Spatio-Temporal Control of Synergistic Gel Disintegration Consisting of Boroxole- and Glyco-Based Polymers via Photoinduced Proton Transfer.

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Spatiotemporal Control of Synergistic Gel Disintegration Consisting of Boroxole- and Glyco-Based Polymers via Photoinduced Proton Transfer

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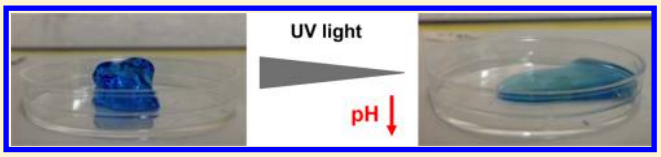
Supporting Information

ABSTRACT: We demonstrate here a local- and remote-control of gel disintegration by using photoinduced proton transfer chemistry of photoacid generator (PAG). The gels were prepared by simply mixing two polymers, poly(*N*-isopropylacrylamide-*co*-5-methacrylamido-1,2-benzoxaborole) (P(NIPAAm-*co*-MAAmBO)) and poly(3-gluconamidopropyl methacrylamide) (PGAPMA) via the synergistic interaction of benzoxaborole and diol groups. The *o*-nitrobenzaldehyde (*o*-NBA) was then loaded into the gel as a PAG. The benzoxaborole-diol interaction was successfully disintegrated upon UV irradiation due to the local pH decrease inside the gel. When the gel was irradiated to a specific gel region, the synergistic interactions were disintegrated only at the exposed region. Of special interest is that the whole material eventually transitioned from gel to sol state, as the generated protons diffused gradually toward the nonilluminated region. The ability of the proposed gel−sol transition system via photoinduced proton diffusion may be beneficial for not only prompt pH changes within the gel but also the design of predictive and programmable devices for drug delivery.



1. INTRODUCTION

Hydrogels are cross-linked three-dimensional materials which have been used in the development of drug delivery system,[1,2] wound dressings,[3,4] superabsorbents,[5] soft actuators,[6] and tissue engineering.[7,8] Recently, the development of "smart" hydrogels with stimuli-responsive properties has been actively pursued because the stimuli-responsive volume phase transitions or sol−gel phase transitions can offer many advantages over more conventional hydrogels.[9−11] Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. The physical stimuli include temperature, electric fields, solvent composition, light, pressure, sound, and magnetic fields, whereas the chemical or biochemical stimuli include pH, ions, and specific molecular recognition events. For example, Miyata and co-workers have reported the specific antigen-responsive hydrogels by grafting the antigen and the corresponding antibody to the polymer network.[12] Reversible swelling/shrinking of the gel was observed upon alternating exposure to antigen-containing and antigen-free solutions. Yoshida and co-workers have demonstrated an autonomic swelling−shrinking oscillation by integrating the chemical oscillation of the Belousov−Zhabotinsky (BZ) reaction into the hydrogel.[13] The BZ reaction is often analogically compared with the TCA cycle, which is a key metabolic process taking place in the living body. In contrast to chemical stimuli, physical stimuli such as light-responsive systems are also attractive and advantageous because they allow local and remote control.[14,15] From this regards, we have been demonstrating a new system that takes both advantages of physical and chemical stimuli. In previous study, we investigated proton-releasing reaction of "photoacid generators" (PAGs)[16−19] into pH-responsive hydrogels to demonstrate rapid proton release upon UV irradiation, resulting in spatial control of gel shrinking.[20] A predictive and programmable drug release was also demonstrated by utilizing a spatiotemporally controllable light signal and a gradually diffusible proton signal.[21] The PAGs have also been used as a trigger to form/collapse gel structures. Javvaji et al. prepared an alginate

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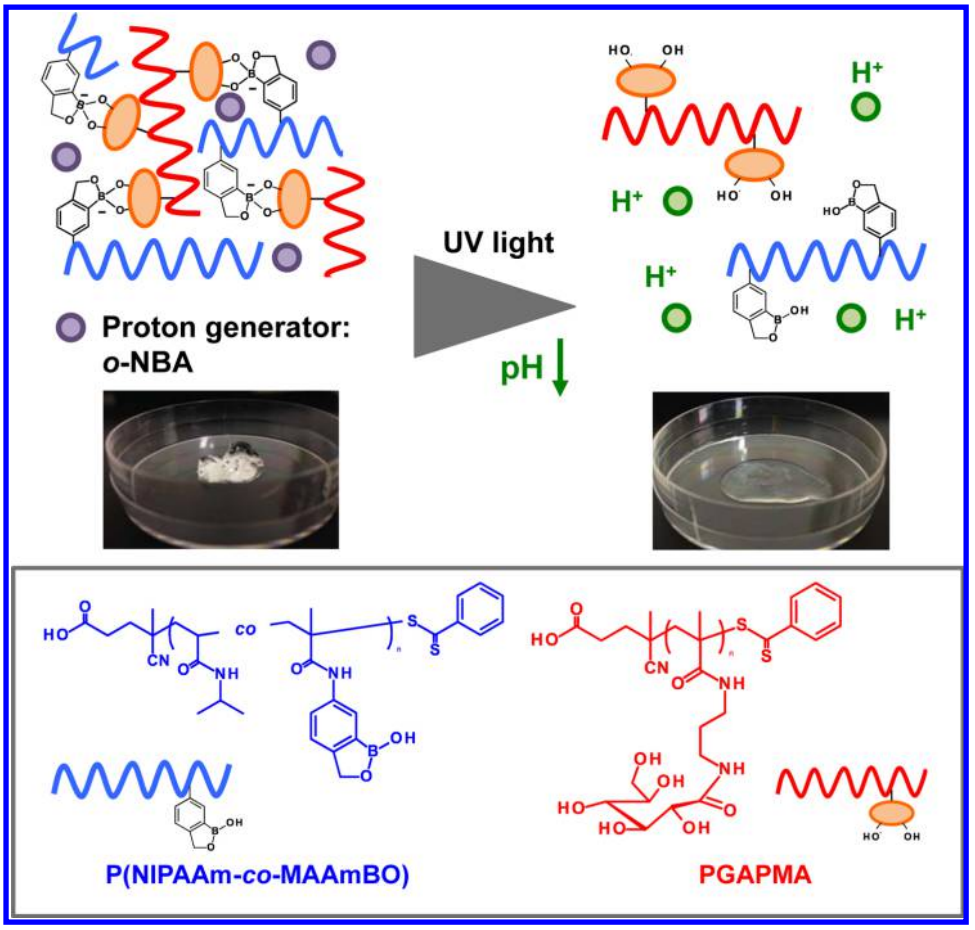

Figure 1. Design concept for the local- and remote-control gel disintegration via photoinduced proton transfer chemistry.

solution containing $CaCO_3$ and PAG. After UV irradiation, the generated Ca^{2+} formed alginate gel networks, that is, "egg-box" junctions.[22] White et al. prepared gels that were composed of catechol-based polymers and iron ions via the coordinative bond.[23] Using the PAG of diphenyliodonium chloride, the gel structures collapsed due to the decrease of solution pH by UV irradiation. In these reports, however, addition of metal ions has been required for the formation of the gel structures.

Recently, we have successfully prepared synergistic gels by simply mixing two types of copolymers without adding metal ions.[24] The copolymers were poly(*N*-isopropylacrylamide-*co*-5-methacrylamido-1,2-benzoxaborole) (P(NIPAAm-*co*-MAAmBO)) and glycopolymers that were synthesized by reversible addition−fragmentation chain transfer (RAFT) polymerization. We chose glucose-derived or galactose-based glycopolymers to form the gel structures as a counter pair because glycopolymers are known as biocompatible materials. The NIPAAm copolymers have been used because dehydrated PNIPAAm chain leads to high stability of gel formation due to the hydrophobic interaction in PBS even in the presence of free glucose. The relationship between the various structures/compositions of glycopolymers (linear polymers, branched polymers, and nanogels) and their roles as gene delivery have been investigated.[25−29] On the other hand, boronic acids and their esters have been applied in a wide range of fields such as stereocontrolled organic synthesis and medical diagnosis/treatment for their reversible interaction with *cis*-diol-containing compounds.[30] In biomaterials field, the interaction of phenylboronic acid (PBA) with glucose has much attention as a trigger for insulin release systems.[31−36] Recently, Hall and co-workers have reported that benzoxaborole group showed a higher affinity than PBA with sugars in pH 7.4 PBS.[37] Benzoxaborole receptors have also been applied in the selective binding of Thomsen-Friedenreich (TF)-antigen disaccharide, delivery of a protein toxin in the cytosol, neutralization of human immunodeficiency virus (HIV), and antitrypanosomal agent.[38−42] Therefore, the synergistic gels consisting of the P(NIPAAm-*co*-MAAmBO)s and glycopolymers are expected to be an excellent biomaterial for various applications.

In this paper, PAG was loaded into the synergistic mixed gel of P(NIPAAm-*co*-MAAmBO) and poly(3-gluconamidopropyl methacrylamide) (PGAPMA) since the interaction between benzoxaborole and sugar moiety was strongly affected by the solution pH (Figure 1). Temperature and pH-responsive gel formation was examined under various conditions. Spatiotemporal gel disintegration was demonstrated via photoinduced proton transfer reaction within the gel.

2. EXPERIMENTAL SECTION

2.1. Materials. The *N*-isopropylacrylamide (NIPAAm) was kindly supplied from Kohjin Co. Ltd. (Japan) and was purified by recrystallization from benzene and hexane. The 5-methacrylamido-1,2-benzoxaborole (MAAmBO) was synthesized and purified according to the protocol given in ref 24. The 1-pyrenemethyl methacrylate (PyMA) was purified by recrystallization from ethanol. The 3-gluconamidopropyl methacrylamide (GAPMA) was synthesized and purified according to the protocol given in refs 25−27. The 4-

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cyanopentanoic acid dithiobenzoate (CTP) was obtained from Wako Pure Chemical Industries (Japan) and used as received. *O*-Nitrobenzaldehyde (*o*-NBA) was purchased from Tokyo Chemical Industry Co. Ltd. (Japan) and used as received. All other chemicals and solvents were used as received. Distilled water used in this study was purified with a Millipore Milli-Q system.

2.2. Synthesis of P(NIPAAm-*co*-MAAmBO) and PGAPMA. The reversible addition−fragmentation chain transfer (RAFT) polymerization was employed to synthesize the polymers with a narrow distribution of molecular weight. The polymerization methods of P(NIPAAm-*co*-MAAmBO) and PGAPMA were described in the Supporting Information (see Scheme S1). Briefly, NIPAAm (986 mg, 8.72 mmol), MAAmBO (210 mg, 9.69×10^{-1} mmol), CTP (6.76 mg, 2.42×10^{-2} mmol), and 4,4′-azobis-4-cyanovaleric acid (ACVA; 2.67 mg, 9.54×10^{-3} mmol; $[NIPAAm]_0/[MAAmBO]_0/[CTP]_0/[ACVA]_0$ = 360/40/1/0.4) were dissolved in 5 mL of *N*,*N*-dimethylformamide (DMF). After degassing with nitrogen gas for 30 min, the mixture was allowed to polymerize for 24 h at 70 °C. The resulting P(NIPAAm-*co*-MAAmBO) was purified by dialysis against ethanol and acetone and was dried under reduced pressure. For PGAPMA, GAPMA (1.98 g, 6.19 mmol), CTP (4.32 mg, 1.55×10^{-2} mmol), and ACVA (1.71 mg, 6.10×10^{-3} mmol; $[GAPMA]_0/[CTP]_0/[ACVA]_0$ = 400/1/0.4) were dissolved in a mixture solution of methanol (2 mL) and Milli-Q water (8 mL). After degassing with nitrogen gas for 30 min, the mixture was allowed to polymerize for 24 h at 70 °C. The resulting PGAPMA was purified by dialysis in Milli-Q water and was collected by freeze-drying.

2.3. Preparation of Gel Consisting of P(NIPAAm-*co*-MAAmBO) and PGAPMA. Gels were prepared by simple mixing the solution of P(NIPAAm-*co*-MAAmBO) and PGAPMA. P(NIPAAm-*co*-MAAmBO) and PGAPMA were completely dissolved in 200 μL of NaOH solution (pH 10, 5 wt %) and 100 μL of NaOH solution (pH 10, 10 wt %), respectively, at 4 °C. A drop (10 μL) of 2 M NaOH was added to the P(NIPAAm-*co*-MAAmBO) solution. Then, the P(NIPAAm-*co*-MAAmBO) solution was mixed with the PGAPMA solution to form gel structure. After the gelation, the gel was stored in 5 mL of 0.01 M NaOH solution for at least 3 h. The prepared gels were immersed in a solution (0.01 M NaOH) containing 20 mM *o*-NBA and bromocresol green for 3 h at 20 °C. The immersed gels were washed by Milli-Q water before the UV irradiation.

2.4. Characterizations. ^{1}H NMR spectra of copolymers were taken with a JNM-GSX300 spectrometer operating at 300 MHz (JEOL, Tokyo, Japan) to confirm successful synthesis and determine the chemical composition of the synthesized copolymers. Molecular weight (M_n) and polydispersity (M_w/M_n) of the synthesized copolymers were determined by gel permeation chromatography (GPC) with TOSOH TSK-GEL a-2500 and a-4000 using RI-2031 refractive index detector (JASCO International Co., Ltd., Tokyo, Japan) and Waters Ultrahydrogel linear WAT011545 columns and Viscotek model 270 dual detector for copolymers of PNIPAAm (DMF including 10 mM LiBr, 1 mL/min, 40 °C) and PGAPMA (0.50 M sodium acetate/0.50 M acetic acid buffer, 1.0 mL/min), respectively. Transmittance of a solution at 500 nm was continuously recorded at a heating rate of 1.0 °C/min by a UV−vis spectrometer V-550 (JASCO International Co., Ltd., Tokyo, Japan). Synthesized copolymers were dissolved in aqueous solution at the given concentration. Dynamic light scattering (DLS) was performed with a DLS-8000 series (Otsuka Electronics Co., Ltd., Osaka, Japan) using a light scattering apparatus equipped with He−Ne laser and temperature controller. All samples were kept at given temperatures to reach the equilibrium prior to the measurements. We obtained the diameter data using the Marquardt method (cumulative number = 80). For UV irradiation, the super high-pressure Hg lamp (250 SXUI2150HQ, Ushio, Tokyo, Japan) was used (365 nm, 5.0 mW/cm^2) with a heat-absorbing filter (HA-50 Hoya, Tokyo, Japan).

3. RESULTS AND DISCUSSION

3.1. Synthesis of Boroxole- and Glyco-Based Polymers. Poly(*N*-isopropylacrylamide-*co*-5-methacrylamido-1,2-benzoxaborole) (P(NIPAAm-*co*-MAAmBO)) and poly(3-gluconamidopropyl methacrylamide) (PGAPMA) were synthesized by the reversible addition−fragmentation chain transfer (RAFT) polymerization as shown in (Scheme S1(A), Supporting Information). The M_n and M_w/M_n of the PGAPMA were determined by GPC to be 23800 g/mol and 1.30, respectively. For P(NIPAAm-*co*-MAAmBO) and P(NIPAAm-*co*-MAAmBO-*co*-1-pyrenemethyl methacrylate (PyMA)) (Scheme S2, Supporting Information), however, the determinations of M_n and M_w/M_n by our GPC system were difficult due to the strong interaction of MAAmBO residues with the column. Therefore, we alternatively used only PyMA as a comonomer instead of MAAmBO for the GPC measurement. P(NIPAAm-*co*-PyMA) was synthesized under the same condition as P(NIPAAm-*co*-MAAmBO). The resulting M_n and M_w/M_n of P(NIPAAm-*co*-PyMA) were 10800 g/mol and M_w/M_n 1.29, respectively. MAAmBO content in the P(NIPAAm-*co*-MAAmBO) was determined to be 12 mol % by ^{1}H NMR (Figure S1, Supporting Information).

3.2. Synergistic Interactions between Benzoboroxole And Hydroxyl Groups. We have previously demonstrated that mixing of P(NIPAAm-*co*-MAAmBO) and PGAPMA spontaneously form cross-linked hydrogel structures due to the interaction of the MAAmBO with hydroxyl groups of the sugars.[24] Although other conventional *cis*-diols such as poly(vinyl alcohol) (PVA) can also interact with boronic acid,[30,43] PGAPMA has many advantages over conventional PVA; for example, it can be copolymerized easily with other functional monomers to form multifunctional materials with unique biological properties.[25−29] Figure 2 shows the time-dependent changes in transmittance of the PBS solution containing both P(NIPAAm-*co*-MAAmBO) and PGAPMA at 10 °C (pH 7.4). The transmittance gradually decreased with time because the complexation reaction occurred under this condition. DLS studies were also performed and the obtained hydrodynamic diameters are plotted in the same graph. Interestingly, nanoaggregates (nanogels) with narrow PDI were observed. Both diameter and PDI continuously increased with time; that is, 58 ± 13 (PDI 0.085), 69 ± 36 (0.12), 83 ± 17 (0.063), 109 ± 29 (0.077), 153 ± 42 (0.13), 197 ± 65 (0.16), 243 ± 56 (0.079), 295 ± 79 nm (0.084), and 414 ± 201 nm (0.29, multiple peaks) after 5, 10, 15, 30, 45, 60, 90, 120, and 180 min, respectively. In our previous study, nanogels with spherical morphology were formed by dialyzing the formed bulk gel against at pH 12 solution in the presence of free-glucose and stirring in at 4 °C for several days.[24] Therefore, the presented protocol in this study can provide new options for facile preparation of nanogels because this methods is very

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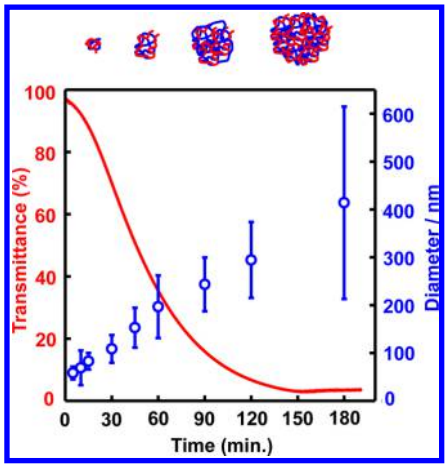

Figure 2. Time dependent changes in transmittance and diameter of the pH 7.4 PBS solution containing P(NIPAAm-*co*-MAAmBO) and PGAPMA (total concentration: 0.2 wt %) at 10 °C.

simple and enables to customize the size of aggregate by a simple mixing of two polymers.

3.3. Temperature-Responsive Behavior of the Synergistic Gel. Figure 3 shows the temperature-responsive behaviors of the resulting nanogels. P(NIPAAm-*co*-MAAmBO) and PGAPMA were mixed at different weight ratios and the measurement was started after the copolymers were completely mixed. The transmittance of the mixture solution at mixing ratio of 1/1 was decreased as temperature increased. This behavior corresponds very well to the transmittance change of the P(NIPAAm-*co*-MAAmBO) solution as shown in Figure S2 (Supporting Information). The transmittance change, on the other hand, became more broad and shifted to higher temperature when mixing ratio of P(NIPAAm-*co*-MAAmBO) and PGAPMA was 1/5. This result is most likely due to the incorporation of hydrophilic PGAPMA. To elucidate this hydrophilic shift, pyrene-labeled polymer, P(NIPAAm-*co*-MAAmBO-*co*-PyMA) has also synthesized because pyrene is a prominent standard probe by taking the intensity ratio I_1/I_3 of the first and third vibronic emission bands.[44−47] Large ratios reflect a hydrophilic and polar environment, whereas small values indicate a nonpolar, hydrophobic surrounding of the pyrene molecules. Winnik et al., for example, have investigated the conformational changes of temperature responsive polymers using pyrene-labled PNIPAAm.[48,49] As expected, the pyrene senses a more hydrophilic environment when more PGAPMA was added in P(NIPAAm-*co*-MAAmBO-*co*-PyMA) solution (Figure S3, Supporting Information).

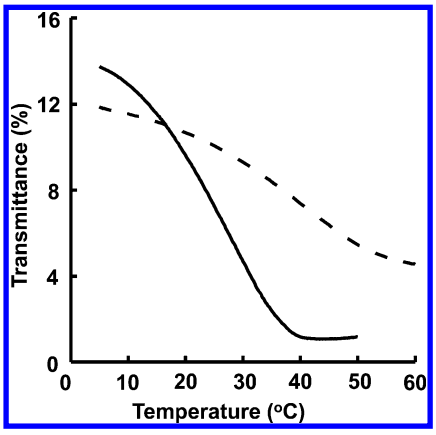

Figure 3. Transmittance changes of the mixture of P(NIPAAm-*co*-MAAmBO) and PGAPMA solutions (pH 7.4 PBS, total concentration: 0.2 wt %) as a function of temperature. The measurement was started after the copolymers were completely mixed. The mixing ratios of P(NIPAAm-*co*-MAAmBO)/PGAPMA are 1/1 (solid line) and 1/5 (dash line), respectively.

3.4. Photoinduced pH Jump Reaction. We have previously demonstrated that an interaction between P(NIPAAm-*co*-MAAmBO) and PGAPMA was strongly affected by the pH, temperature, or glucose concentration.[24] In this study, a local- and remote-control of the benzoxaborole-diol interaction was especially investigated by using photoinduced proton transfer chemistry of PAG. We selected *o*-NBA (Scheme S1(B)) as a PAG because it showed the highest proton-releasing efficiency among their derivatives we have studied (the proton releasing efficiencies were 1.0×10^{-4}, 2.0×10^{-3}, 2.0×10^{-2}, 5.9×10^{-1}, and 9.5% for *m*-NBA, 4-hydroxy-*m*-NBA, 5-hydroxy-*o*-NBA, *p*-NBA, and *o*-NBA, respectively).[21] First, effect of pH on the LCST of P(NIPAAm-*co*-MAAmBO) was examined. Figure S4 (Supporting Information) shows the temperature-dependent transmittance changes of P(NIPAAm-*co*-MAAmBO) at pH 2 and 12. The sharp decrease of the transmittance was observed around 15 °C in pH 2 solution, while no or little change was observed in pH 12. This is because MAAmBO is negatively charged above the pK_a (7−8). Next, we examined the effect of *o*-NBA on the LCST of P(NIPAAm-*co*-MAAmBO). P(NIPAAm-*co*-MAAmBO) and *o*-NBA were dissolved in pH 8.4 solution (above the pK_a). Figure 4 shows the transmittance changes of P(NIPAAm-*co*-MAAmBO) before and after UV irradiation. Only slight decrease of transmittance was observed at pH 8.4 (before UV irradiation) due to the repulsion force between negatively charged MAAmBO. By UV irradiation for 5 min, on the other hand, the solution pH was found to decrease to 3.7 (below the pK_a) and thus the sharp decrease of the transmittance was observed around 15 °C. These data suggested that *o*-NBA can be used to control the interaction of P(NIPAAm-*co*-MAAmBO) and PGAPMA by UV irradiation. Therefore, next we demonstrate the local and remote control of the benzoxaborole-diol interaction by UV irradiation.

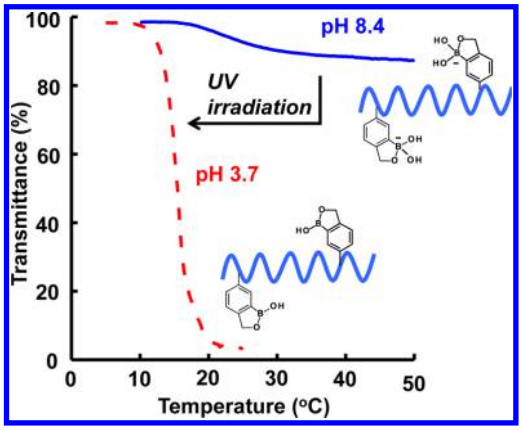

Figure 4. Transmittance changes of P(NIPAAm-*co*-MAAmBO) solution (0.1 wt %, pH 8.4) in the presence of 10 mM NBA as a function of temperature before (solid blue) and after (dash red) UV irradiation for 5 min.

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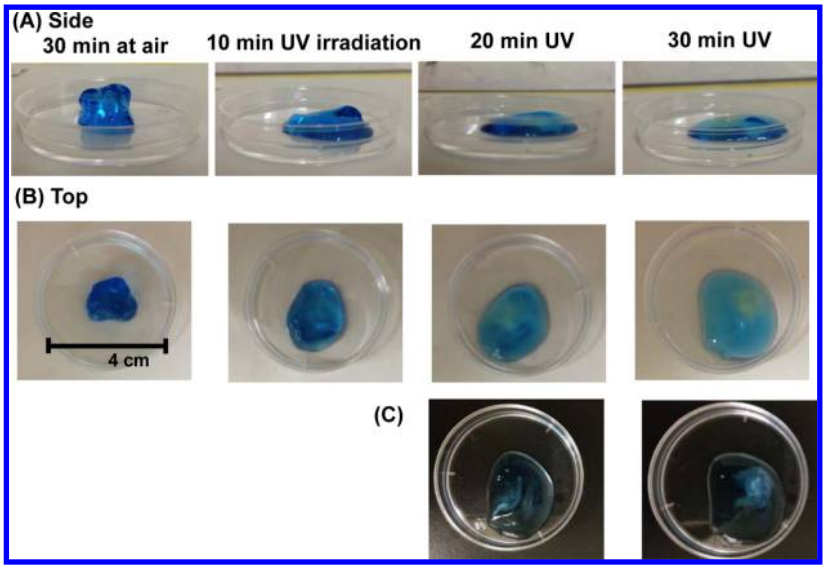

Figure 5. Photographs of the hydrogels consisting of P(NIPAAm-*co*-MAAmBO) and PGAPMA after UV irradiation. (A) side views and (B) top views. The gels were prepared by simply mixing P(NIPAAm-*co*-MAAmBO) and PGAPMA in pH 8 solution at 20 °C. The *o*-NBA was then loaded into the gel (20 mM). To visualize the pH profile inside the gels, bromocresol green was also loaded into the gel as indicator, whose color varies with the pH level (yellow < pH 3.8, blue > pH 5.4). To visualize the turbidity, images were also taken with black paper on the back (C).

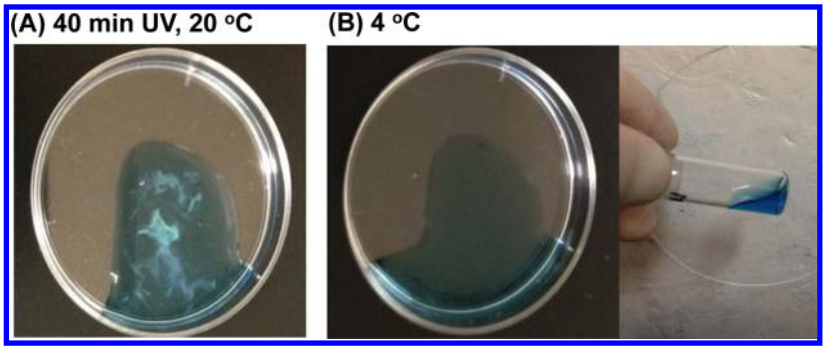

Figure 6. Photographs of the hydrogels consisting of P(NIPAAm-*co*-MAAmBO) and PGAPMA. The photographs were taken 40 min after UV irradiation at (A) 20 and (B) 4 °C.

3.5. Remote Control of Hydrogel Disintegration by UV Irradiation. First, the gels were prepared by simply mixing P(NIPAAm-*co*-MAAmBO) and PGAPMA in pH 8 solution at 20 °C. The *o*-NBA was then loaded into the gel (20 mM). To visualize the pH profile inside the gels, we used an indictor, bromocresol green, whose color varies with the pH level (yellow < pH 3.8, blue > pH 5.4).[20] The gel maintained its shape in air (under Vis-light for 30 min), as seen in the left images of Figure 5A,B. The gel was locally irradiated by UV at the center of the top surface of gel for 30 min. After UV irradiation, the gel shape started to collapse because the synergistic interactions between P(NIPAAm-*co*-MAAmBO) and PGAPMA were disintegrated. Although a local shape change was hardly observed because the gel was brittle, the color of the irradiated area started to change from blue to yellow, indicating local pH decrease. Under this pH condition, P(NIPAAm-*co*-MAAmBO) and PGAPMA cannot form the synergistic interactions. Of special interest is that the whole material eventually transitioned from gel to sol state, as the generated protons diffused gradually toward the nonilluminated region. This observation is consistent with our previous reports on the time-dependent profile of the proton concentrations inside the hydrogels as well as simulations of proton diffusion kinetics.[20,21] The local pH decrease can be also confirmed from images in Figure 5C. The regions in which the solution is turbid correspond to regions having yellow color in Figure 5B. This turbidity is due to the phase transition of P(NIPAAm-*co*-MAAmBO) at lower pH than its pK_a value (see Figure 4). Therefore, the turbidity disappeared when temperature was decreased to 4 °C (below the LCST; Figure 6). We did not observe the effects of UV irradiation itself on the gel structure in the absence of *o*-NBA. To provide insight into the mechanical properties of the gels, rheological characterization was also carried out. Figure S5 in the Supporting Information shows the frequency dependencies of the elastic modulus G' and viscous modulus G'' for the gels formed by P(NIPAAm-*co*-MAAmBO) and PGAPMA. Before UV irradiation, the G' is always higher than G'' over the whole frequency range investigated, indicating a solid state. Although typical crossover of the storage modulus and loss modulus ($G' < G''$) was not clearly observed after UV irradiation, these values became much lower and the frequency-dependency was more significant, indicating a liquid state. These results indicate that the spatiotemporal control of synergistic gel formation consisting of boroxole- and glyco-based polymers was successfully achieved using photoinduced proton transfer chemistry. Although further understandings of the effects of temperature, pH, and polymer concentrations on the dynamic gel−sol

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transition processes are required, the proposed system may prove promising for programmable, controlled delivery applications with applications of multistep stimuli.

4. CONCLUSION

In summary, the photoacid generator-loaded smart hydrogels consisting of P(NIPAAm-*co*-MAAmBO) and PGAPMA were prepared by the reversible benzoxaborole-diol interactions. Spatiotemporal gel−sol transition was achieved by UV irradiation via photoinduced proton transfer chemistry. UV irradiation caused the disintegration of the benzoxaborole-diol interactions in the exposed region due to the pH decrease. The generated protons were found to diffuse throughout the gel, resulting complete disintegration of the gel eventually. Our approach would become an attractive candidate for spatiotemporal control of pH-dependent gel formations.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of P(NIPAAm-*co*-MAAmBO), PGAPMA, P(NIPAAm-*co*-MAAmBO-*co*-PyMA), and nanogels. Fluorescent intensities and rheological properties of mixture of the copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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