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# pH- and Sugar-Responsive Gel Assemblies Based on Boronate–Catechol Interactions

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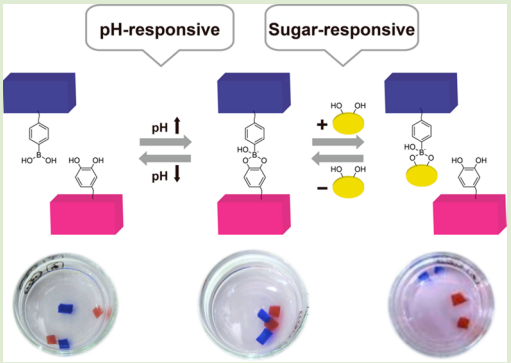
Supporting Information

**ABSTRACT:** The interaction between poly(acrylamide) gels carrying phenylboronic acid (PB gel) and catechol moieties (CAT gel) respectively is investigated. The PB gel forms an assembly with the CAT gel on a macroscopic scale in basic aqueous media. The adhesion strength is estimated by stress–strain measurements. The assembly and disassembly of the gels are reversibly switched by varying the pH of the medium. The adhesion strength is tunable by competitive monosaccharide molecules in accordance with the association constant with PB moieties.




Living organisms are built up with a variety of self-assemblies, which play crucial roles for our life activities. Most of these assemblies respond properly to the external environment and stimuli to move, deliver various chemicals, and transfer genetic information. Inspired by these highly controlled intelligent assemblies, chemists and materials scientists have developed artificial stimuli-responsive materials,[1−8] as represented by drug delivery systems,[9,10] actuators,[11−13] and sensors.[14−16] Among all stimuli-responsive materials, specific biomolecule-responsive materials possess a great potential for medical diagnosis systems.[17−20]

Boronic acids (BAs) are universally utilized as tools for molecular recognition in the supramolecular chemistry.[21,22] BAs are known to form boronic ester derivatives with various diol compounds, including saccharides in both organic and aqueous media.[23] The formation and dissociation of boronic ester derivatives show the reversible complex formation by pH control. Taking advantage of these unique features, BAs have been utilized as sensors or separation tools for synthetic molecules or naturally occurring molecules.[24] Recently, the molecular recognition of BAs have been utilized for saccharide-responsive sol–gel switching materials,[25] pH-responsive self-healing materials,[26] pH-responsive gel assembly systems,[27] and pH and sugar-responsive protein delivery systems.[28] Catechol (CAT) scaffolds are often seen in naturally occurring compounds, as represented by dopamine, a famous neurotransmitter. CAT moieties are also utilized for adhesion of some kinds of mussels onto the surfaces of many substances.[29,30] A previous study reported that catechol forms cyclic boronate ester with phenylboronic acid (PB) in basic aqueous medium with a higher binding constant ($K \sim 1.8 \times 10^4$ L mol$^{-1}$) compared to most saccharides.[23]

Previously, we have reported macroscopic observations of various noncovalent interactions such as host–guest interaction[31] and metal–ligand interaction.[32] Through these studies, we have realized the amplification of the selectivity for guest molecules on a polymer side chain. Even if differences between association constant ($K_a$) of host molecules with guest molecules are comparable in the low molecular weight model systems, we can observe amplifying the selectivity of host object with guest object in macroscopic self-assembly events in hydrogel systems. A small difference in binding constant ($K$) of BAs with many saccharides should be discriminated by introducing BAs into the hydrogels to construct sugar-responsive gel assembly systems.

Here we establish a pH and sugar-responsive gel assembly system based on the reversible interaction between PB and CAT. The assembly between PB and CAT hydrogels can be controlled on a macroscale by adjusting pH and adding competitive saccharides.

PB and CAT gels were prepared by homogeneous radical copolymerization of 4-vinylphenylboronic acid or 4-vinylcatechol with acrylamide (AAm) and *N*,*N*′-methylenebis-

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(acrylamide) (MBAAm) initiated by 2,2′-azobis-(isobutyronitrile) (AIBN) in dimethyl sulfoxide (DMSO; Supporting Information, Schemes S3 and S4). After the polymerization, the gel was repeatedly washed with DMSO and water to give transparent hydrogels. Figure 1 depicts the

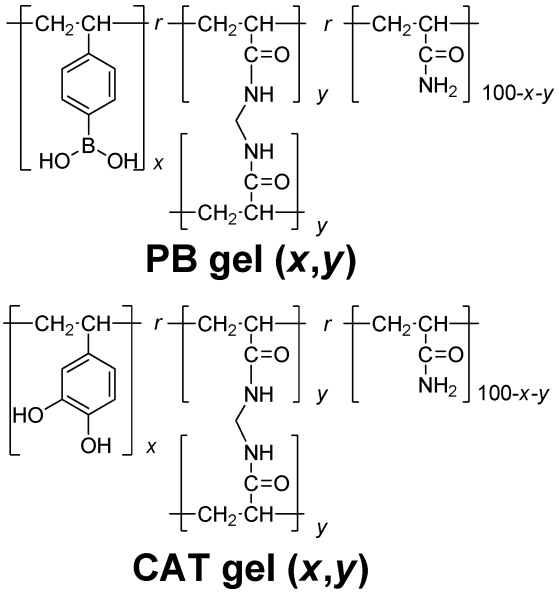


**Figure 1.** Chemical structures of the gels used in this study.

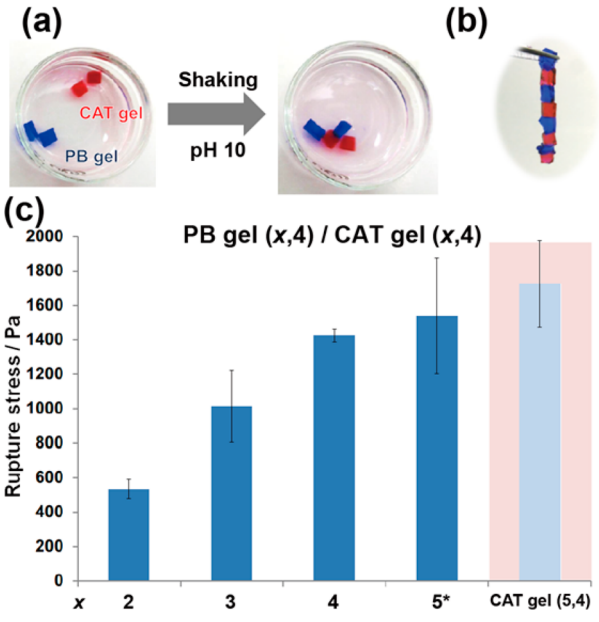


**Figure 2.** (a) Photographs of the PB gel (4,4) (blue) and the CAT gel (4,4) (red) shaken in pH 10 $Na_2CO_3$/$NaHCO_3$ buffer solution. (b) Photograph of the gel assembly picked up with a tweezers. (c) The rupture stress between PB gel (*x*,4) and CAT gel (*x*,4) (*x* = 2−5); *x* = 5*. The PB gel (5,4)/CAT gel (5,4) assembly ruptured not at the joined interface, but the CAT gel itself was broken. The rupture strength of the CAT gel (5,4) is comparable to that of the PB gel (5,4)/CAT gel (5,4).

chemical structures of PB gel (*x*,*y*) and CAT gel (*x*,*y*). Here *x* and *y* represent the mol % content of the PB or the CAT and the mol % content of the MBAAm units, respectively. The $^1$H solid state field gradient magic angle spinning (FGMAS) NMR

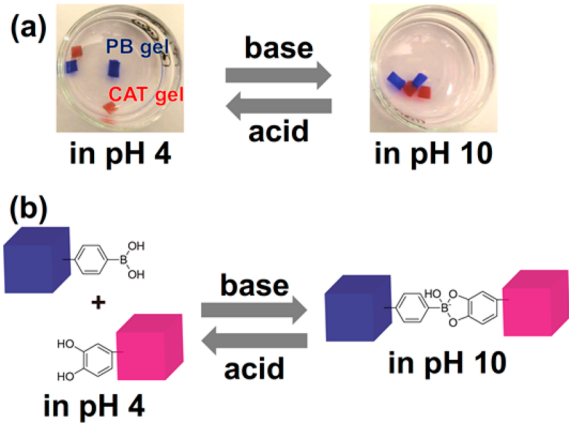


**Figure 3.** (a) Photographs of PB gel (4,4) (blue) and CAT gel (4,4) (red) shaken in pH 4 and pH 10 buffer solutions, respectively. (b) Schematic illustration of the pH-responsive gel assembly between PB and CAT gels.

and FT-IR spectroscopies confirmed the successful introduction of PB or CAT moieties into each gel (Supporting Information, Figures S2 and S3).

The self-assembly test was first carried out. PB gels and CAT gels were cut in small pieces (3 × 3 × 3 mm$^3$) and stained with coomassie brilliant blue (blue, PB gel) or rose bengal (red, CAT gel) for visibility, respectively. Figure 2a shows a typical example of gel assembly tests. When two PB gel (4,4) pieces and two CAT gel (4,4) pieces were agitated in 0.1 M $Na_2CO_3$/$NaHCO_3$ buffer (pH 10), a gel assembly was immediately formed. The same kinds of gels have no interaction each other, but different kinds of gels selectively adhered together to form an alternating assembly. As shown in Figure 2b, the adhesion strength between these gels was strong enough to stand up under its own weight. Competitive experiments confirmed the interaction between PB and CAT moieties. PB gel (4,4) and CAT gel (4,4) formed no assemblies in the presence of PB or CAT (10 mM) (Supporting Information, Figure S5). These results show that competitive molecules block the interaction between PB and CAT moieties on the surface of gels to inhibit the formation of macroscopic assembly. From these experiments, PB and CAT gels adhere through the formation of cyclic boronate ester between PB and CAT moieties at the side chain of polymers in basic conditions.

Stress−strain measurements were conducted to estimate the adhesion strength of both gels quantitatively. Cuboid-shaped gels (10 × 5 × 2 mm$^3$) were attached together and the adhesion strengths between the gels were estimated by tensile tester (Supporting Information, Scheme S5 and Figure S6). The maximal stress value obtained from the stress−strain curve was regarded as rupture stress. Figure 2c shows the rupture stress for pairs of the PB gel (*x*,4) and CAT gel (*x*,4) (*x* = 2−5). The rupture stress increases as *x* increases. The joined gel pieces of PB gel (5,4)/CAT gel (5,4) were ruptured not at the interfaces of the gels but broken from the CAT gel itself, indicating that the adhesion strength between gel pieces is stronger than the material strength of the gel itself.

We investigated the influence of the pH on the gel assembly. PB and CAT gels formed a macroscopic self-assembly at pH 10 (0.1 M $Na_2CO_3$/$NaHCO_3$ buffer) as described above. After replacing pH 10 buffer with 0.1 M $CH_3COOH$/$CH_3COONa$ buffer (pH 4), the gel assembly was dissociated. After raising pH to 10 again, the gels reformed an assembly (Figure 3a).


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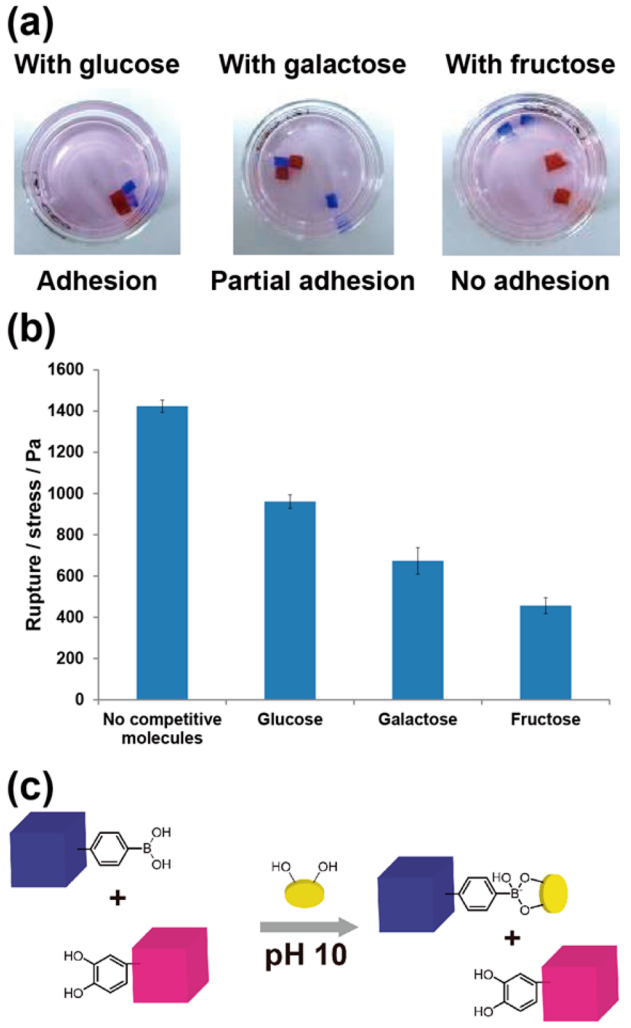


**Figure 4.** (a) Photographs of PB gel (4,4) (blue) and CAT gel (4,4) (red) shaken in the presence of glucose (3 mM, left), galactose (3 mM, middle), and fructose (3 mM, right) in pH 10 buffer, respectively. (b) The rupture stress between PB gel and CAT gel immersed in the aqueous buffer solutions of glucose (3 mM), galactose (3 mM), and fructose (3 mM), respectively. (c) Schematic illustration of the inhibition of the assembly between PB gel and CAT gel by competitive saccharides.

This is because the cyclic boronate ester is reversibly formed and dissociated between PB and CAT around the p$K_a$ 8.90–9.32 (Figure 3b).[33,34] This result is consistent with the model experiments (Supporting Information, Figure S4), that is pH-dependent gel formation from the mixture of linear polymers modified with PB or CAT moieties (Supporting Information, Schemes S1 and S2 and Figure S1). These results indicate that assembly and disassembly of gels can be regulated by pH.

Finally, we controlled the assembly between PB and CAT gels by adding competitive saccharide molecules. Figure 4a shows results of assembly tests between PB gel (4,4) and CAT gel (4,4) in the presence of various monosaccharides as competitive molecules. PB gel (4,4) and CAT gel (4,4) were shaken in the 3 mM aqueous buffer solutions (pH 10) containing competitive monosaccharides (glucose, galactose, and fructose) for 5 min. Although all four pieces of the gels formed an assembly in the presence of glucose, three of four gels assembled by adding galactose. Moreover, adding fructose inhibited the formation of macroscopic assembly. Figure S7 shows the concentration dependence of the saccharides on the formation of the gel assembly. As the saccharide concentration increases, the adhesion strength decreases, resulting in a partial or full dissociation. Stress–strain measurements estimated the adhesion strength in the case of PB gel (4,4) and CAT gel (4,4) immersed in the buffer solution of 3 mM competitive saccharide molecules (Figures 4b and S8). The rupture stresses are lower in the presence of saccharides than that in their absence. A previous study reported that the $K$ of PB with glucose, galactose, and fructose are $1.1 \times 10^2$, $2.8 \times 10^2$, and $4.4 \times 10^3$ L mol$^{-1}$ in aqueous basic media, respectively.[23] A saccharide with a larger $K$ value inhibited the gel assembly more effectively. The experimental results show that the PB gel can discriminate the competitive saccharides on a macroscale (Figure 4c). Also, the gel assembly between the PB gel and the CAT gel can be controlled by simply changing the variety and concentration of the saccharide molecules.

In conclusion, we successfully controlled assembly and disassembly of PB and CAT gels by pH or competitive saccharide molecules. It is proven that not only host–guest or metal–ligand interactions but also reversible covalent bond formation can be visualized on a macroscale by using hydrogel as a matrix. This system has a great potential for a biomolecule-responsive gel assembly system.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental section, spectral studies, competitive experiments, and movies are included. 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.

## ■ ACKNOWLEDGMENTS

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