Hydrogel Self-Assembly

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Redox-Responsive Macroscopic Gel Assembly Based on Discrete Dual Interactions**

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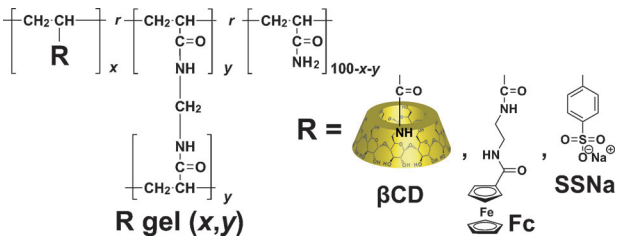
Abstract: *The macroscopic self-assembly of polymeric hydrogels modified with β-cyclodextrin (βCD gel), ferrocene (Fc gel), and styrenesulfonic acid sodium salt (SSNa gel) was investigated. Under reductive conditions, the Fc gel selectively adhered to the βCD gel through a host–guest interaction. On the other hand, the oxidized ferrocenium (Fc^+) gel selectively adhered to the SSNa gel through an ionic interaction under oxidative conditions. The adhesion strength was estimated by a tensile test. We finally succeeded in forming an ABC-type macroscopic assembly of all three gels through two discrete noncovalent interactions.*

In biological systems, there are various types of functional molecules, the organization of which into macroscopic assemblies is based on selective molecular recognition. In artificial systems, macroscopic self-assemblies have been created mainly through macroscopic physical interactions.[1–9] On the other hand, complementary complex formation should be more effective for the construction of multifunctional macroscopic self-assemblies, which have much potential as highly functional materials, such as stimuli-responsive materials,[10–14] self-healing materials,[15–20] artificial muscles,[21–25] and other materials.[26] We previously developed various stimuli-responsive macroscopic assemblies based on polymeric hydrogels modified with cyclodextrins (CDs) and guest molecules.[27a] The AB-type gel assembly and dissociation can be controlled by various external stimuli, such as light,[27b] chemicals,[27c] temperature,[27d] the pH value,[27e] and metal–ligand interactions.[27f] Such macroscopic assemblies are reminiscent of the selective organization of functional molecules in cells.

Ferrocene (Fc) is one of the most common redox-responsive compounds and undergoes reversible one-electron oxidation. Fc has the unique property that it acts as a hydrophobic guest compound for CDs in its reduced state (Fc)[28] and as a hydrophilic cationic guest compound for calixarene derivatives in its oxidized state (Fc^+).[29] For the construction of precisely controlled macroscopic self-assemblies, one stimulus should regulate multiple interactions. Previously, polymers modified with Fc produced redox-responsive materials, such as sol–gel phase-transition materials,[30–32] self-healing materials,[33a] responsive gel actuators,[33b,34–36] and others.[37] We think that Fc can be utilized as a good probe molecule for the observation of two or more discrete interactions on a macroscopic scale. Herein we report an ABC-type redox-responsive gel assembly system based on host–guest interactions between CD and Fc and cation–anion interactions between Fc^+ and sodium *p*-styrenesulfonate (SSNa). Each functional moiety is incorporated into the poly(acrylamide) (pAAm) gel network. Redox stimuli change the Fc electronic state and switch the discrete dual interactions between these gels to form different types of gel assemblies on a macroscopic scale.

Scheme 1 shows the chemical structures of the β-cyclodextrin gel (βCD gel (*x*,*y*)), the ferrocene gel (Fc gel (*x*,*y*)), and the sodium *p*-styrenesulfonate gel (SSNa gel (*x*,*y*)). The βCD gel and the SSNa gel were prepared by homogeneous radical copolymerization of βCD or SSNa monomers, *N*,*N*′-methylenebis(acrylamide) (MBAAm), and acrylamide (AAm); the reaction was initiated by the redox pair ammonium peroxodisulfate (APS)/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) in water (see Schemes S1 and S3 in the Supporting Information). The Fc gel was prepared by homogeneous radical copolymerization of the inclusion complex formed between the Fc monomer (Fc-AAm) and βCD with MBAAm and AAm by using 2,2′-azobis[2-(2-imidazolin-2-yl)-propane] dihydrochloride (VA-044) as a water-soluble radical initiator. βCD was washed out of the gel after the polymerization (see Scheme S2).[38] The parameters *x* and *y* represent the amount (mol%) of the βCD/Fc/SSNa monomer and the MBAAm unit in the polymer. Solid-



Scheme 1. Chemical structures of the gels used in this study. The parameters *x* and *y* represent the amount (mol%) of the βCD/Fc/SSNa monomer and *N*,*N*′-methylenebis(acrylamide) (MBAAm) used in the preparation of each gel.

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state field-gradient magic-angle-spinning (FGMAS) ^{1}H NMR spectroscopy and Fourier transform infrared (FTIR) spectroscopy (see Figures S1 and S2 in the Supporting Information) suggested the successful introduction of βCD/Fc/SSNa units into the gels.

We first investigated the interaction between the βCD gel and the Fc gel. Figure 1a shows a typical gel-aggregation experiment. Both gels were cut into cubes ($5\times5\times5$ mm^3) and shaken together in water (see the Experimental Section for details). The βCD gel (clear and colorless) was stained with a red dye (rose bengal) for visibility. The βCD gel (3,2) and the Fc gel (3,2) assembled together within a few minutes to form a large aggregate (Figure 1a; see Movie S1 in the Supporting Information). On the other hand, this aggregate was not formed when a competitive host compound (βCD) or a competitive guest compound (sodium adamantanecarbonate) was added to the external solution (Figure 2a; see also Figure S3). βCD and Fc form an inclusion complex through a host–guest interaction with a relatively high association constant ($K_a = 17\times10^3$ L mol^{-1}).[28] βCD showed a much higher association constant for the adamantane derivative ($K_a = 35\times10^3$ L mol^{-1})[39] than that for Fc. These results indicate that the βCD gel and the Fc gel adhered to one another through the formation of inclusion complexes at the interfaces of the gels (Figure 1c).

In the next step, we investigated the effect of redox stimuli on the aggregation between the βCD gel and the Fc gel (Figure 1b). When the Fc gel was immersed in the aqueous solution of ceric ammonium nitrate (CAN; 50 mM), an oxidizing agent, the color of the gel changed from orange to green, which is the characteristic color of the ferrocenium cation (Fc^+). This result indicates that one-electron oxidation of the Fc moieties took place inside the gel.[33b] The oxidized gel did not adhere to the βCD gel at all when they were shaken together in water (Figure 1b). βCD shows high affinity for Fc in its reduced state owing to its hydrophobic nature, but the oxidized form, Fc^+, exhibits low affinity for βCD owing to its cationic nature.[40]

Next, the interaction between the Fc and SSNa gels was investigated. Figure 1d shows a typical procedure for the gel-aggregation test. The Fc gel (3,2) and the SSNa gel (3,2) (with black beads embedded in the gel for visibility) formed no aggregate when shaken in water. On the other hand, immersion of the Fc gel in aqueous CAN (50 mM) for 1 h caused the Fc^+ gel to aggregate with the SSNa gel (Figure 1e; see Movie S2).

When a competitive host compound (calix[6]arene hexasulfonic acid sodium salt (CS6)) was added, no aggregate was formed (Figure 2b). CS6 has a relatively high association constant for the Fc^+ derivative ($K_a = 24\times10^3$ L mol^{-1}).[29] CS6 served as a competitive host molecule for Fc^+ moieties to inhibit the aggregation between the Fc^+ gel and the SSNa gel. These results indicate that the Fc^+ gel and the SSNa gel adhered through a cation–anion interaction at the interfaces of the gels (Figure 1f).

The adhesion strength between the βCD gel and the Fc gel was measured by using a creepmeter (see Scheme S4). The combined gel pieces were pulled toward opposite sides, and

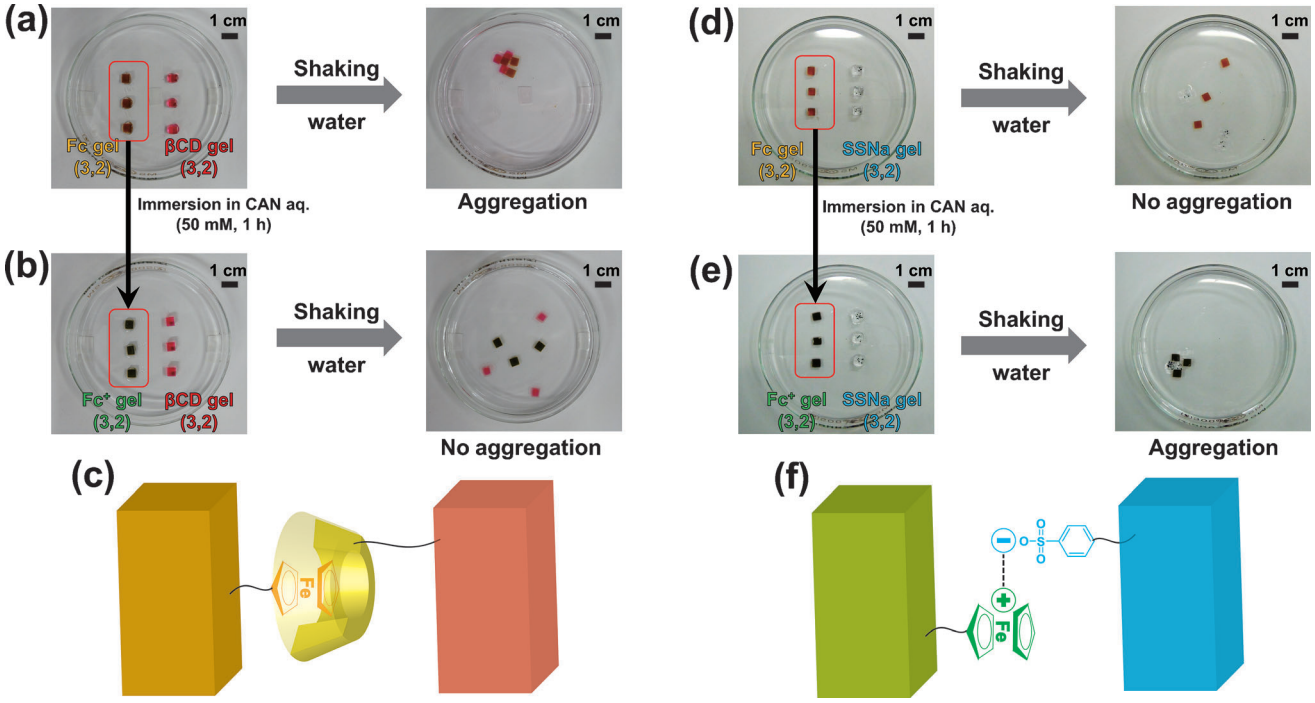

Figure 1. a) Photographs of the aggregation test between the Fc gel (3,2) and the βCD gel (3,2). b) Photographs of the aggregation test between the Fc^+ gel (3,2) and the βCD gel (3,2). c) Schematic illustration of the aggregate between the Fc gel and the βCD gel. d) Photographs of the aggregation test between the Fc gel (3,2) and the SSNa gel (3,2). e) Photographs of the aggregation test between the Fc^+ gel (3,2) and the SSNa gel (3,2). f) Schematic illustration of the aggregate between the Fc^+ gel and the SSNa gel. The βCD gel was stained with a red dye (rose bengal), and black beads are embedded in the SSNa gel for visibility. Scale bar: 1 cm.

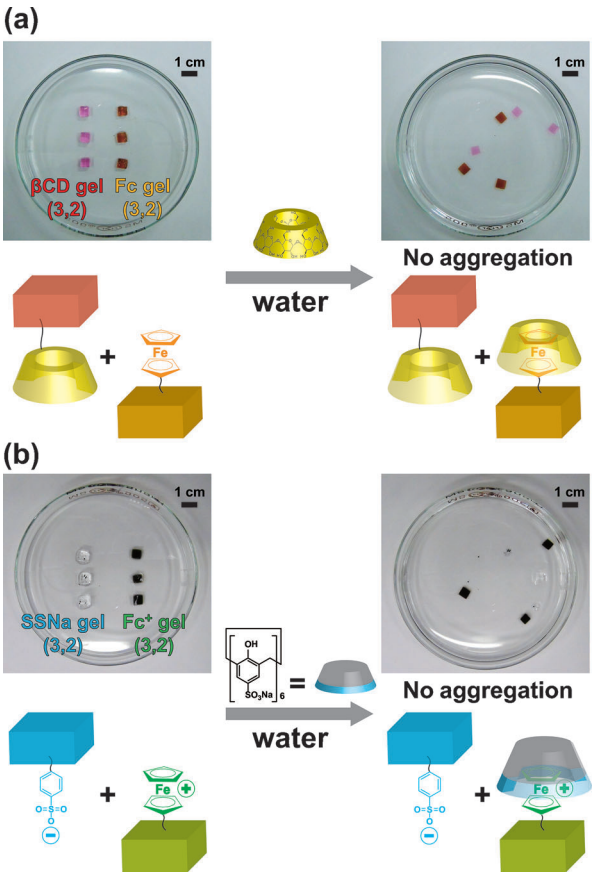

Figure 2. a) Photographs and schematic illustration of the competitive experiment in the case of the βCD gel–Fc gel system with a competitive host (βCD). After the addition of βCD, no aggregation between the βCD gel and the Fc gel was observed. b) Photographs and schematic illustration of the competitive experiment in the case of the Fc^+ gel–SSNa gel system with a competitive host (CS6). The addition of CS6 resulted in no aggregation between the Fc^+ gel and the SSNa gel. Scale bar: 1 cm.

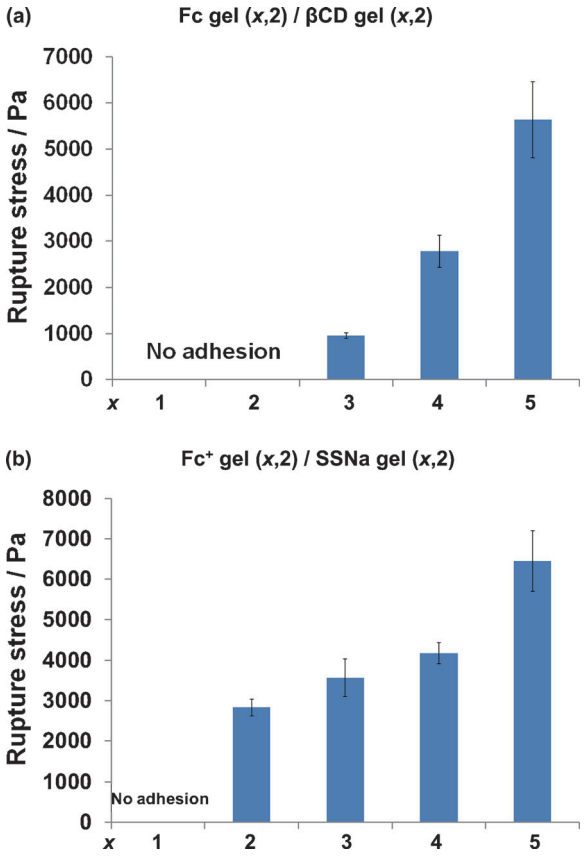

Figure 3. a) Rupture stress between the Fc gel (x,2) and the βCD gel (x,2) (x = 1, 2, 3, 4, and 5). b) Rupture stress between the Fc^+ gel (x,2) and the SSNa gel (x,2) (x = 1, 2, 3, 4, and 5). The rupture stress was estimated from the obtained stress–strain curves (see Figure S4) as the maximal force divided by the surface-to-surface area. The stress values are an average of three independent experiments. Error bars are the standard deviation.

the rupture stress was estimated from the obtained stress–strain curves (see Figure S4) as the maximal force divided by surface-to-surface area. The rupture stress for the βCD gel (x,2)–Fc gel (x,2) (x = 1, 2, 3, 4, and 5) increased as a function of the content (x) of βCD and Fc moieties (Figure 3a). This result indicates that the amount of host and guest moieties directly affects the adhesion strength. The adhesion strength between the Fc^+ gel (x,2) and the SSNa gel (x,2) was also measured in the same way (see Figure S5). The adhesion stress between the Fc^+ gel (x,2) and the SSNa gel (x,2) increased as the amount (mol%) of the Fc and the SSNa units increased (Figure 3b). These results clearly show that the number of Fc^+ and styrenesulfonate anion moieties has a direct influence on the adhesion strength.

Finally, we carried out an adhering-partner-switching experiment by using the three gels together. Figure 4a shows photographs of the experimental procedure. First, we prepared two pieces of the Fc gel (3,2) and immersed one in water and the other in aqueous CAN (50 mM) to obtain a Fc gel and a Fc^+ gel. After 1 h, βCD gels (3,2) and SSNa gels (3,2) were put on the left and right sides of the Fc gel or Fc^+ gel, respectively. When the Fc gel and Fc^+ gel located in the middle position of the three gels were picked up, the Fc gel adhered with only the βCD gel, whereas the Fc^+ gel stuck to only the SSNa gel (Figure 4b; see Movie S3). This behavior is a case of all-or-nothing selectivity on the macroscale.

We also carried out an experiment to control the sequence of the assembly (Figure 4c). First, half of the volume of the Fc gel (4,2) ($10 \times 5 \times 5\ mm^3$) was immersed in aqueous CAN (50 mM), whereas the other half volume of the gel was exposed to air. After 10 min, an Fc/Fc^+ gel with an oxidized surface on one side and a reduced surface on the opposite side was obtained. When this Fc/Fc^+ gel was shaken together with the βCD gel (5,2) and the SSNa gel (5,2) in water, three gels formed an ABC-type assembly with the composition βCD gel–Fc/Fc^+ gel–SSNa gel in that order (Figure 4d; see Movie S4). This assembly was formed because Fc or Fc^+ moieties associated with βCD or SSNa moieties through different types of interactions (Figure 4e). From these experiments, it was found that the Fc gel can discriminate the βCD gel and the SSNa gel through two discrete types of non-covalent interactions (host–guest and ion–ion interactions) according to the redox state of the Fc moieties.

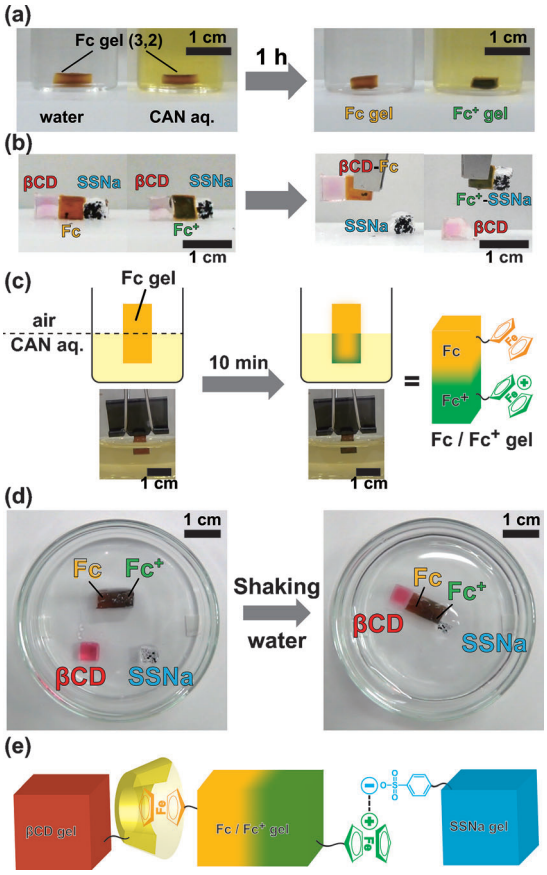

Figure 4. a) Photographs of the oxidation of the Fc gel. The Fc gel (3,2) immersed in aqueous CAN (50 mM) changed its color from orange to green. b) Photographs of the adhering-partner-switching experiment with the Fc gel (3,2) and the Fc^+ gel (3,2). c) Photographs and schematic illustration of the procedure used to make an Fc/Fc^+ gel. First, half of the volume of the Fc gel (4,2) ($10\times5\times5$ mm^3) was immersed in aqueous CAN (50 mM), whereas the opposite half volume of the gel was exposed to air. After 10 min, an Fc/Fc^+ gel with an oxidized surface on one side and a reduced surface on the opposite side was obtained. d) Photographs of the experimental procedure to make an ABC-type assembly. e) Schematic illustration of the ABC-type assembly with the composition βCD gel–Fc/Fc^+ gel–SSNa gel. Scale bar: 1 cm.

In conclusion, we successfully developed a redox-responsive gel assembly system by using an Fc gel that was able to effectively recognize a suitable adhering partner on a macroscopic scale. In previous studies, we utilized only single noncovalent interactions to form simple AB-type assemblies. The Fc/Fc^+ gel can form a sequentially controlled ABC-type macroscopic assembly on the basis of two discrete noncovalent interactions. This intelligent macroscopic self-assembly system has much potential for use not only in medical applications (for example, as a stimuli-responsive drug-delivery system), but also in materials science (for example, as a selective adhesive). We are now investigating the surface density of the functional groups and the surface properties of the gels (the effective depth and roughness).

Experimental Section

Preparation of the gels: The βCD gel, the Fc gel, and the SSNa gel were obtained by radical copolymerization of βCD, Fc, and SSNa monomers with AAm and MBAAm. Experimental details are described in the Supporting Information.

Formation of gel aggregates: To test the formation of gel aggregates, three pieces of each gel cube ($5\times5\times5$ mm^3) were shaken together with water (30 mL) in a petri dish (10 cm in diameter and 1.5 cm in depth). The average rotational speed was 5×10^2 r.p.m.

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