Photoresponsive Materials

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# Photoswitchable Supramolecular Hydrogels Formed by Cyclodextrins and Azobenzene Polymers**

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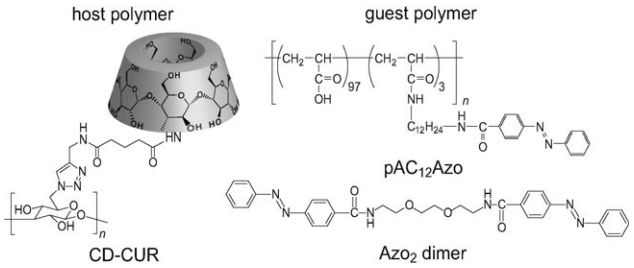
Hydrogels are ubiquitous in nature, especially in living organisms.[1] Synthetic hydrogels are used, for example, for tissue engineering, drug delivery systems (DDS), and medical treatment.[2] There are mainly two kinds of gels: physical gels[3] and chemical gels.[4] Hydrogels with noncovalent cross-linking points are supposed to be more versatile and easily tunable than those with covalent bonds. Although low-molecular-weight physical gels exhibit photoresponsible 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 C6 positions by the modified α-CD to obtain CD-CUR with a substitution degree of 98%. When the azo-modified poly(acrylic acid) ($pAC_{12}Azo$), 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)/$pAC_{12}Azo$ mixture, the CD-CUR/poly(acrylic acid) (pAA, without the azo unit) mixture, and the CD-CUR/azo-guest-dimer ($Azo_2Dimer$) 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 $pAC_{12}Azo$ play important roles in the formation of the supramolecular hydrogel. Figure 1 a–d shows the zero-shear viscosities ($\eta_0$) for CD-CUR/$pAC_{12}Azo$ (a), CUR/$pAC_{12}Azo$ (b), CD-CUR/pAA (c), and CD-CUR/$Azo_2Dimer$ (d), respectively. Although CUR/$pAC_{12}Azo$, CUR/$Azo_2Dimer$, and CD-CUR/pAA showed low viscosities (less than 3 Pa s), CD-CUR/$pAC_{12}Azo$ 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 $pAC_{12}Azo$ were mixed in different monomer unit ratios (CD/Azo = 4:1, 1:1, 1:4), the largest $\eta_0$ value was obtained for the 1:1 monomer ratio of CD-CUR/$pAC_{12}Azo$, thus indicating the effective formation of complementary inclusion complexes (Figure 1 e–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/$pAC_{12}Azo$ hydrogel. Addition of α-CD to the CD-CUR/$pAC_{12}Azo$ hydrogel led to the transformation of the gel into the sol. Figure 2 b shows zero shear viscosities ($\eta_0$) for CD-CUR/$pAC_{12}Azo$ in the presence of four equivalents of α-CD per azo unit of $pAC_{12}Azo$. The $\eta_0$ value of CD-CUR/$pAC_{12}Azo$ with additional α-CD was similar to that of CUR/$pAC_{12}Azo$




***Scheme 1.*** Structures of the compounds used.

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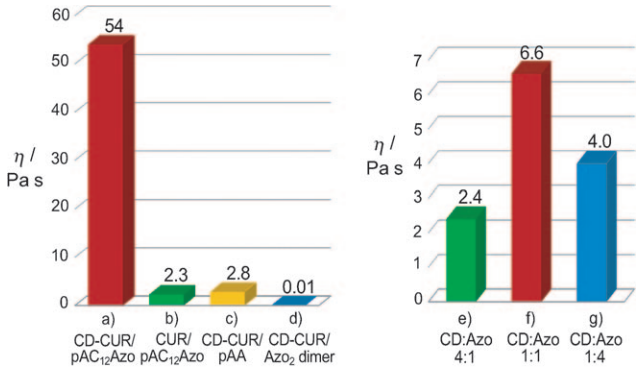


***Figure 1.*** Zero-shear viscosities for a) CD-CUR/pAC$_{12}$Azo (4.0 wt%/8.6 wt%; 1:1 CD/Azo), b) CUR/pAC$_{12}$Azo (0.5 wt%/8.6 wt%; 1:1 glucopyranose/Azo), c) CD-CUR/pAA (4.0 wt%/7.2 wt%; 1:1 CD/acryl), d) CD-CUR/Azo$_2$Dimer (4.0 wt%/1.7 wt%; 1:1 CD/Azo). Concentration ratios and monomer unit ratios are shown in parentheses. The concentration ratios of CD-CUR/pAC$_{12}$Azo 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 pAC$_{12}$Azo. When four equivalents of 1,12-decanedicarboxylate sodium salt ($C_{12}CA_2Na_2$) per α-CD group of CD-CUR were added to the CD-CUR/pAC$_{12}$Azo 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/pAC$_{12}$Azo hydrogel did not affect the viscosity as shown in Figure 2d. The viscosity of CD-CUR/pAC$_{12}$Azo/TEG is comparable to that of CD-CUR/pAC$_{12}$Azo. The association constant of α-CD with $C_{12}CA_2Na_2$ is significantly larger than that with TEG ($C_{12}C_2Na_2$: $K_a = 5400\,M^{-1}$;[19–20] TEG: $K_a < 10\,M^{-1}$). The association constant of α-CD with the *trans*-azobenzene unit of pAC$_{12}$Azo has been reported to be $K_a = 1100\,M^{-1}$,[21] thus indicating that $C_{12}CA_2Na_2$ functions as an 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/pAC$_{12}$Azo hydrogel. These results indicate that the complex formation between the α-CD unit in CD-CUR and the azo group in pAC$_{12}$Azo led to the formation of the supramolecular hydrogel.

Photoirradiation with UV light ($\lambda = 365$ nm) caused an isomerization of the *trans*-azo group in pAC$_{12}$Azo to the *cis*-azo group (*trans*/*cis* = 12:88), whereas visible light ($\lambda$=430 nm) or heating (60 °C) caused the isomerization of the azo group from *cis* to *trans* (*trans*/*cis* = 75:25; Figure 3). UV irradiation ($\lambda = 365$ nm) of the supramolecular hydrogel consisting of CD-CUR/pAC$_{12}$Azo caused a decrease in the viscosity of the hydrogel to give the sol. The average $\eta_0$ value for CD-CUR/pAC$_{12}$Azo after photoirradiation was 9 Pa s (Figure 2e). In contrast, UV irradiation at $\lambda = 430$ 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/pAC$_{12}$Azo could be repeatedly induced by using both UV and visible light. The

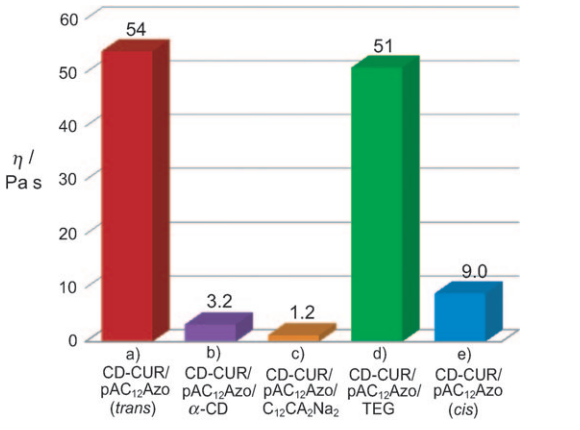


***Figure 2.*** Zero-shear viscosities for CD-CUR/pAC$_{12}$Azo, CD-CUR/pAC$_{12}$Azo a) alone and b) in the presence of 4 equiv of α-CD per azo unit, c) 4 equiv of $C_{12}CA_2Na_2$ per α-CD unit, d) 4 equiv of TEG per α-CD unit, and e) CD-CUR/pAC$_{12}$Azo after UV irradiation. CD-CUR/pAC$_{12}$Azo was mixed in a 1:1 ratio of the α-CD unit and the azo unit (4.0 wt/8.6 wt%).

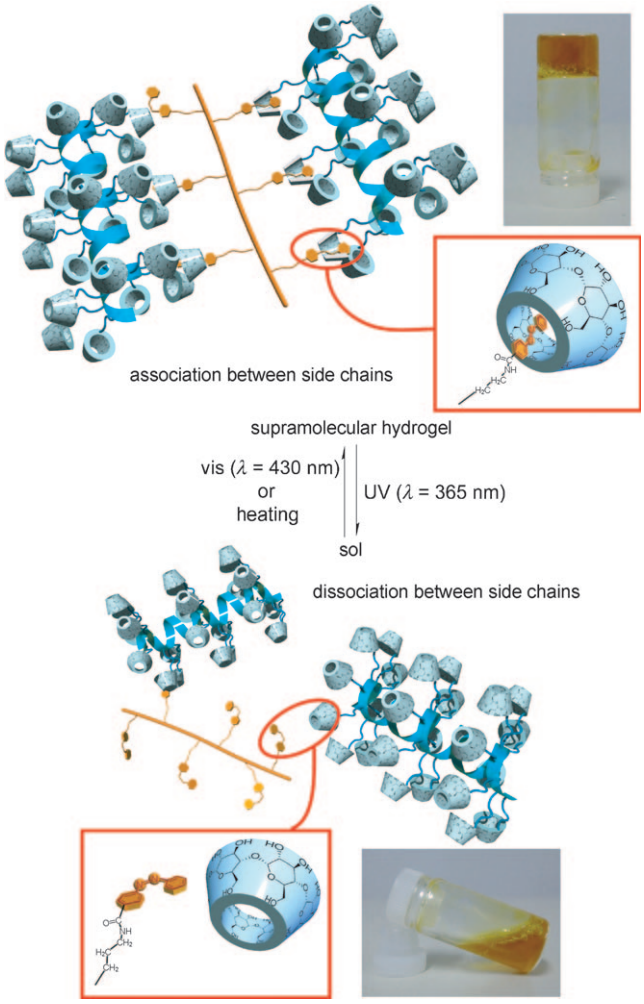


***Figure 3.*** Schematic representation of the interactions of the α-CD unit (cylindrical shapes) with azobenzene moieties (yellow shapes) upon irradiation with UV (365 nm) and visible light (430 nm) or heating at 60 °C.

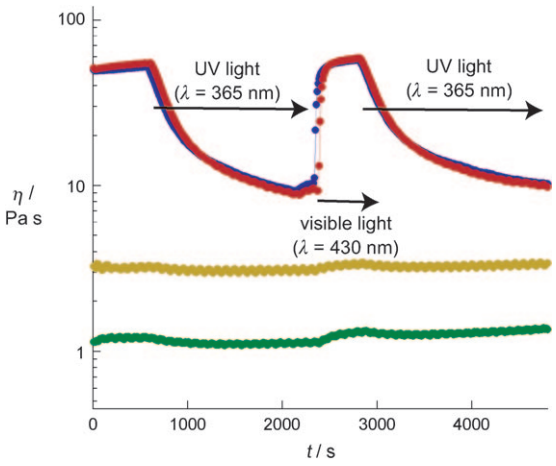


***Figure 4.*** Zero-shear viscosity change for CD-CUR/$pAC_{12}$Azo after repeated photoirradiation with UV ($\lambda = 365$ nm) and visible light ($\lambda = 430$ nm, red line). Photoisomerization behavior of CD-CUR/$pAC_{12}$Azo in the presence of 4 equiv of $C_{12}CA_2Na_2$ (green line), TEG (blue line), and α-CD (yellow line), respectively.

association constant of α-CD with the *trans*-azobenzene unit ($K_a = 1100\,M^{-1}$) is much larger than that with the *cis*-azobenzene ($K_a = 4.1\,M^{-1}$).[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/$pAC_{12}$Azo after photoirradiation, even when mixing TEG with the CD-CUR/$pAC_{12}$Azo hydrogel (Figure 4; blue line). On the other hand, the change of viscosity in the CD-CUR/$pAC_{12}$Azo hydrogel in the presence of α-CD (yellow line) or $C_{12}CA_2Na_2$ (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 $C_{12}CA_2Na_2$, 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 $pAC_{12}$Azo was studied by 2D NOESY spectra before and after photoirradiation (Figure S14a in the Supporting Information). The CD-CUR/$pAC_{12}$Azo 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 $pAC_{12}$Azo, hence indicating that the side chain of $pAC_{12}$Azo was included in the α-CD cavity of CD-CUR in aqueous solutions. After photoirradition 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 $pAC_{12}$Azo 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/$pAC_{12}$Azo.

In conclusion, we successfully designed a photoswitchable supramolecular sol–gel system that contains CD-CUR and $pAC_{12}$Azo. 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 hydrogels 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 $pAC_{12}$Azo. 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), $CuBr_2$ (14 mg, 0.06 mmol), and propylamine (7 mL, 148 mmol) were added to a solution of 6-azido-curdlan (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. $^1$H NMR (500 MHz, [$D_6$]DMSO, 30 °C): $\delta = 1.73$ (br, $CH_2(CH_2)_2$), 2.12 (br, $CH_2$CONH), 3.30–4.15 (br, CH(1)–CH(5) (CD), CH(2)–CH(6) (CUR), and $CH_2$NHCO overlapping with HOD), 4.50 (m, $CH_2OH$(6) (CD)), 4.78 (m, $CH_2$(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, $CH_2CONH$). $^{13}$C NMR (125 MHz, [$D_6$]DMSO, 30 °C): $\delta = 172.3$ (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).

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