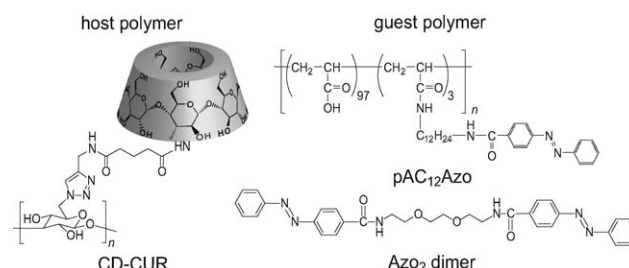


Photoswitchable Supramolecular Hydrogels Formed by Cyclodextrins and Azobenzene Polymers**

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Hydrogels are ubiquitous in nature, especially in living organisms.^[1] Synthetic hydrogels are used, for example, for tissue engineering, drug delivery systems (DDS), and medical treatment.^[2] There are mainly two kinds of gels: physical gels^[3] and chemical gels.^[4] Hydrogels with noncovalent cross-linking points are supposed to be more versatile and easily tunable than those with covalent bonds. Although low-molecular-weight physical gels exhibit photoresponsive elastic and photoswitchable properties,^[5–9] hydrogels formed by host–guest interactions should be more sensitive to external stimuli than low-weight-molecular low-molecular-weight physical gels.^[10–17] Although there are some reports on stimuli-responsive hydrogels that undergo a phase transition,^[8–9] there have been few reports on light-responsive hydrogels formed by host–guest interactions. We found previously that the mixture of a host polymer that contains cyclodextrins (CDs) and a guest polymer that contains azobenzene (Azo) showed a viscosity change after photoirradiation.^[18] However, we could not obtain a hydrogel from the mixture of both polymers. To obtain a hydrogel, we decided to use curdlan (β -1,3 glucan, CUR) as a backbone because CUR has a rather rigid structure and CDs can be attached to each monomer unit in the polymer chain. We succeeded in obtaining a supramolecular hydrogel by mixing a CUR that is functionalized with CDs (CD-CUR) and a guest polymer that has Azo moieties attached to it (Scheme 1). This is the first example of a light-responsive hydrogel obtained from a CD polymer and a guest polymer.

CD-CUR was prepared by a cycloaddition reaction between propargylamide-modified α -CD and 6-azido-curdlan (see the Supporting Information). CUR was substituted at the



Scheme 1. Structures of the compounds used.

C6 positions by the modified α -CD to obtain CD-CUR with a substitution degree of 98%. When the azo-modified poly(acrylic acid) (pAC₁₂Azo), 8.6 wt %) and CD-CUR (4.0 wt %) were mixed in a 1:1 ratio of the monomer units in water, the viscosity of the solution was first increased and then the solution transformed into a gel (Figure S7 in the Supporting Information). On the other hand, the CUR (without the α -CD unit)/pAC₁₂Azo mixture, the CD-CUR/poly(acrylic acid) (pAA, without the azo unit) mixture, and the CD-CUR/azo-guest-dimer (Azo₂Dimer) mixture did not form supramolecular hydrogels (Figure S7 in the Supporting Information). These results indicate that not only the combination between the α -CD unit and the azo unit but also multiple cross-links between CD-CUR and pAC₁₂Azo play important roles in the formation of the supramolecular hydrogel. Figure 1a–d shows the zero-shear viscosities (η_0) for CD-CUR/pAC₁₂Azo (a), CUR/pAC₁₂Azo (b), CD-CUR/pAA (c), and CD-CUR/Azo₂Dimer (d), respectively. Although CUR/pAC₁₂Azo, CUR/Azo₂Dimer, and CD-CUR/pAA showed low viscosities (less than 3 Pa s), CD-CUR/pAC₁₂Azo showed a viscosity of 54 Pa s, which is eighteen times higher than the viscosity of comparable systems. We have studied the effects of the host–guest ratio on the viscosity change of the system. When CD-CUR and pAC₁₂Azo were mixed in different monomer unit ratios (CD/Azo = 4:1, 1:1, 1:4), the largest η_0 value was obtained for the 1:1 monomer ratio of CD-CUR/pAC₁₂Azo, thus indicating the effective formation of complementary inclusion complexes (Figure 1e–g).

To clarify the complementary interaction between the α -CD unit and the *trans*-azo group, competitive host and guest molecules were added to the CD-CUR/pAC₁₂Azo hydrogel. Addition of α -CD to the CD-CUR/pAC₁₂Azo hydrogel led to the transformation of the gel into the sol. Figure 2b shows zero shear viscosities (η_0) for CD-CUR/pAC₁₂Azo in the presence of four equivalents of α -CD per azo unit of pAC₁₂Azo. The η_0 value of CD-CUR/pAC₁₂Azo with additional α -CD was similar to that of CUR/pAC₁₂Azo

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[**] This research was supported by the CREST project, Japan Science and Technology Agency. S.T. appreciates a JSPS fellowship from MEXT of Japan. The authors thank Seiji Adachi (Osaka University) for his helpful advice on the measurement of 2D NOESY spectra.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201003567>.

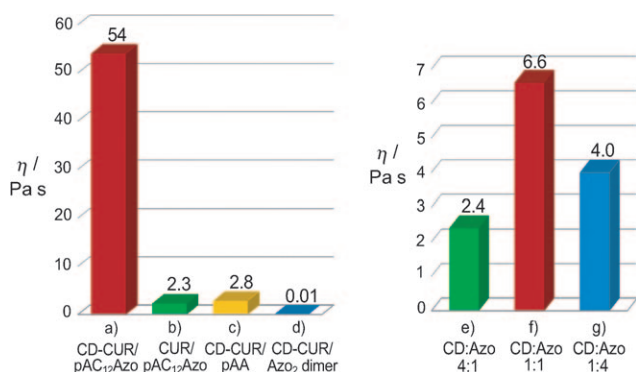


Figure 1. Zero-shear viscosities for a) CD-CUR/pAC₁₂Azo (4.0 wt%/8.6 wt%; 1:1 CD/Azo), b) CUR/pAC₁₂Azo (0.5 wt%/8.6 wt%; 1:1 glucopyranose/Azo), c) CD-CUR/pAA (4.0 wt%/7.2 wt%; 1:1 CD/acryl), d) CD-CUR/Azo₂Dimer (4.0 wt%/1.7 wt%; 1:1 CD/Azo). Concentration ratios and monomer unit ratios are shown in parentheses. The concentration ratios of CD-CUR/pAC₁₂Azo are e) 1.0 wt%/5.3 wt%, f) 2.0 wt%/4.3 wt%, and g) 4.0 wt%/2.3 wt%.

or CD-CUR/pAA. These results indicate that an excess of α -CD inhibits the complex formation between the α -CD unit in CD-CUR and the *trans*-azo unit in pAC₁₂Azo. When four equivalents of 1,12-decanedicarboxylate sodium salt (C₁₂CA₂Na₂) per α -CD group of CD-CUR were added to the CD-CUR/pAC₁₂Azo hydrogel, the viscosity was significantly decreased to give a sol (Figure 2c). On the other hand, the addition of tetraethylene glycol (TEG) to the CD-CUR/pAC₁₂Azo hydrogel did not affect the viscosity as shown in Figure 2d. The viscosity of CD-CUR/pAC₁₂Azo/TEG is comparable to that of CD-CUR/pAC₁₂Azo. The association constant of α -CD with C₁₂CA₂Na₂ is significantly larger than that with TEG (C₁₂CA₂Na₂: $K_a = 5400 \text{ M}^{-1}$; [19–20] TEG: $K_a < 10 \text{ M}^{-1}$). The association constant of α -CD with the *trans*-azobenzene unit of pAC₁₂Azo has been reported to be $K_a = 1100 \text{ M}^{-1}$, [21] thus indicating that C₁₂CA₂Na₂ functions as an

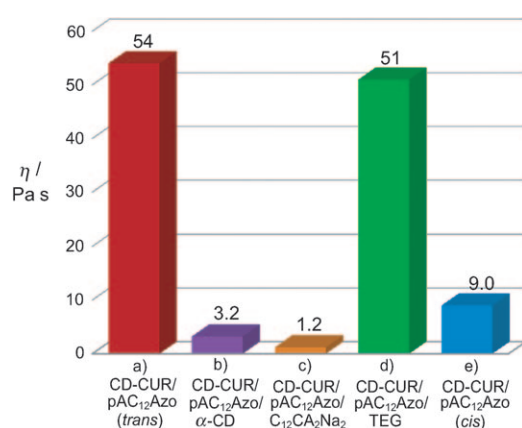


Figure 2. Zero-shear viscosities for CD-CUR/pAC₁₂Azo, CD-CUR/pAC₁₂Azo a) alone and b) in the presence of 4 equiv of α -CD per azo unit, c) 4 equiv of C₁₂CA₂Na₂ per α -CD unit, d) 4 equiv of TEG per α -CD unit, and e) CD-CUR/pAC₁₂Azo after UV irradiation. CD-CUR/pAC₁₂Azo was mixed in a 1:1 ratio of the α -CD unit and the azo unit (4.0 wt%/8.6 wt%).

effective competitive guest. TEG did not act as a competitive guest for the α -CD unit even after addition of TEG to the CD-CUR/pAC₁₂Azo hydrogel. These results indicate that the complex formation between the α -CD unit in CD-CUR and the azo group in pAC₁₂Azo led to the formation of the supramolecular hydrogel.

Photoirradiation with UV light ($\lambda = 365 \text{ nm}$) caused an isomerization of the *trans*-azo group in pAC₁₂Azo to the *cis*-azo group (*trans/cis* = 12:88), whereas visible light ($\lambda = 430 \text{ nm}$) or heating (60°C) caused the isomerization of the azo group from *cis* to *trans* (*trans/cis* = 75:25; Figure 3). UV irradiation ($\lambda = 365 \text{ nm}$) of the supramolecular hydrogel consisting of CD-CUR/pAC₁₂Azo caused a decrease in the viscosity of the hydrogel to give the sol. The average η_0 value for CD-CUR/pAC₁₂Azo after photoirradiation was 9 Pa s (Figure 2e). In contrast, UV irradiation at $\lambda = 430 \text{ nm}$ (or heating) of the sol state recovered the viscosity of the system to give the hydrogel within two minutes (Figure 4, red line). The viscosity changes of CD-CUR/pAC₁₂Azo could be repeatedly induced by using both UV and visible light. The

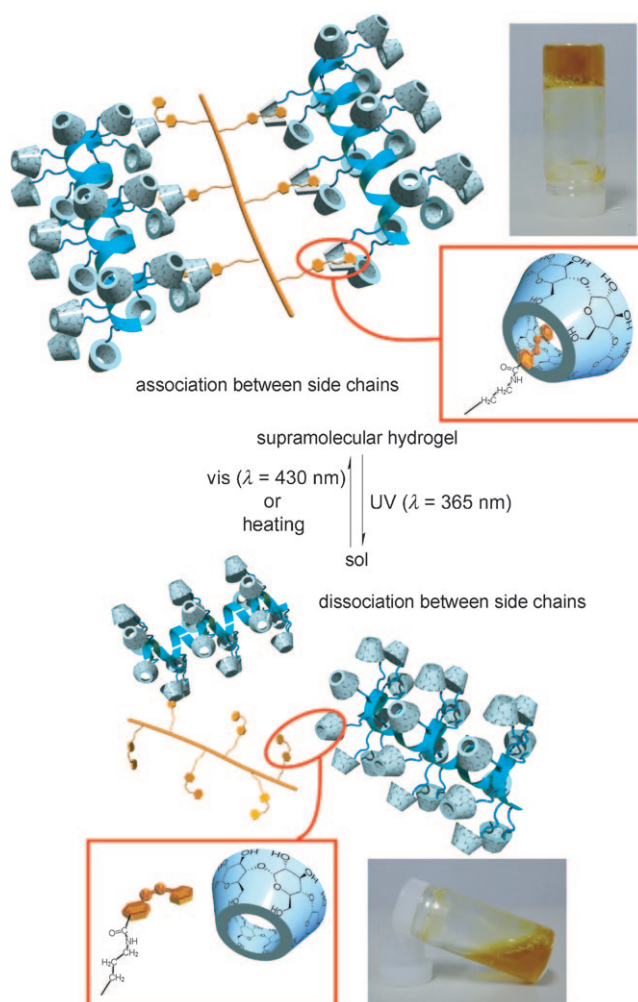


Figure 3. Schematic representation of the interactions of the α -CD unit (cylindrical shapes) with azobenzene moieties (yellow shapes) upon irradiation with UV (365 nm) and visible light (430 nm) or heating at 60°C .

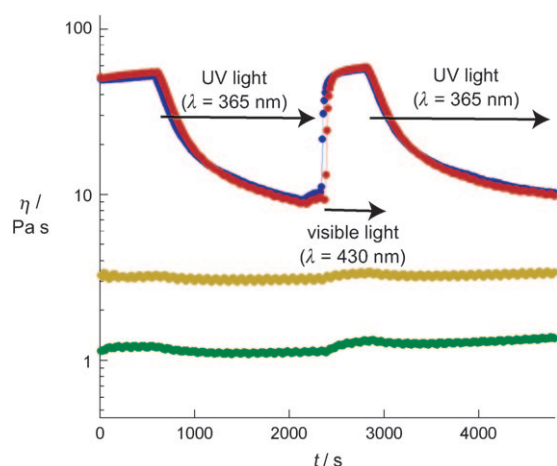


Figure 4. Zero-shear viscosity change for CD-CUR/pAC₁₂Azo after repeated photoirradiation with UV ($\lambda = 365$ nm) and visible light ($\lambda = 430$ nm, red line). Photoisomerization behavior of CD-CUR/pAC₁₂Azo in the presence of 4 equiv of C₁₂CA₂Na₂ (green line), TEG (blue line), and α -CD (yellow line), respectively.

association constant of α -CD with the *trans*-azobenzene unit ($K_a = 1100 \text{ M}^{-1}$) is much larger than that with the *cis*-azobenzene ($K_a = 4.1 \text{ M}^{-1}$).^[21–22] These results indicate that the control of the association and dissociation between the α -CD unit and the azo unit by photoirradiation affected the phase transition. TEG has an insignificant effect on the viscosity change of CD-CUR/pAC₁₂Azo after photoirradiation, even when mixing TEG with the CD-CUR/pAC₁₂Azo hydrogel (Figure 4; blue line). On the other hand, the change of viscosity in the CD-CUR/pAC₁₂Azo hydrogel in the presence of α -CD (yellow line) or C₁₂CA₂Na₂ (green line) was negligible, because the azo unit just associates and dissociates during the isomerization in the presence of large amounts of α -CD. In the presence of C₁₂CA₂Na₂, the *cis/trans* isomerization of the azo unit takes place outside the α -CD cavity.

The interaction of the α -CD moieties of CD-CUR with pAC₁₂Azo was studied by 2D NOESY spectra before and after photoirradiation (Figure S14a in the Supporting Information). The CD-CUR/pAC₁₂Azo system with the *trans*-azo group showed that the inner protons of the α -CD unit were correlated to the protons of the *trans*-azo group and alkyl moieties in pAC₁₂Azo, hence indicating that the side chain of pAC₁₂Azo was included in the α -CD cavity of CD-CUR in aqueous solutions. After photoirradiation of the NMR sample at $\lambda = 365$ nm, 88% of the *trans*-azo units isomerized to the *cis* configuration (*trans/cis* = 12:88). The *cis*-azo unit of pAC₁₂Azo showed no correlation peaks to the α -CD moieties in CD-CUR (Figure S14b in the Supporting Information). These results indicate that photoirradiation causes dissociation of inclusion complexes of CD-CUR/pAC₁₂Azo.

In conclusion, we successfully designed a photoswitchable supramolecular sol–gel system that contains CD-CUR and pAC₁₂Azo. Although the microscale switching of the inclusion complex between α -CD and azo compounds by light is well-known, the morphological change has been difficult to achieve on the macroscale because the association constant of α -CD with azo compounds is small.^[21] Supramolecular hydro-

gels could be formed by using a main chain with a sufficient length and an adequate number of guest molecules to generate multiple cross-links between CD-CUR and pAC₁₂Azo. Additionally, the morphology of the supramolecular hydrogels can be switched by photoirradiation with the appropriate wavelength to control the formation of an inclusion complex. The inclusion complex of azo and α -CD acts as a supramolecular fastener between the side chains. Thus, the connection or disconnection between the two polymers can be controlled by light.

Experimental Section

Synthesis of CD-CUR: 3-propargylamide glutaric α -CD (430 mg, 0.37 mmol), L-ascorbic acid (34 mg, 0.19 mmol), CuBr₂ (14 mg, 0.06 mmol), and propylamine (7 mL, 148 mmol) were added to a solution of 6-azido-curdan (40 mg, 0.21 mmol in glucose unit) in DMSO (10 mL). The solution was stirred for one week, and then dialyzed by distilled water for one week. The dialyzed solution was lyophilized to afford CD-CUR as a white powder in 63% yield. ¹H NMR (500 MHz, [D₆]DMSO, 30 °C): δ = 1.73 (br, CH₂(CH₂)₂), 2.12 (br, CH₂CONH), 3.30–4.15 (br, CH(1)–CH(5) (CD), CH(2)–CH(6) (CUR), and CH₂NHCO overlapping with HOD), 4.50 (m, CH₂OH(6) (CD)), 4.78 (m, CH₂(6) (CD), CH(1) (CUR)), 5.11 (br, CHOH(4) (CUR)), 5.40 (m, CHOH(2) (CD)), 5.60 (m, CHOH(3) (CD)), 5.86 (br, CHOH(2) (CUR)), 7.69 (br, CHNHCO), 8.00 (s, triazole-H), 8.22 ppm (br, CH₂CONH). ¹³C NMR (125 MHz, [D₆]DMSO, 30 °C): δ = 172.3 (amido), 132.0 (triazole), 129.2 (triazole), 102.9 (C1 (CD)), 102.6 (C1 (CUR)), 83.6 (C3 (CUR)), 72.5 (C3,C4,C5 (CD), C2,C4,C5 (CUR)), 60.6 (C6 (CD)), 35.4 (alkyl).

Received: June 11, 2010

Published online: September 6, 2010

Keywords: azo compounds · cyclodextrins · gels · host–guest systems · supramolecular chemistry

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