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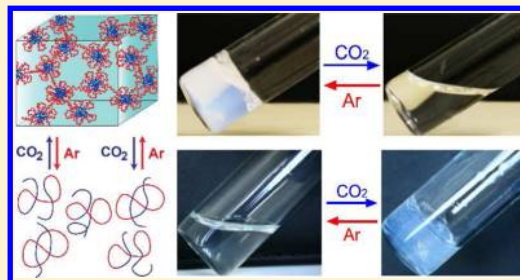
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Two-Way CO₂-Switchable Triblock Copolymer HydrogelsDehui Han,[†] Olivier Boissiere,[‡] Surjith Kumar,[†] Xia Tong,[†] Luc Tremblay,[‡] and Yue Zhao^{*,†}[†]Département de chimie and [‡]Département de médecine nucléaire et de radiobiologie and Centre d'imagerie moléculaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, Canada J1K 2R1

S Supporting Information

ABSTRACT: CO₂-responsive ABA triblock copolymer hydrogels are described. Through rational block copolymer design, these hydrogels could undergo either CO₂-induced gel-to-sol or the reverse sol-to-gel transition. While the middle block B is water-soluble, the solubility of the two end blocks A can be switched by CO₂. For the gel-to-sol transition, the A block was made to have a lower critical solution temperature (LCST) that can increase upon CO₂ bubbling, while for the sol-to-gel transition, the A block was designed to have a LCST that decreases with CO₂. Repeated cycles of hydrogel formation and dissociation could be achieved by simply passing CO₂ and an inert gas alternately through the solution, at a constant temperature and without adding acids and bases for pH change. Moreover, CO₂-induced release of an encapsulated protein was demonstrated.



■ INTRODUCTION

Stimuli-responsive hydrogels are materials of considerable interest that have been explored as carriers for controlled drug release, scaffolds for tissue engineering, and actuators as well as sensors in biomedical devices.^{1–4} As compared to chemically cross-linked hydrogels, those prepared from triblock copolymers have the distinct feature of being able to undergo reversible sol–gel transition in response to stimuli.^{5–22} With ABA-type triblock copolymers, to achieve this switchability, while the middle B block is a water-soluble polymer and has a large molecular weight, the two end blocks A are chosen to be a polymer whose water solubility is sensitive to stimuli such as change in temperature or pH.^{9–20} Generally, this type of hydrogel comprises a network of interconnected “flower” micelles that are self-assembled by the ABA triblock copolymer when the A blocks become insoluble (or dehydrated) in water. If the A block is a thermosensitive polymer displaying a lower critical solution temperature (LCST), the gel state is observed when the solution temperature is above the LCST; in case the A block is a weak polyelectrolyte, the gelation occurs at a certain pH depending on the pK_a of the polybase or polyacid. Temperature and pH changes are by far the two most explored stimuli.^{9–20} Light-responsive ABA triblock copolymer hydrogel was also reported by using a photothermal effect.²³ In this paper, we describe the use of carbon dioxide (CO₂) as an efficient trigger to control either the gel-to-sol or the opposite sol-to-gel transition based on rational triblock copolymer designs. As an example of possible applications, CO₂-triggered release of a protein was also investigated.

■ EXPERIMENTAL SECTION

Random copolymers containing CO₂-responsive acid comonomer units were synthesized using reversible addition–fragmentation chain transfer (RAFT) polymerization. ABA triblock copolymers were

prepared by means of atom transfer radical polymerization (ATRP) using Br-PEO-Br macroinitiator (20 000 g/mol). Details on the syntheses and characterizations are given in the Supporting Information.

■ RESULTS AND DISCUSSION

Block Copolymer Design. Figure 1 is a schematic illustration of our two-way CO₂-controllable hydrogels and the ABA triblock copolymer design making use of CO₂-switchable LCST. On the one hand, we could design ABA triblock copolymer of which the A block has LCST that can increase upon bubbling CO₂ in aqueous solution. As shown in our previous study,²⁴ this can be achieved by introducing a number of comonomer units containing tertiary amine groups in the structure of a thermosensitive polymer. With CO₂ in water, tertiary amine groups can be protonated,^{24–32} and the increased polarity can result in an increased LCST for the A block from LCST-1 to LCST-2 via a comonomer effect.^{24,33,34} With such an ABA triblock copolymer, hydrogel can be formed at T_{solution} in the absence of CO₂ because the A block is insoluble. Upon CO₂ bubbling, the hydrogel should be dissociated since the A block becomes soluble as a result of the increase in LCST. Upon removal of CO₂ by passing an inert gas (e.g., argon) through the solution, gelation should reappear as the initial LCST is recovered. This is CO₂-induced gel-to-sol transition. On the other hand, following the same principle, if the LCST of the A block can be decreased upon CO₂ bubbling, from LCST-1 to LCST-3, the opposite switching, i.e., CO₂-induced gelation, could be realized at T'_{solution} since the initially soluble A block becomes insoluble in

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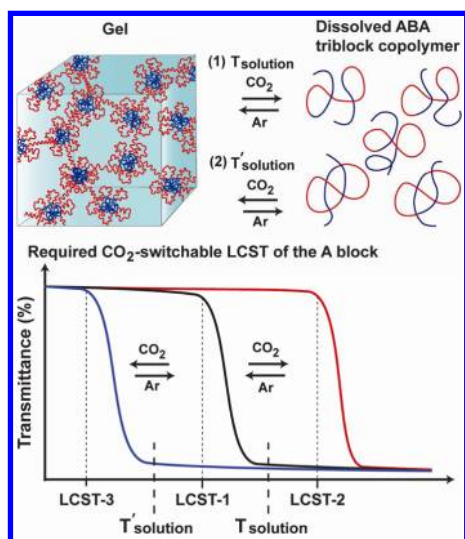


Figure 1. Schematic illustration of CO₂-induced gel-to-sol and reverse sol-to-gel transition of hydrogels and the ABA triblock copolymer design making use of CO₂-switchable LCST.

the presence of CO₂. This is CO₂-induced sol-to-gel transition. We also demonstrate such reversibly switchable hydrogel and

show that the required ABA triblock copolymer can be designed by using a thermosensitive A block containing weak acid comonomer units of which the protonation under CO₂ in water reduces the degree of ionization and, consequently, lowers the LCST. A reaction scheme for the protonation of tertiary amine and carboxylic acid comonomer units in LCST polymers upon CO₂ bubbling in water is shown in the Supporting Information (Figure S3). Although the reversible change between dissolved and gelled state can be achieved thermally by switching the solution temperature above and below the LCST, or by adjusting the solution pH, the switching using CO₂ and an inert gas at constant temperature is particularly appealing. Aside from valorizing CO₂ in polymer and materials chemistry, reversible gelation and dissociation cycles can be accomplished without repeated heating and cooling or without adding repeatedly acids or bases required for pH changes. In the latter case, using gases allows one to avoid the salt accumulation that can contaminate materials and deteriorate the switching performance. Regardless of the number of repeated cycles, the polymer solution returns to the initial state after removal of CO₂.

CO₂-Induced Gel-to-Sol Transition. Figure 2 shows a set of results for ABA triblock copolymer hydrogel that can undergo CO₂-induced gel-to-sol transition. The block copoly-

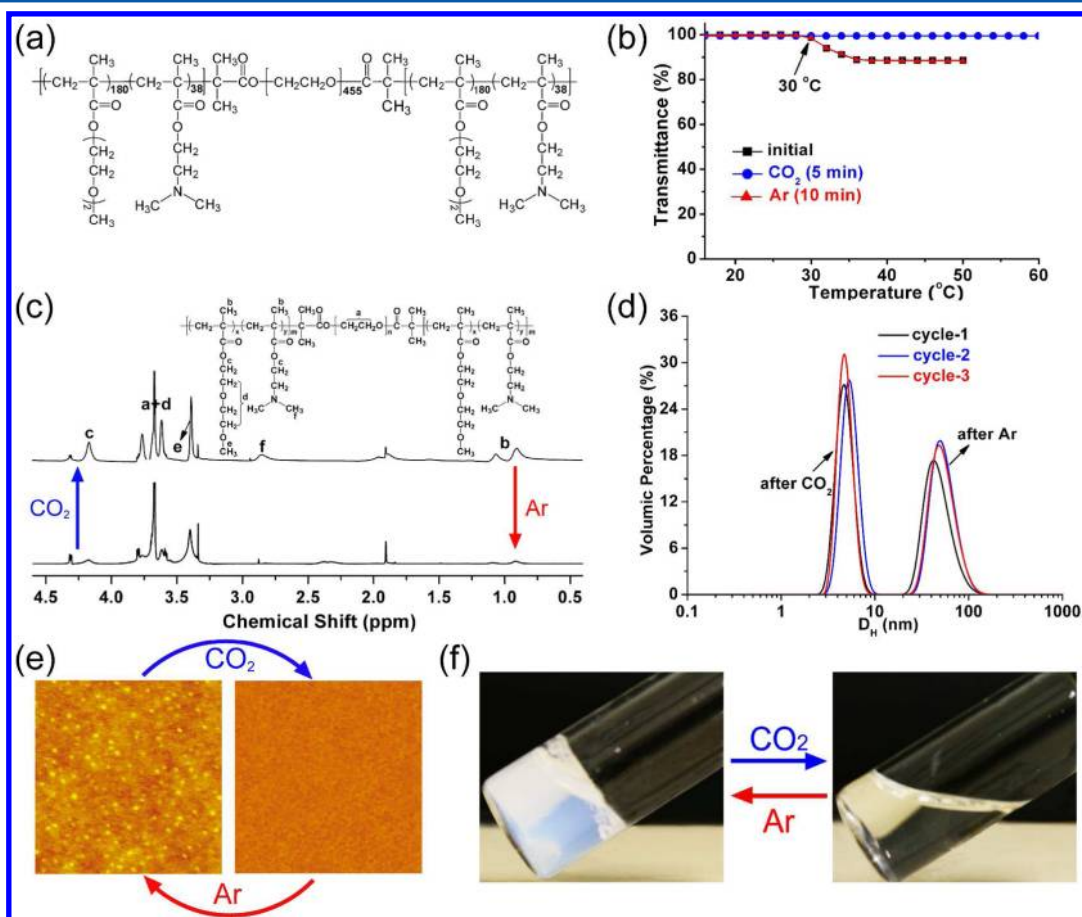


Figure 2. (a) Structure of the ABA-type triblock copolymer $P(\text{MEO}_2\text{MA}_{180}\text{-co-DMAEMA}_{38})\text{-}b\text{-PEO}_{455}\text{-}b\text{-P}(\text{MEO}_2\text{MA}_{180}\text{-co-DMAEMA}_{38})$. (b) Transmittance vs temperature for a triblock copolymer aqueous solution (3.0 mg/mL) before CO₂, after CO₂, and after Ar bubbling through the solution. (c) ¹H NMR spectra of the triblock copolymer in D₂O at 37 °C after alternating bubbling with CO₂ and Ar. (d) Size distribution of a triblock copolymer aqueous solution (1.0 mg/mL) at 37 °C after alternating bubbling with CO₂ and Ar (three cycles). (e) AFM height images recorded by casting a triblock copolymer aqueous solution (1.0 mg/mL) at 37 °C after CO₂ and Ar bubbling (size: 1 μm × 1 μm). (f) Photographs showing the reversible gel-to-sol transition upon alternating bubbling with CO₂ and Ar at 37 °C.

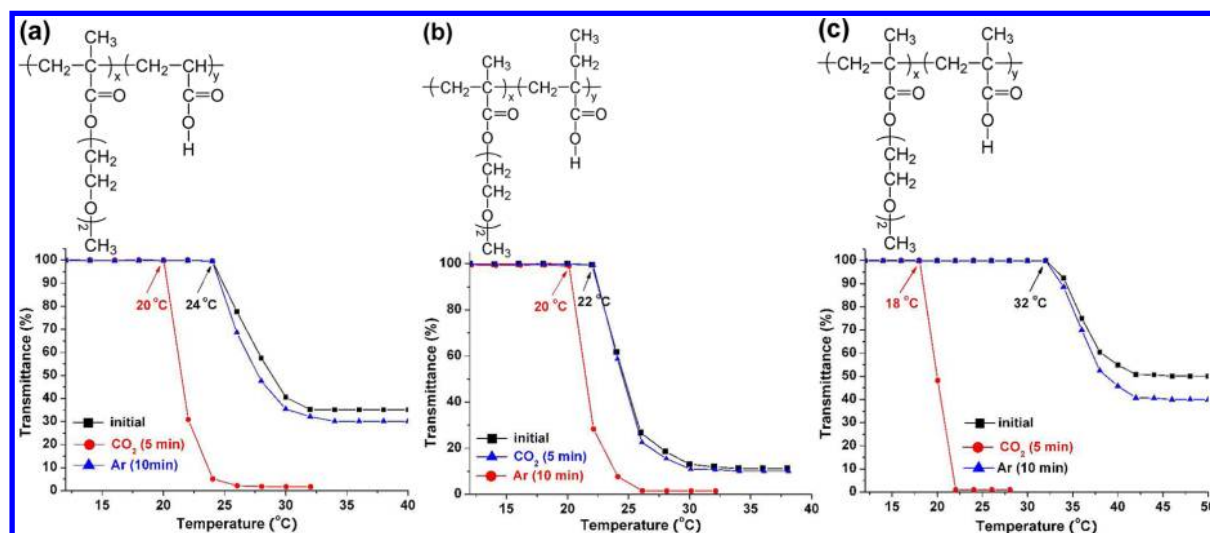


Figure 3. Transmittance vs temperature for aqueous solutions of (a) P(MEO₂MA-*co*-AA) (5 mol % of AA), (b) P(MEO₂MA-*co*-EAA) (6 mol % of EAA), and (c) P(MEO₂MA-*co*-MAA) (5 mol % of MAA) before CO₂, after CO₂, and after Ar bubbling, the polymer concentration being 3.0 mg/mL.

mer chemical structure is shown in Figure 2a. While the middle block is water-soluble poly(ethylene oxide) (PEO), the end blocks are a random copolymer of 2-(2-methoxyethoxy)ethyl methacrylate and *N,N*-dimethylaminoethyl methacrylate (P(MEO₂MA-*co*-DMAEMA)). The triblock copolymer was synthesized using ATRP, and its composition was determined as P(MEO₂MA_{180-*co*}-DMAEMA₃₈)-*b*-PEO₄₅₅-*b*-P(MEO₂MA_{180-*co*}-DMAEMA₃₈) (details in Supporting Information). The content of CO₂-responsive DMAEMA units in the A block is thus ~17 mol %. Thermosensitive PMEO₂MA with DMAEMA comonomer units displays a CO₂-switchable LCST.²⁴ The CO₂-controllable micelle formation by this triblock copolymer at dilute concentrations of 1 or 3 mg/mL in water was first investigated. Figure 2b shows the transmittance measurement result. The ABA triblock is soluble in cold water; on heating a decrease in transmittance is observed at ~30 °C, suggesting formation of micelles due to the dehydration of the A blocks. The same polymer solution, after bubbling with CO₂ (flow rate ~50 mL/min), shows no detectable decrease in transmittance on heating, indicating that the A block remains soluble in water up to 60 °C due to a CO₂-induced increase in LCST. Subsequently, by purging the solution with Ar (flow rate ~60 mL/min), the initial transmittance decrease on heating is recovered at the same temperature, indicating complete removal of CO₂. This observation suggests that the triblock copolymer micelles formed at, say, 37 °C (the body temperature) could be dissociated by passing CO₂ and reassembled by passing Ar through the solution. The formation of micelles and their gas switchability at 37 °C were further confirmed by several techniques. Figure 2c shows the ¹H NMR spectra of the solution recorded after alternating bubbling with CO₂ and Ar. With CO₂, the resonance peaks of both blocks are visible due to the solubility; while after CO₂ removal with Ar, the characteristic peak of PEO remains the same, but the peaks of the A blocks have their intensity reduced and become broadened, indicating chain aggregation of the A blocks. Figure 2d shows the DLS measurement result. The reversible dissociation of micelles with CO₂ and their reassembly with Ar over three cycles are visible. AFM images recorded by casting the aqueous solution after bubbling with CO₂ and Ar,

respectively, are given in Figure 2e. The reversible micelle disassembly with CO₂ and formation upon Ar bubbling are consistent with the DLS results. As seen from the picture in Figure 2f, by increasing the polymer concentration to 10% (100 mg/mL), indeed the triblock copolymer P(MEO₂MA_{180-*co*}-DMAEMA₃₈)-*b*-PEO₄₅₅-*b*-P(MEO₂MA_{180-*co*}-DMAEMA₃₈) self-assembles into hydrogel at 37 °C. This relatively low polymer concentration for gelation is typical for hydrogels of ABA triblock copolymers forming a network of flower micelles.^{8,12–16} Upon passing CO₂ into the hydrogel, a gel-to-sol transition occurs quickly, as the triblock copolymer turns to be soluble in water. The hydrogel is reformed by bubbling Ar into the solution. Many cycles could be repeated. The results in Figure 2 clearly confirm the triblock copolymer design toward gas-controllable hydrogels with CO₂-induced gel-to-sol transition.

CO₂-Induced Sol-to-Gel Transition. In order to achieve the opposite switching behavior of ABA triblock copolymer hydrogel, i.e., CO₂-induced sol-to-gel transition, the A block should possess a LCST (or water solubility) that can be decreased upon CO₂ bubbling. As discussed earlier with Figure 1, we anticipated that this could be obtained by using a weak acid comonomer as the CO₂-responsive trigger in the A block. Upon protonation of acid groups, the reduced degree of ionization of the comonomer units should reduce the polymer water solubility and result in a decrease in LCST, contrary to the effect of protonated tertiary amine groups.²⁴ We investigated the use of acrylic acid (AA), methacrylic acid (MAA), and ethylacrylic acid (EAA) monomers to this end. Figure 3 shows the results obtained by incorporating these three acid comonomer units into PMEO₂MA.

Indeed, for all random copolymers of PMEO₂MA containing a similar amount of AA, MAA, and EAA, after bubbling CO₂ through the solution, the apparent cloud point decreased and could be recovered upon subsequent purging with Ar to remove CO₂. The results also show that, among the used acid comonomers, MAA turned out to be the most effective for use as the comonomer for polymers to exhibit CO₂-induced decrease in LCST. Similar to the tertiary-amine monomers for CO₂-induced increase in LCST,²⁴ the commercially available MAA makes it easy to access to a wide range of polymers whose

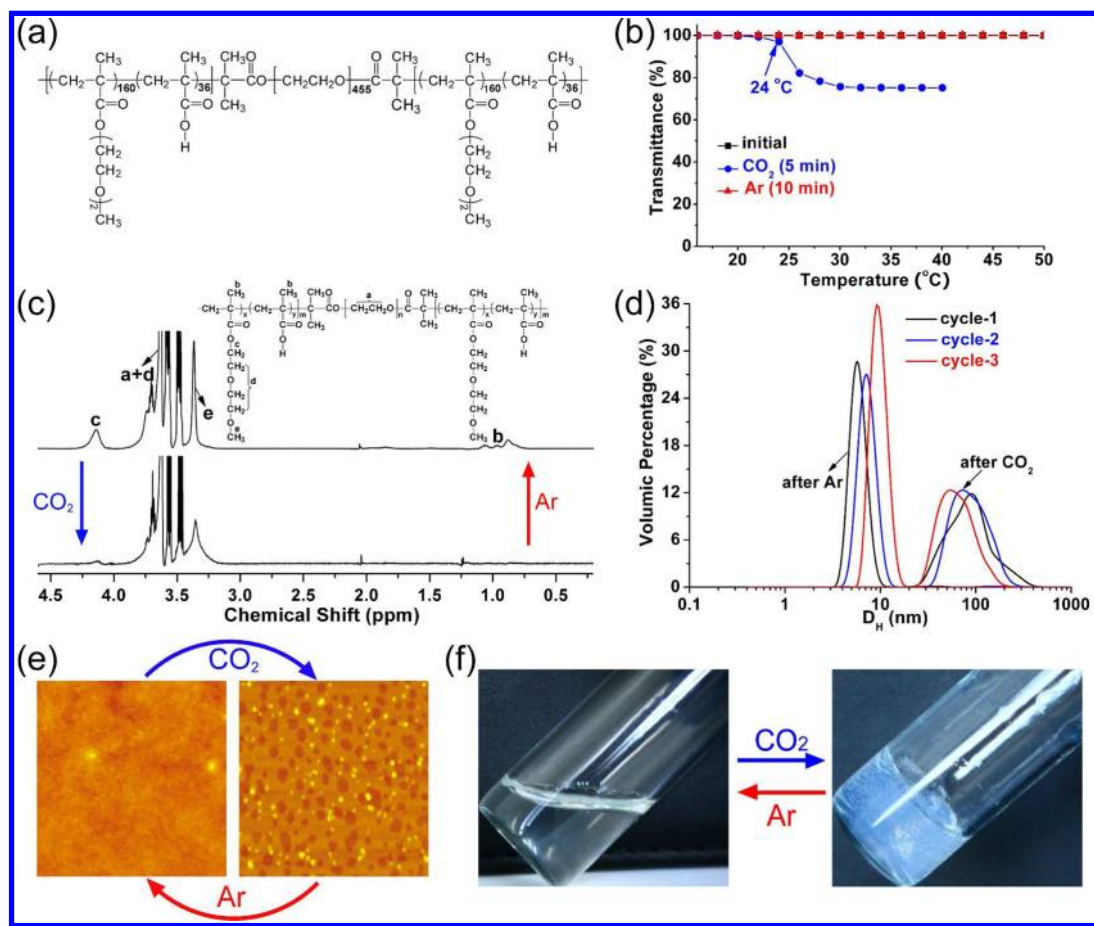


Figure 4. (a) Structure of the ABA triblock copolymer $P(\text{MEO}_2\text{MA}_{160}\text{-co-MAA}_{36})\text{-}b\text{-PEO}_{455}\text{-}b\text{-}P(\text{MEO}_2\text{MA}_{160}\text{-co-MAA}_{36})$. (b) Transmittance vs temperature for a triblock copolymer aqueous solution (3.0 mg/mL) before CO_2 , after CO_2 , and after Ar bubbling through the solution. (c) ^1H NMR spectra of the triblock copolymer in D_2O at 35°C after alternating bubbling with CO_2 and Ar. (d) Size distribution of a triblock copolymer aqueous solution (1.0 mg/mL) at 35°C after alternating bubbling with CO_2 and Ar (three cycles). (e) AFM height images recorded by casting a triblock copolymer aqueous solution (1.0 mg/mL) at 35°C after CO_2 and Ar bubbling (size: $1\ \mu\text{m} \times 1\ \mu\text{m}$). (f) Photographs showing the reversible sol-to-gel transition upon alternating bubbling with CO_2 and Ar at 35°C .

LCST can be decreased by CO_2 . The actual decrease in LCST depends on the content of MAA in the polymer. We also prepared a random copolymer of $\text{P(MEO}_2\text{MA)}$ containing about 16 mol % of MAA. With this order of MAA amount, the switching between solubility upon Ar and insolubility upon CO_2 can be achieved at room or body temperatures (Figure S4).

On the basis of the above results, we designed, synthesized, and studied another ABA triblock copolymer aiming at hydrogel with CO_2 -induced sol-to-gel transition. The results are summarized in Figure 4. The used triblock copolymer sample, structure in Figure 4a, is $P(\text{MEO}_2\text{MA}_{160}\text{-co-MAA}_{36})\text{-}b\text{-PEO}_{455}\text{-}b\text{-}P(\text{MEO}_2\text{MA}_{160}\text{-co-MAA}_{36})$. While the middle block is the same PEO, the end blocks are a random copolymer of $\text{P(MEO}_2\text{MA)}$ containing MAA comonomer units at a content of ~ 18 mol %. The transmittance measurements of a dilute polymer solution (3 mg/mL), results in Figure 4b, show that on heating the triblock copolymer is totally soluble up to 50°C . After bubbling with CO_2 , a decrease in transmittance on heating appears at about 24°C , indicating a CO_2 -induced decrease in LCST of the A blocks. Similar to the first triblock copolymer, various techniques were also utilized to confirm the formation of micelles at dilute polymer concentrations of 1 or 3 mg/mL as well as the switchability in response to the gases at 35°C . The results in Figure 4 show that indeed the switching

behavior is reversed as designed. The ^1H NMR spectra in Figure 4c show that the resonance peaks of the A block, $P(\text{MEO}_2\text{MA}_{160}\text{-co-MAA}_{36})$, become less visible after CO_2 bubbling and are recovered after purge with Ar. Likewise, the DLS results in Figure 4d show formation of micellar aggregates after passing CO_2 through the solution and their dissociation upon Ar bubbling over three cycles. This opposite gas-controllable micelle formation and disassembly can also be seen from the AFM images in Figure 4e. Finally, as seen in Figure 4f, using a triblock copolymer solution at a higher concentration (10%), the initially soluble triblock copolymer at 35°C turns to hydrogel upon passing CO_2 into the solution, and it is dissolved upon purge with Ar. Again, many cycles could be repeated.

CO_2 -Triggered Protein Release. In contrast with chemically cross-linked hydrogels that can undergo reversible volume transition (expansion and contraction) triggered by stimuli, self-assembled physical hydrogels of ABA triblock copolymers can accomplish reversible gel-to-sol transition between gelled and dissolved state. The easy control of such transition by using CO_2 and an inert gas at a constant solution temperature and without adding acids or bases is interesting and may find applications. In the case of CO_2 -induced sol-to-gel transition, the triblock copolymer may be explored as a gas-tunable rheology modifier, since its aggregation and gelling, which

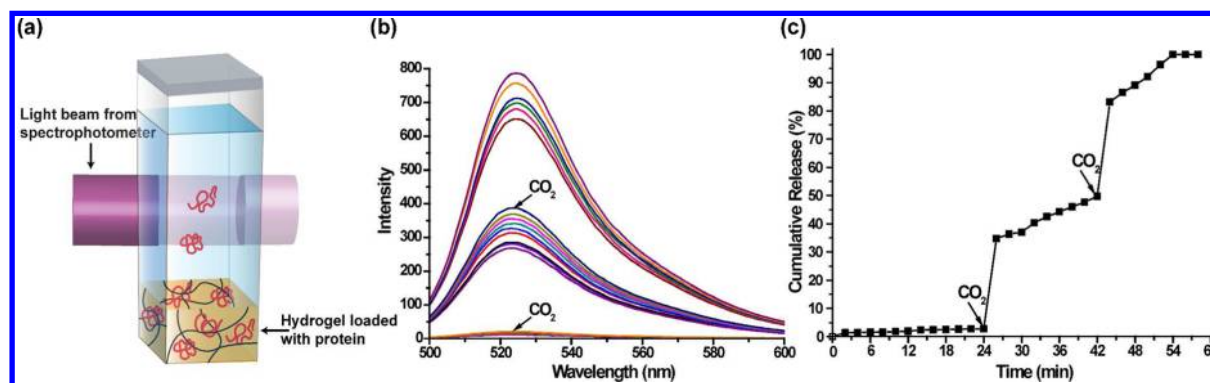


Figure 5. (a) Illustration of the setup used to monitor the protein release. (b) Fluorescence emission spectra of FITC-BSA released from the hydrogel at 37 °C in response to CO₂ ($\lambda_{\text{ex}} = 488$ nm). (c) Profile of cumulative release of FITC-BSA in response to CO₂.

should affect the viscosity of the solution, can be controlled by passing CO₂ through the solution. For CO₂-induced gel-to-sol transition, CO₂ may be used as a stimulus to trigger the dissociation of hydrogel and release of payloads. To test this, we investigated CO₂-triggered release of a protein entrapped in the hydrogel of P(MEO₂MA₁₈₀-*co*-DMAEMA₃₈)-*b*-PEO₄₅₅-*b*-P(MEO₂MA₁₈₀-*co*-DMAEMA₃₈). In this experiment, the block copolymer (60 mg) and fluorescein isothiocyanate conjugated bovine serum albumin (FITC-BSA, 0.086 mg) were dissolved into water (Milli-Q, 0.6 mL) at 10 °C; the solution was transferred into a fluorescence cell and heated to 37 °C to form the gel. Prior to the measurement, the gel was washed with warm water (37 °C) three times to remove unloaded protein, before fresh water was added into the cell. As illustrated in Figure 5a, with the hydrogel resting at the bottom of the cell thermostated at 37 °C, protein molecules released into water could be monitored by its fluorescence emission ($\lambda_{\text{ex}} = 488$ nm) measured at the upper part of the cell. Figure 5b shows the fluorescence emission spectra of FITC-BSA recorded as a function of time. Without CO₂, only weak fluorescence was detected, indicating effective trapping of the large protein by the hydrogel. After 1.0 mL of CO₂ was injected into the sealed cell, the fluorescence intensity jumped; then the increase in emission intensity slowed down but remained faster than before CO₂ injection. A similar result was obtained after a second injection of 1.0 mL of CO₂. After the second injection, the hydrogel was visually dissolved completely, and the measured fluorescence corresponds to the maximum protein release. By plotting the normalized fluorescence intensity at the peak (525 nm), Figure 5c shows the temporal cumulative release of FITC-BSA in response to CO₂ in water. The stepwise protein release triggered by CO₂ as a result of the gel-to-sol transition at 37 °C is clearly visible. The results show that the hydrogel dissolution and the resultant protein release can readily be controlled by the amount of CO₂. This feature is important for the perspective of using CO₂ as a trigger in the body for controlled release of bioactive substances.²⁷ Indeed, the basis of CO₂-switchable function or property of water-soluble polymers is the CO₂-controllable LCST, which is dependent on the amount of CO₂. Since the LCST of polymer carriers, such as the hydrogel in the present case, could be tuned by their structures, they can be made to respond to CO₂ only above a critical concentration. If the concentration of CO₂ in a diseased region is higher than the normal amount, in principle, polymer carriers could be designed to be responsive to CO₂ only in such regions.

CONCLUSIONS

We reported the rational design, synthesis, and study of first ABA triblock copolymer hydrogels that are responsive to the presence of CO₂ in water. The key to the design is to have an A block whose LCST can be shifted reversibly by passing CO₂ and an inert gas alternately in solution. We showed that incorporating either tertiary-amine or methacrylic acid comonomer units into PMEO₂MA in ABA triblock copolymers of PMEO₂MA-*b*-PEO-*b*-PMEO₂MA, either increase or decrease in the LCST of the A block upon CO₂ bubbling could be obtained, resulting in either CO₂-induced gel-to-sol or the reverse sol-to-gel transition. In both cases, repeated cycles of hydrogel formation and dissociation could be achieved by simply passing CO₂ and Ar alternately through the solution and this at a constant temperature and without adding acids or bases for pH change. As a possible application, we also demonstrated that the release of a protein (FITC-BSA) entrapped in such hydrogels could readily be triggered by CO₂. The robust switching using CO₂ and an inert gas should open more possibilities for applications of ABA triblock copolymer hydrogels. The underlying mechanism is general, and the triblock copolymer design can easily be applied to many polymers.

ASSOCIATED CONTENT

Supporting Information

Details of polymer syntheses and characterizations. 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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