomers. The isolated polymer product was dried under vacuum to obtain PSB-*b*-P(OEGMA-*co*-MEO$_2$MA) (PSB-POEG; 0.49 g, 61% yield).

Preparation of W/O emulsion using PSB-POEG as an emulsifier

Chloroform (9.9 mL) was added to 0.1 mL of phosphate buffered saline (PBS(–)) containing 15 mg of PSB-POEG, followed by sonication using an ultrasonic homogenizer (Sonifier SFX250, Branson Ultrasonics Corp., CT, USA) at 20% amplitude for 3 min.

***Preparation of PAAm and CD-PAAm microgels by inverse miniemulsion
polymerization***

Acryloyl-CD, AAm, MBAA, VA-044, and PSB-POEG (15 mg) were dissolved in 0.1
mL PBS(–). To 9.9 mL of chloroform, a PBS(–) solution containing all components of
the inverse miniemulsion polymerization was added, and the water-chloroform mixture
was sonicated using an ultrasonic homogenizer (Sonifier SFX250, Branson Ultrasonics
Corp., CT, USA) at 20% amplitude for 3 min to form a W/O emulsion. The
polymerization was performed at 45 °C for 5 h. After adding 10 mL of water to the
reaction mixture, the chloroform was removed under reduced pressure. The resulting
aqueous dispersion of microgels was poured into seamless cellulose tubing (Biotech CE
Dialysis Tubing, molecular cut-off: 1000 kDa, Repligen Corp., MA, USA) and dialyzed
against ultrapure water. The PAAm microgel was synthesized using a method similar to
that of the CD-PAAm microgel, without acryloyl-CD. The synthesis conditions are
summarized in Table 1.

Characterization

GPC measurements

GPC measurements were conducted using a Shimadzu Prominence HPLC system
(Shimadzu Corp., Kyoto, Japan) equipped with PFG 100 Å and PFG 1000 Å columns
(Polymer Standards Service GmbH, Germany) at 40 °C under a flow rate of 1.0
mL•min^{-1} using a refractive index detector. TFE solution containing 20 mM sodium
trifluoroacetate was used as the eluent. M_n, M_w, *and* M_w/M_n *(Đ)* were calculated using
near-monodisperse poly(methyl methacrylate) standards.

Dynamic light scattering measurements

Dynamic light scattering (DLS) measurements were conducted at 25 °C using an ELS-Z1000 spectrometer (Otsuka Electronics Co., Ltd., Osaka, Japan) equipped with a He–Ne laser (λ = 633.8 nm). The detection angle was fixed at 165°. The diameter and polydispersity index were calculated using the cumulant method, and the size distribution was obtained using Marquardt analysis.

Interfacial tension measurements

Interfacial tension was measured using the pendant drop technique using a contact angle meter (DMo-502, Kyowa Interface Science Co., Ltd., Saitama, Japan). A pendant drop of PBS(–) containing PSB-POEG was prepared in chloroform at 25 °C using an 18G teflon-coated needle. The interfacial tension was determined using the Young-Laplace equation (1).

$$\Delta\rho = \gamma \cdot (1/r_1 + 1/r_2) \tag{1}$$

where $\Delta\rho$ is the density difference, γ is the interfacial tension, and r_1 and r_2 are the radii of curvature of the surface [32].

Swelling measurements

To a 2.0 mL aqueous CD-PAAm microgel dispersion, 1.0 mL of an aqueous BPA solution (120 mg/L) was added. The diameters of the CD-PAAm microgels were measured using DLS. The swelling ratio, (V/V_0) of the CD-PAAm microgels was determined using Equation (2)

$$\text{swelling ratio} = V/V_0 = (d/d_0)^3 \qquad\qquad (2)$$

where d is the cumulant diameter of the CD-PAAm microgels in the presence of BPA at various incubation time, and d_0 is the cumulant diameter of the CD-PAAm microgels in the absence of BPA.

Results and Discussion

Synthesis of PSB-POEG

In conventional inverse miniemulsion polymerization, an amphiphilic emulsifier is used to stabilize the water-oil interface. To ensure stable dispersion in aqueous media, emulsifiers adsorbed on the surface of the resulting microgels are removed by thorough washing with a polar solvent. Our water-soluble emulsifier, consisting of an extremely hydrophilic zwitterionic polymer block and a hydrophilic/oleophilic polymer block with an oligo(ethylene glycol) side chain, facilitates the stabilization of water-chloroform interfaces in W/O emulsions and its removal from the surface of the resulting microgels through simple dialysis. In this study, we designed a water-soluble block copolymer comprising a hydrophilic PSB and a hydrophilic/oleophilic P(OEGMA-*co*-MEO$_2$MA) block as an emulsifier for inverse miniemulsion polymerization. In contrast to our previous water-soluble emulsifier, PMPC-*b*-POEGMA, PSB was employed as the hydrophilic block of a water-soluble emulsifier instead of PMPC to ensure the versatility of the zwitterionic polymer block within the water-soluble emulsifier. Copolymers of OEGMA and MEO2MA exhibit an LCST-type phase transition [33]. The LCST decreases with increasing MEO$_2$MA composition in P(OEGMA-*co*-MEO$_2$MA) because of the hydrophobic nature of MEO$_2$MA. Therefore, the copolymerization of OEGMA with MEO$_2$MA was expected to assist in the distribution

of the P(OEGMA-*co*-MEO$_2$MA) block of the water-soluble emulsifier into chloroform. In fact, we previously succeeded in the formation of W/O emulsion using PMPC-*b*-P(OEGMA-*co*-MEO$_2$MA) as a water-soluble emulsifier [30]. PSB-*b*-P(OEGMA-*co*-MEO$_2$MA) (PSB-POEG) was synthesized *via* the RAFT polymerization of SB, followed by that of OEGMA and MEO$_2$MA (Scheme 1). Figure 1a shows the ^{1}H NMR spectrum of PSB. By comparing the integration of the dithiobenzoyl protons of the RAFT agent terminus (8.1–7.5 ppm, protons i, j, and k) with the methylene protons next to the sulfonate group of PSB (3.0 ppm, proton h), the polymerization degree of PSB ($D_{p\,PSB}$) was determined to be 47. Using the resulting PSB as a macroRAFT agent, PSB-POEG was synthesized *via* RAFT copolymerization of OEGMA and MEO$_2$MA. Figure 1b shows the ^{1}H NMR spectrum of PSB-POEG. Characteristic resonances for both PSB and P(OEGMA-*co*-MEO$_2$MA) were observed, including signals attributed to the methyl protons of the dimethylammonium groups of PSB (3.3 ppm, proton e) and methoxy protons of P(OEGMA-*co*-MEO$_2$MA) (3.4 ppm, protons o and v). The molecular weight distribution of PSB shifted toward a higher molecular weight without a shoulder derived from unreacted PSB after the RAFT copolymerization of OEGMA and MEO$_2$MA using a PSB macroRAFT agent (Figure 2). By comparing the overall integration of the methylene proton of both OEGMA and MEO$_2$MA (4.2 ppm, protons k and r) with the overall integration of the 3.9–3.5 ppm region (protons d, f, m, n, s, t, and u), in which 17.6 protons of OEGMA, 6 protons of MEO$_2$MA, and 4 protons of SB are resonated, the F_{OEGMA} of P(OEGMA-*co*-MEO$_2$MA) was determined to be 0.64. The polymerization degree of P(OEGMA-*co*-MEO$_2$MA) ($D_{p\,POEG}$), obtained by integrating the methylene resonance of P(OEGMA-*co*-MEO$_2$MA) at 4.2 ppm (protons k and r) against the methylene resonance of PSB at 3.0 ppm (proton h), was determined to be 105. Table 2 summarizes results of the PSB and PSB-POEG synthesis.

W/O emulsion formation using PSB-POEG as a water-soluble emulsifier

PSB dissolves in a limited number of solvents, including water, trifluoroethanol, hexafluoroisopropanol, and ionic liquids. The solution properties of PSB are influenced by several factors, such as the concentration, molecular weight, and ionic strength [34-36]. PSB with a molecular weight greater than 20 kDa exhibits an upper critical solution temperature (UCST)-type phase transition owing to intra- and intermolecular dipole-dipole interactions. The addition of salt induces the shielding of dipole-dipole interactions, resulting in the dissolution of high molecular weight PSB in water. In this study, phosphate buffered saline (PBS (–)) with an ionic strength of 160 mM was used to dissolve and distribute the PSB block of PSB-POEG in the water phase. Figure 3 shows the effect of PSB and PSB-POEG concentrations on the interfacial tension between water and chloroform. The interfacial tension between water and chloroform slightly decreased with increasing PSB concentration. In contrast, the interfacial tension decreased drastically above 0.91 μM of PSB-POEG and remained unchanged above 7.9 μM. The drastic decrease in the interfacial tension indicates that PSB-POEG stabilizes the interface between water and chloroform by distributing the PSB and P(OEGMA-*co*-MEO$_2$MA) blocks in the water and chloroform phases, respectively. The interfacial tension and critical micelle concentration (CMC) were approximately 23 mN/m and 7.9 μM, respectively. These values are comparable to those of a previously reported PMPC-*b*-P(OEGMA-*co*-MEO$_2$MA) system (i.e., the interfacial tension and CMC were 20 mN/m and 5.6 μM, respectively) [30]. This result indicates that PSB-POEG acts as a surfactant in the water-chloroform two-phase system, exhibiting the comparable surface activity with PMPC-*b*-POEGMA, as previously reported by our group [28-30]. In addition, the effect of $D_{\text{p POEG}}$ of PSB-POEGs on CMC was evaluated in a water-chloroform two-phase system (Figure S1). As a result, CMC decreased with increasing

$D_{\text{p POEG}}$ and remained unchanged at $D_{\text{p POEG}} > 105$. Therefore, PSB-POEG having D_{p} $_{\text{PSB}}$ of 48 and $D_{\text{p POEG}}$ of 105 is suitable for preparing a W/O emulsion in a water-chloroform two-phase system. The interfacial activity measurements revealed that the combination of an extremely hydrophilic zwitterionic polymer and hydrophilic/oleophilic POEGMA is essential for designing a water-soluble emulsifier that stabilizes the water-chloroform interface.

The W/O emulsion was prepared by adding a PBS(–) solution containing PSB-POEG to chloroform, followed by sonication using a probe-type sonicator. Figure 4a shows photographs of the W/O emulsion prepared using PSB-POEG in a water-chloroform two-phase system. The milky appearance after sonication of the water-chloroform two-phase system in the presence of PSB-POEG indicates the successful formation of a W/O emulsion. On the other hand, the obvious creaming was observed after incubation for 24 h at room temperature. The size of the water droplets was evaluated using dynamic light scattering (DLS) equipped with backscatter optics. Figure 4b shows the change in the diameter of water droplets in the W/O emulsion prepared using PSB-POEG as a function of time after sonication. The diameter of the water droplets increased after sonication and reached equilibrium after 5 h with a diameter of approximately 500 nm. Although a slight increase in the size of the water droplets was observed in the initial stage, the water droplets in the W/O emulsion did not merge to induce phase separation after 5 h (Figure 4a). Despite the creaming induced by the strong buoyant force of relatively large water droplets, the PSB-POEG stabilized the water-chloroform interface and prevented the coalescence of water droplets, acting as an emulsifier. Water droplets covered with PSB-POEG emulsifiers in a W/O emulsion provide a submicron-scale reaction vessel for the preparation of smart microgels with a hydrophilic gel network.

Preparation of PAAm microgels with CD ligands (CD-PAAm microgels)

Water droplets stabilized with PSB-POEG as a water-soluble emulsifier in the W/O emulsion provide a submicron-scale reaction vessel that enables the polymerization of water-soluble monomers and cross-linkers dissolved in water droplets to obtain microgels with a hydrophilic polymer network. In this study, AAm, acryloyl-CD, and MBAA were copolymerized in water droplets in a W/O emulsion to obtain CD-PAAm microgels composed of a hydrophilic PAAm microgel network with CD ligands (Figure 5). In conventional inverse miniemulsion polymerization, an oleophilic radical initiator is typically employed. In this study, the water-soluble radical initiator VA-044 was applied to prevent chain elongation from the PSB-POEG emulsifiers with the RAFT agent terminus located in a chloroform continuous phase. After polymerization, the chloroform continuous phase was exchanged with water, followed by dialysis to remove the PSB-POEG emulsifier. Figure 6 shows the size distribution of the resulting CD-PAAm microgel in water. The water droplets containing monomers and an initiator had a monomodal size distribution with cumulant diameters of 230-350 nm (Figure 6a-c, Table 3). The diameter of the water droplets containing monomers and an initiator in the W/O emulsion was smaller than that of the water droplets in the W/O emulsion prepared using PBS(–) (i.e., approximately 500 nm). The decrease in the size of the water droplets implied that the monomers and initiator dissolved in the water droplets acted as lipophobes to support emulsification. After polymerization of monomers in water droplets, the chloroform continuous phase was exchanged with water. Figures 6d-f show the size distributions of the CD-PAAm microgels with CD contents of 0 (i.e., PAAm microgel), 5.0, and 9.8 mol%. The monomodal size distributions of the resulting CD-PAAm microgels indicate that PAAm, acryloyl-CD, and MBAA were copolymerized in the individual water droplets of the W/O emulsion without undesirable interparticle cross-linking and fusion of water droplets during

polymerization. The cumulant diameter of the CD-PAAm microgels was smaller than

that of the water droplets before polymerization (Table 3). In general, polymerization in

an appropriately formulated miniemulsion with a high monomer concentration yields

polymer particles that are similar in size to the initial droplets [37]. However, our lower

monomer concentration (2-3 times less than conventional inverse miniemulsion

polymerization) was insufficient to grow the microgel network within the entirety of the

initial droplets [38,39]. These results indicate that water-dispersible submicron-scale

CD-PAAm microgels were successfully prepared by inverse miniemulsion

polymerization using a water-soluble PSB-POEG emulsifier.

BPA-responsive behavior of CD-PAAm microgels

BPA is an important industrial chemical that is used as a monomer in the manufacture

of polycarbonate plastics and epoxy resins. We prepared BPA-responsive soft materials

containing CD ligands, such as BPA-responsive hydrogels [13], microgel valves [16],

and organic-inorganic hybrid nanoparticles [17]. These BPA-responsive soft materials

change in size in response to BPA because the CDs form sandwich-like CD-BPA-CD

complexes with BPA, resulting in an increase in the cross-linking density. The

macroscale BPA-responsive hydrogel, as previously reported by our group, required

approximately 20 h to reach equilibrium swelling after the addition of BPA. In general,

the swelling and shrinkage of hydrogels are governed by diffusion-limited transport of

polymer chains in water. Therefore, a decrease in the size of the stimuli-responsive

hydrogel allows rapid changes in its size owing to an increase in the surface area.

Therefore, rapid BPA-responsiveness can be accomplished using CD-PAAm microgels

with a size of approximately 150 nm prepared *via* inverse miniemulsion polymerization

using a water-soluble PSB-POEG emulsifier. Figure 7a shows the changes in the

swelling ratio of CD-PAAm microgels with CD contents of 0, 5, and 9.8 mol% as a

function of time after the addition of BPA. Here, a swelling ratio of less than 1.0 means that the microgel shrinks in response to BPA. The microgel without the CD ligands remained unchanged in the presence of BPA. In contrast, the CD-PAAm microgels shrank immediately after the addition of BPA and attained equilibrium swelling within 20 min. The equilibrium swelling ratio of CD-PAAm microgels in the presence of BPA decreased with increasing CD content (Figure 7b). We previously reported that a macroscale PAAm hydrogel without CD ligands adsorbed only a minute amount of BPA, resulting in no change in size upon exposure to BPA [13]. Therefore, the unchanged swelling ratio of the microgel without CD ligands (i.e., PAAm microgel) upon exposure to BPA indicates a minute amount of nonspecific adsorption of BPA. We examined the effect of BPA addition on the size of poly(diethylaminoethyl methacrylate) (PDEA) microgels with and without CD ligands prepared *via* soap-free emulsion polymerization (Figure S2). Regardless of the presence of CD ligands, the resulting PDEA microgels shrank in the presence of BPA owing to the nonspecific adsorption of BPA onto the PDEA microgel network through hydrophobic interactions (Figure S3). These results indicate that the prevention of nonspecific adsorption by hydrophilic gel network is essential for recognizing a hydrophobic target molecule. The shrinkage behavior of the CD-PAAm microgels prepared in this study can be explained by the tentative model schematically illustrated in Figure 8. When BPA was added to the CD-PAAm microgel dispersion, it diffused easily into the CD-PAAm microgel. The CD ligands in the CD-PAAm microgels formed sandwich-like CD-BPA-CD complexes with BPA, which acted as dynamic cross-links. Consequently, the cross-linking density of the CD-PAAm microgels increased, resulting in shrinkage. Moreover, the increase in the CD content of the CD-PAAm microgels resulted in an increase in the cross-linking density based on complex formation between CD and BPA. Therefore, the CD-PAAm

microgel with a CD content of 9.8 mol% exhibited greater shrinkage than that with a CD content of 5.0 mol% in response to BPA. Our previous study on the BPA-responsive macroscale hydrogel revealed that the elastic modulus increased after immersion in an aqueous BPA solution owing to the increase in the cross-linking density based on the CD-BPA-CD complex formation [13]. Although the changes in elasticity of CD-PAAm microgel could not be measured because of its submicron scale size, the elasticity of CD-PAAm microgel suggests to increase upon the addition of BPA. The rapid BPA-responsiveness of the CD-PAAm microgels compared to previously reported BPA-responsive bulk hydrogels was attributed to the large surface area of the CD-PAAm microgels. These BPA-responsive CD-PAAm microgels, prepared *via* inverse miniemulsion polymerization using a water-soluble PSB-POEG emulsifier, provide a useful platform for designing rapidly responsive soft nanomaterials for use in molecular sensors, separation substrates, and drug delivery carriers. Detailed studies on the kinetics of BPA-responsive shrinkage and changes in the mechanical properties of CD-PAAm microgels are currently under investigation.

Conclusion

This paper reports the preparation of BPA-responsive microgels composed of a hydrophilic PAAm network with CD ligands for BPA *via* inverse miniemulsion polymerization using a water-soluble PSB-POEG emulsifier. The PSB-POEG emulsifier was synthesized *via* RAFT polymerization. The resulting PSB-POEG stabilized the water-chloroform interface in the W/O emulsion by decreasing the interfacial tension, similar to PMPC-*b*-POEGMA previously reported by our group. These results demonstrate the versatility of zwitterionic blocks in designing water-soluble emulsifiers. Because the PSB block exhibits the upper critical solution temperature (UCST)-type phase transition, the water-soluble PSB-POEG emulsifier will

provide the platform to prepare UCST-type thermoresponsive soft nanomaterials. Water droplets in the W/O emulsions stabilized with PSB-POEG allowed the preparation of BPA-responsive microgels *via* inverse miniemulsion copolymerization of AAm, acryloyl-CD, and MBAA. The resulting CD-PAAm microgels exhibited rapid shrinkage in response to BPA owing to the formation of CD-BPA-CD complexes acting as dynamic cross-links, without nonspecific adsorption of BPA onto the hydrophilic microgel network. The proposed method for preparing hydrophilic microgels by inverse miniemulsion polymerization using a water-soluble emulsifier can be applied to prepare molecularly imprinted and bioconjugated microgels. In addition, the formation of molecular complexes between CD ligands and drugs, such as dapsone, doxorubicin, and curcumin, suggests that hydrophilic microgels with CD ligands can serve as platforms for designing drug carriers. Our proposed method for preparing microgels *via* inverse miniemulsion polymerization using a water-soluble emulsifier will contribute significantly to the development of molecular sensors, separation substrates, and drug delivery carriers.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Investigation: F. T. and Y. N. supervision: A. K. and T. M. writing – original draft: A. K. writing – review and editing: A. K., F. T., Y. N., and T. M.

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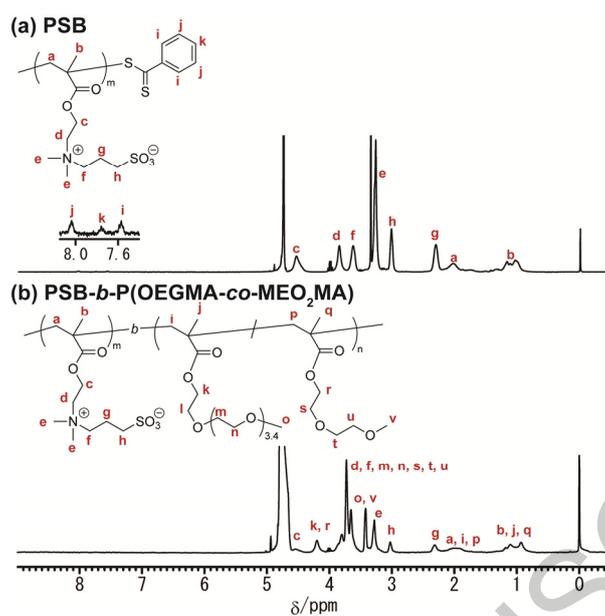
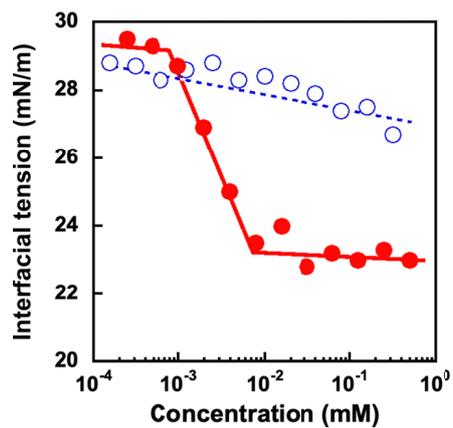**Figure 1.** ^{1}H NMR spectra of (a) PSB and (b) PSB-POEG. (400 MHz, D$_2$O)
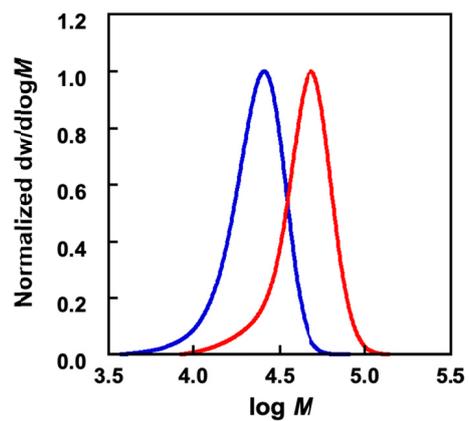
Figure 2. Molecular weight distributions of PSB (blue) and PSB-POEG (red).

Figure 3. Change in the interfacial tension of water-chloroform interface as a function of the concentration of PSB (○) and PSB-POEG (●).
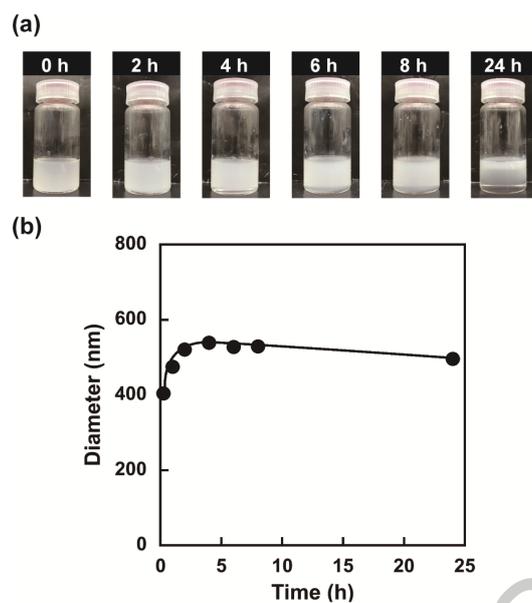
Figure 4. (a) Photographs of the sonicated PBS(–)/chloroform two-phase system containing the PSB-POEG emulsifier. (b) Changes in the diameter of water droplets stabilized with the PSB-POEG emulsifier in the W/O emulsion as a function of time after sonication.
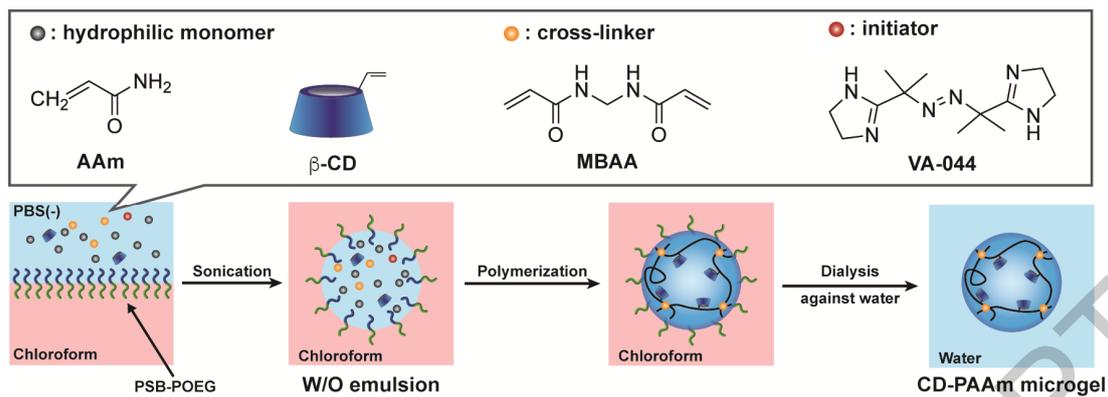
Figure 5. Schematic image of the preparation of the CD-PAAm microgel *via* inverse miniemulsion polymerization.
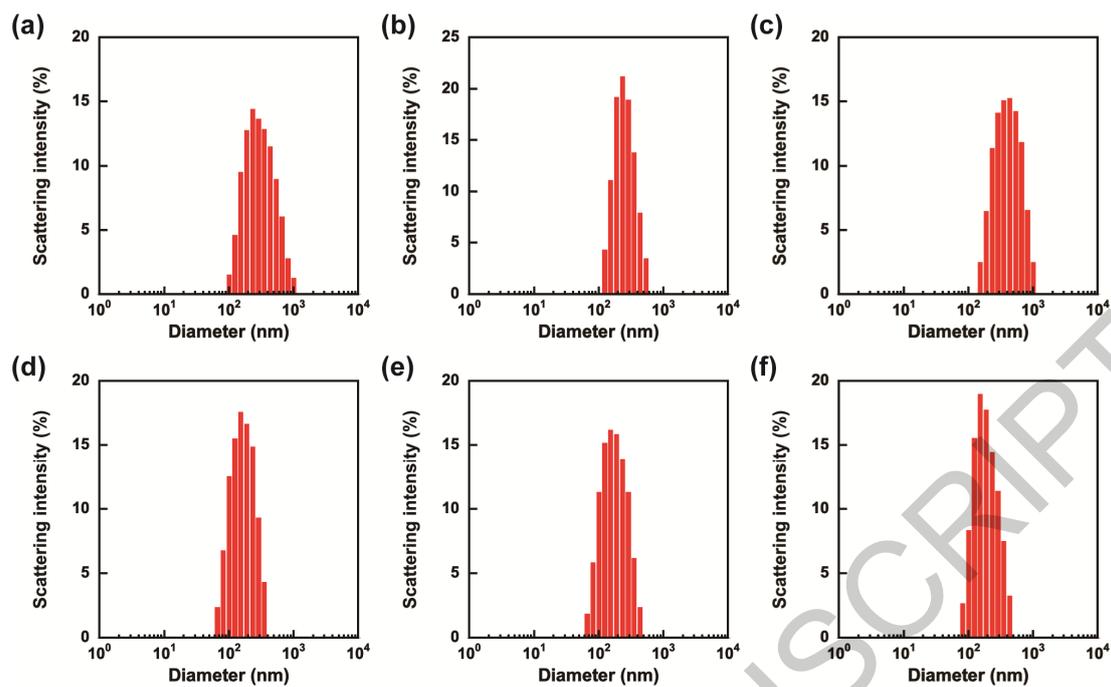
Figure 6. Size distributions of water droplets containing monomers and an initiator dispersed in a chloroform continuous phase (a-c) and CD-PAAm microgels in water (d-f). The CD contents were 0 (a, d), 5.0 (b, e), and 9.8 (c, f).
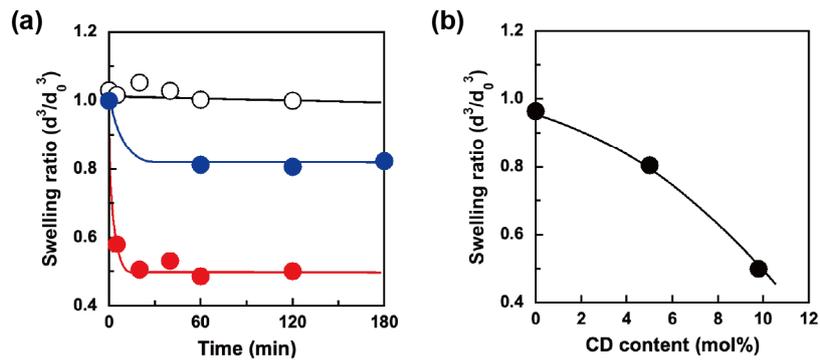
Figure 7. (a) Changes in the swelling ratios of CD-PAAm microgels with CD contents of 0 (○), 5.0 (●) and 9.8 mol% (●) as a function of time after the addition of BPA. The concentration of BPA in the microgel dispersion was 40 mg/L. (b) Effect of CD content on the equilibrium swelling ratio of PAAm and CD-PAAm microgels in the presence of BPA (40 mg/L).
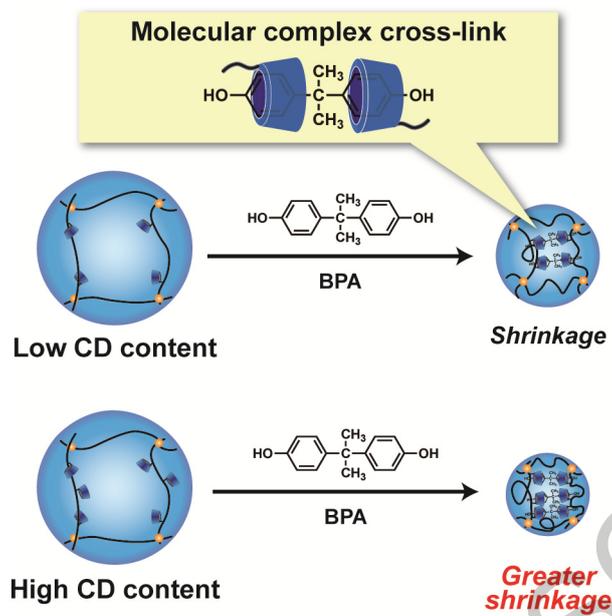
Figure 8. Schematic illustration of the BPA-responsive behavior of CD-PAAm microgels.
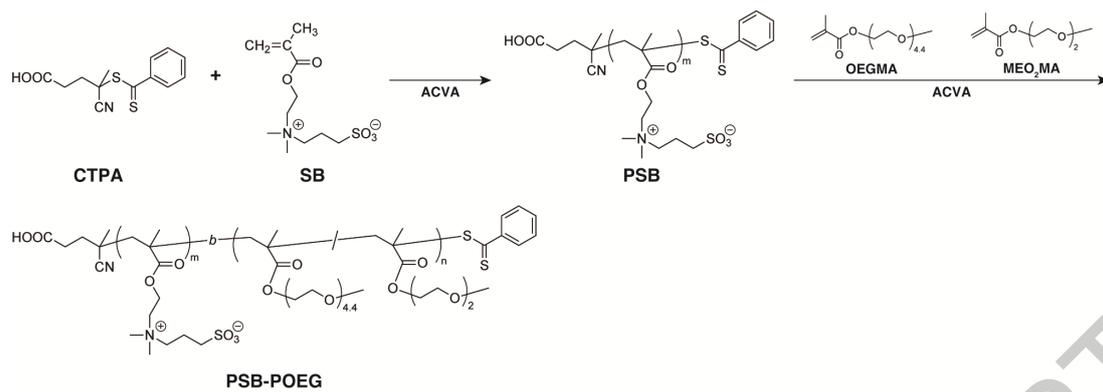
Scheme 1. Synthesis of PSB-POEG.

Table 1. Synthesis condition of CD-PAAm microgels

CD content (%)	AAm	acryloyl-CD	MBAA	VA-044
0	4.5 mg (63 µmol)	–	16 µg (0.10 µmol)	36 µg (0.11 µmol)
5.0	4.2 mg (60 µmol)	3.6 mg (3.0 µmol)	16 µg (0.10 µmol)	36 µg (0.11 µmol)
9.8	4.0 mg (57 µmol)	7.4 mg (6.2 µmol)	16 µg (0.10 µmol)	36 µg (0.11 µmol)

Table 2. Results of the synthesis of PSB macroRAFT agent and PSB-POEG.

	F_{OEGMA} [a]	D_p [a]		M_n ($\times 10^4$) [a]	M_n ($\times 10^4$) [b]	M_w ($\times 10^4$) [b]	$Đ$ [b]
		PSB	P(OEGMA-*co*-MEO$_2$MA)				
PSB macroRAFT agent	–	47	–	1.31	2.12	2.43	1.15
PSB-POEG	0.64	47	105	4.04	4.13	4.70	1.14

[a] calculated from ^{1}H NMR; [b] Calculated from GPC curves using near-monodisperse poly(methyl methacrylate) calibration standards.

Table 3. Cumulant diameter and polydispersity index of monomer solution droplets in W/O emulsion and CD-PAAm microgels.

CD content (%)	Monomer solution droplets in chloroform (Before polymerization)		Microgels in water (After polymerization)	
	Diameter (nm)	Polydispersity index	Diameter (nm)	Polydispersity index
0	261	0.207	146	0.209
5.0	230	0.112	151	0.183
9.8	346	0.186	169	0.170
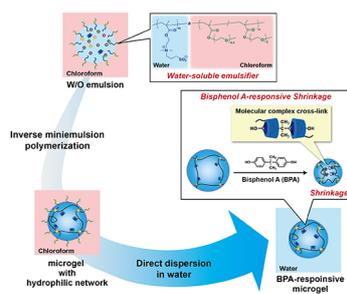
GraphicalAbstract1

Supporting Information

Bisphenol A-responsive microgel comprising hydrophilic poly(acrylamide) network

Akifumi Kawamura[a, b]*, Fumiya Tanaka[a], Yuriko Nishimura[a], and Takashi Miyata[a, b]

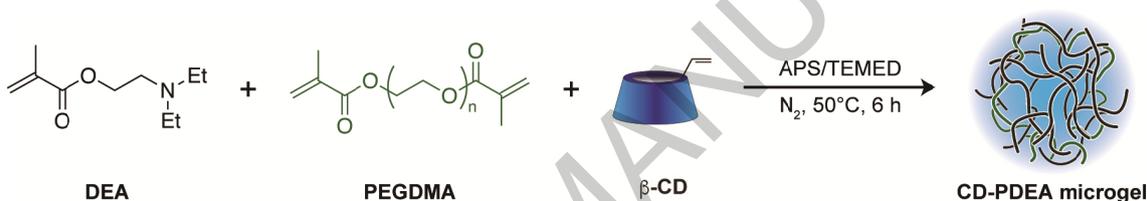[a]*Department of Chemistry and Materials Engineering, Kansai University, Suita, Osaka, Japan*

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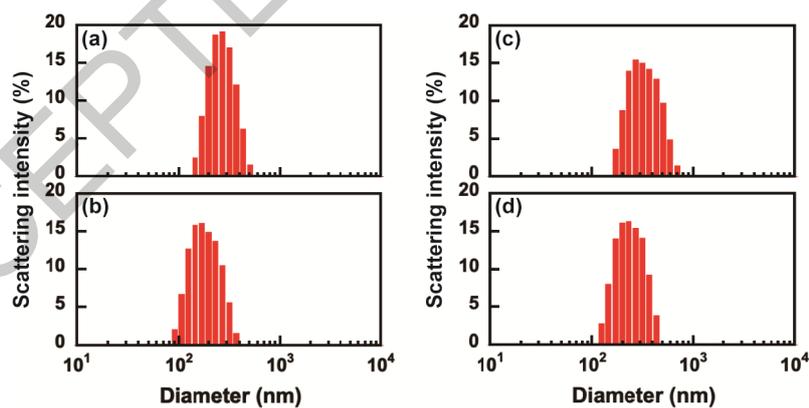
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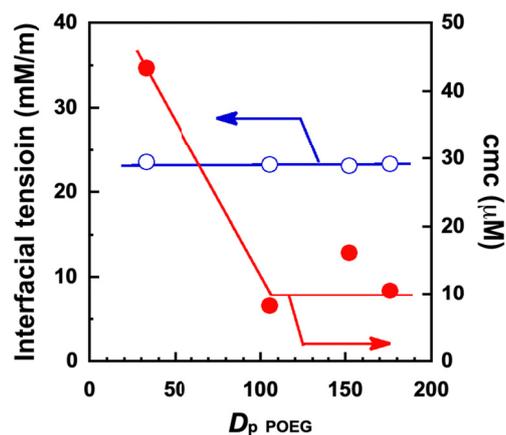
Figure S1. Effect of $D_{p\ POEG}$ on the interfacial tension (○) and CMC (●) of the water-chloroform two-phase system.

Figure S2. Synthesis of CD-PDEA microgels *via* soap-free emulsion polymerization.

Figure S3. Size distributions of PDEA microgels before (a) and after the addition of BPA (c). Size distributions of CD-PDEA microgels before (c) and after the addition of BPA (d). The BPA concentration was 20 mg/L.

Synthetic Method

Synthesis of 4-[(3-methacryloyloxypropyl)dimethylammonio]butane-1-sulfonate (SB) [1]

An amount of 10.0 mL of acetone solution containing 1,3-propanesultone (7.77 g, 0.0636 mol) was added dropwise to 15.8 mL of acetone solution containing *N,N*-dimethylaminoethyl methacrylate (5.00 g, 0.0318 mol) for 30 min and then the mixture was stirred at room temperature for 24 h. The produced white solid was collected by filtration and washed with acetone (31.6 mL). The product was then dried under vacuum to obtain SB as a white solid (8.21 g, 92% yield)

^{1}H NMR (400MHz, D$_2$O) δ ppm: 6.17 (*s*, 1H, C*H*$_2$=C–), 5.79 (*s*, 1H, C*H*$_2$=C–), 4.66 (*m*, 2H, -C(=O)O-C*H*$_2$–), 3.84 (*t*, *J* = 8 Hz, 2H, –C(=O)O-CH$_2$-C*H*$_2$-N$^+$–), 3.60 (*m*, 2H, –N$^+$-C*H*$_2$-CH$_2$SO$_3^-$), 3.23 (*s*, 6H, C*H*$_3$-N$^+$–), 2.99 (*t*, *J* = 8 Hz, 2H, –C*H*$_2$-SO$_3^-$), 2.28 (*quint*, *J* = 8 Hz, 2H, –N$^+$CH$_2$-C*H*$_2$-CH$_2$SO$_3^-$), 1.95 (*s*, 3H, CH$_2$=C-C*H*$_3$)

Synthesis of Acryloyl-modified β-cyclodextrin (acryloyl-CD)

Acryloyl-CD was synthesized via 5 step reaction by previously reported method as illustrated in Scheme S1 [2].
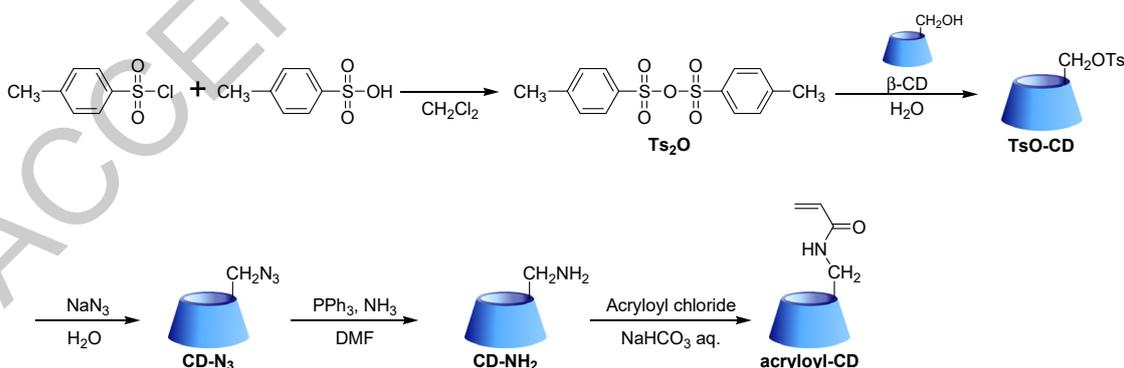
Scheme S1. Synthetic scheme of acryloyl-CD.

Synthesis of p-toluenesulfonic anhydride (Ts₂O)

p-Toluenesulfonyl chloride (40.13 g, 21 mmol) and *p*-toluenesulfonic acid monohydrate (20.05 g, 11 mmol) were dispersed in 250 mL of dichloromethane. The reaction mixture was stirred for overnight, and then the unreacted *p*-toluenesulfonyl chloride was removed by filtration. The filtrate was evaporated, and then the residue was recrystallized from isopropyl ether to yield Ts₂O as a white solid; yield, 21.9 g (61 %).

Synthesis of 6-O-monotosyl-6-deoxy-β-cyclodextrin (TsO-CD)

β-CD (27.66 g, 24.4 mmol) and Ts₂O (11.64 g, 35.7 mmol) were dispersed in 200 mL of deionized water, and then the suspension was stirred for 2 h. 120 mL of NaOH solution (2.5 M) was added to the reaction mixture, and after 10 min the unreacted Ts₂O was removed by filtration. The filtrate was neutralized by the addition of HCl, affording TsO-CD was collected after cooling at 4 °C for overnight; yield, 9.38 g (29 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.75 (d, J = 8.0 Hz, 2H, Ar–H), 7.44 (d, J = 8.0 Hz, 2H, Ar−H), 5.86–5.66 (m, 13H, O–H of CD), 4.84–4.19 (m, 14H, C–H of CD), 4.59–4.19 (m, 7H, O6–H of CD), 3.36–3.48 (m, overlaps with HOD), 2.09 (s, 3H, CH₃–Ar).

Synthesis of 6-deoxy-6-azide-β-cyclodextrin (CD-N₃)

TsO-CD (3.80 g, 2.95 mmol) and NaN₃ (2.49 g, 38.3 mmol) were dissolved in 555 mL of deionized water, and then stirred for 5 h at 80 °C, followed by pouring into acetone to precipitate the CD-N₃ as a white powder. The obtained CD-N₃ was dried in vacuo; yield, 2.63 g (77 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 5.74 (br, 14H, O–H), 4.88–4.54 (m, 14H, C–H

of CD), 3.85–3.29 (m, overlaps with HOD).

Synthesis of 6-deoxy-6-amino-β-cyclodextrin (CD-NH₂)

CD-N$_3$ (2.50 g, 2.16 mmol), triphenylphosphine (0.65 g, 2.48 mmol) were dissolved in 4.3 mL of DMF, and then the reaction mixture was stirred for overnight at room temperature. After the addition of 5.43 mL of water and 5 mL of DMF, the reaction mixture was stirred at 90°C for 2 h, and then reaction mixture was poured into acetone to precipitate CD-NH$_2$ as a white powder. The obtained CD-NH$_2$ was dried in vacuo; yield, 2.03 g (83 %).

^{1}H NMR (400 MHz, D$_2$O) δ ppm: 5.04 (s, 7H, C1–H of CD), 3.93–3.55 (m, 42H, C2, 3, 4, 5, 6–H of CD).

Synthesis of acryloyl-6-amino-6-deoxy-β-cyclodextrin (acryloyl-CD)

CD-NH$_2$ (1.01 g, 0.89 mmol) was dissolved in 15 mL of NaHCO$_3$ aq. (pH 11). Acryloyl chloride (3.6 mL, 44.2 mmol) was added to the solution of CD-NH$_2$ on ice bath. The solution was stirred for 3 h, and then the reaction mixture was poured into acetone. The precipitate was dried in vacuo to yield acryloyl-CD as a white powder; yield, 0.74 g (70 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.32–6.14 (m, 2H, CH$_2$=CH–), 5.80–5.75 (m, 1H, CH$_2$=CH–), 5.05 (s, 7H, C1–H of CD), 3.94–3.29 (m, 42H, C2, 3, 4, 5, 6–H of CD).

Synthesis of PDEA and CD-PDEA microgel via soap-free emulsion polymerization

DEA, acryloyl-CD, and PEGDMA (M_n: 330) were added to 5 mL of water and dispersed by sonication. Next, 0.1 mL of 3.2 M aqueous TEMED solution and 0.1 mL

of 0.05 M aqueous APS solution were added to 5 mL of monomer dispersion, and then, the mixture was stirred for 6 h at 50 °C at 500 rpm under an argon atmosphere. The reaction mixture was poured into seamless cellulose tubing (molecular weight cut off = 12,000-14,000) and dialyzed against water to purify the resulting microgels. The synthesis conditions are summarized in Table S1.

Table S1. Synthesis condition of PDEA and CD-PDEA microgels

	DEA	acryloyl-CD	PEGDMA
PDEA microgel	12 mg (65 μmol)	–	5.5 mg (17 μmol)
CD-PDEA microgel	12 mg (65 μmol)	4.03 mg (3.4 μmol)	5.5 mg (17 μmol)

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Bisphenol A-responsive microgel comprising hydrophilic poly(acrylamide) network

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Impact Statement

Microgels comprising polyacrylamide networks with β-cyclodextrin ligands were synthesized *via* inverse miniemulsion polymerization using water-soluble emulsifiers. Resulting microgels were easily dispersed in water and shrank upon the addition of BPA.