Supramolecular Chemistry

DOI: 10.1002/anie.200701272

A Chemical-Responsive Supramolecular Hydrogel from Modified Cyclodextrins**

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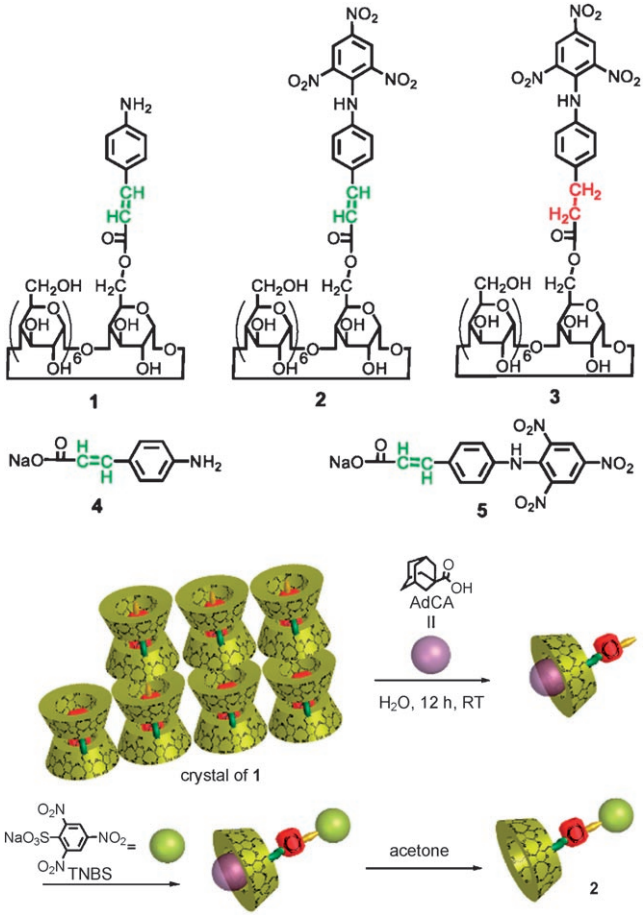
The design and preparation of molecular hydrogels has attracted increasing attention because of their intrinsic scientific interest and technological applications. Elegant hydrogels were reported to lead to new polymeric systems with remarkable properties.[1] Supramolecular gels, in particular, which are held together by noncovalent bonds and showing responses to external stimuli, have the potential to act as biodegradable materials in drug-delivery systems and chemical sensors.[2] Supramolecular gels form from the self-assembly of subunits and lead to the formation of a three-dimensional network of intertwined, elongated fibrils that immobilize the solvent molecules on the macroscopic scale. It is well known that cyclodextrins (CDs) incorporate various guest compounds into their cavities through hydrophobic interactions to form inclusion complexes in aqueous media. We have reported many kinds of supramolecular polymers from modified CDs.[3] Furthermore, CD units can congregate together through hydrogen-bonding interactions, as a consequence of the abundant number of OH groups on the CD ring. Many research groups have reported that the mixture of CDs with polymers resulted in the formation of supramolecular gels.[4] Biodegradable gels without a polymeric backbone seem more advantageous and more applicable to biological applications and environmental protection. To our knowledge, there is no report about gel formation from modified CDs in aqueous solutions in the absence of polymers.[5] Herein, we report for the formation of a supramolecular gel from aqueous solutions of modified CDs.

Previously, we reported the formation of a supramolecular oligomer from 6-aminocinnamoyl-β-CD derivative **1** (Scheme 1).[6] Compound **1** forms crystals from a supersaturated solution. The X-ray structure shows that **1** forms intermolecular complexes in a tail-to-tail fashion and so the dimer stacks tightly through the formation of intermolecular hydrogen bonds to form a head-to-head channel-type structure.[7] Therefore, much attention has been paid to the modification of **1** to avoid formation of the dimer.[3b,6c]



Scheme 1. Compounds **1**–**5** and the synthesis of **2**.

In the current study, a trinitrophenyl group was directly linked to **1** to give [*N*-(2,4,6-trinitrophenyl)-6-amino-*trans*-cinnamoyl]-β-CD (**2**; Scheme 1). The 2D ROESY NMR spectrum (Figure 1) shows the rotational NOE (ROE) interactions between the inner protons of the CD and both protons of 2,4,6-trinitrophenyl (TNB) as well as the cinnamic protons, thus indicating that these units are included in the CD cavities, and that the trinitrophenyl group, a traditional stopper for α-CDs, acts as a good guest for β-CD. The observed C(1)H protons are widely dispersed in the range from $\delta = 4.8$ to 5.5 ppm, which is due to the reduction of the sevenfold symmetry of the modified CD after inclusion of the substituent at the 6-position of the β-CD in the other CD cavity.[8] Protons a and b in the cinnamoyl moiety show strong

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[**] This work was partially supported by Grant in-Aid no. S14103015 for Scientific Research, and has been conducted with financial support from the 21st Century COE (Center of Excellence) program of the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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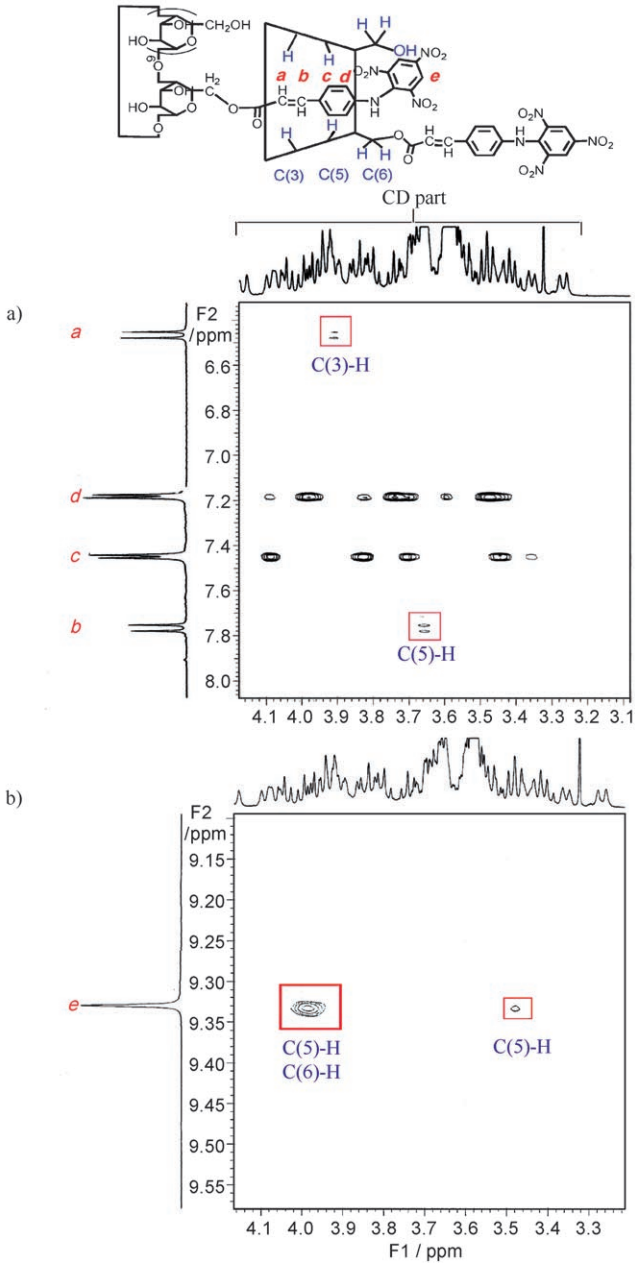

Figure 1. 2D ROESY ^{1}H NMR spectra of **2** (5 mM, D_2O, 30 °C). The correlations of the protons of the CD with the protons of cinnamoyl moiety (a), and the protons of CD with the protons of the TNB group (b).

correlations with the C(3)H and C(5)H protons of the β-CD, respectively. Furthermore, the protons of the 2,4,6-trinitrophenyl ring show correlations with the C(5)H and C(6)H protons of the β-CD, which is indicative of the formation of the tail-to-head structure instead of a tail-to-tail structure. The model compounds sodium 6-aminocinnamoyl acid (**4**) and *N*-(2,4,6-trinitrophenyl)-6-aminocinnamoyl salt (**5**) were also synthesized (Scheme 1). It was found by Job's plots that 1:1 inclusion complexes were formed between the β-CD and **4** and **5**. Furthermore, the Benesi–Hildebrand plots show that the affinity of β-CD for **4** is markedly enhanced: over four times greater than that for **5** (see the Supporting Information). Vapor pressure osmometry (VPO) measurements of **2** indicate that the molecular weight is about 16000 at 5 mM in aqueous solutions, as evident from the high affinity—about 13 times that of the monomer (Figure 2). These results imply that the modified β-CD formed supramolecular fibrils as the initial step of supramolecular gelation.

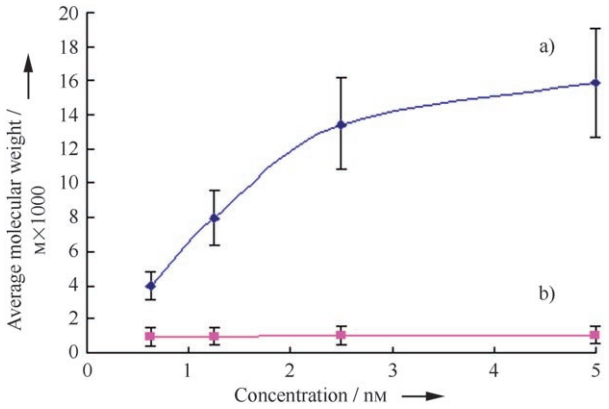

Figure 2. Effect of the concentration on the molecular weight of **2** (a) and α-CD (b) as observed by VPO measurements at 40 °C.

The novel modified-CD supramolecules **2** were prepared in aqueous solutions at 70 °C followed by cooling down to room temperature. When the concentration was changed from 5 mM to 10 mM, the clear solution became a mixture of gel and solution (Figure 3). Increasing the concentration of **2** to 20 mM, a russet-colored hydrogel was formed with a phase transition temperature of approximately 50 °C; the critical gel concentration was calculated to be 2.9 wt %.

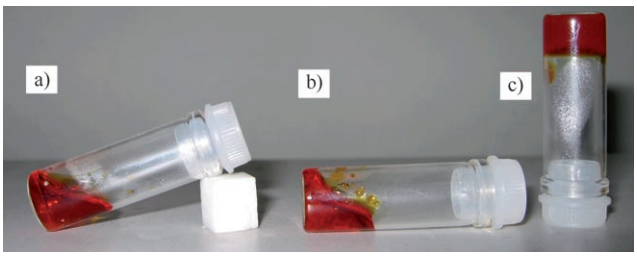

Figure 3. Concentration-dependence of the supramolecular gel at 25 °C a) 5 mM, b) 10 mM, and c) 20 mM.

In contrast, [*N*-(2,4,6-trinitrophenyl)-6-aminohydrocinnamoyl]-β-CD (**3**) forms a precipitate when the super-saturated solution is cooled down (see the Supporting Information). In our previous studies it was found that modified CDs with flexible hydrocinnamic groups formed self-inclusion complexes in water, while the rigid cinnamic group inhibited formation of the intramolecular complex.[5a,9] These findings are also supported by comparing the circular dichroism spectra of **2** and that of **3** in the presence of β-CD in water (see the Supporting Information).

The morphology of **2** was investigated by optical microscopy (see the Supporting Information) and atom force

microscopy (AFM). The optical micrograph is characteristic of supramolecular fibrils. The AFM image is typical for a small organic molecular gel: all the fibrils cross-link each other to form a three-dimensional network (Figure 4). The

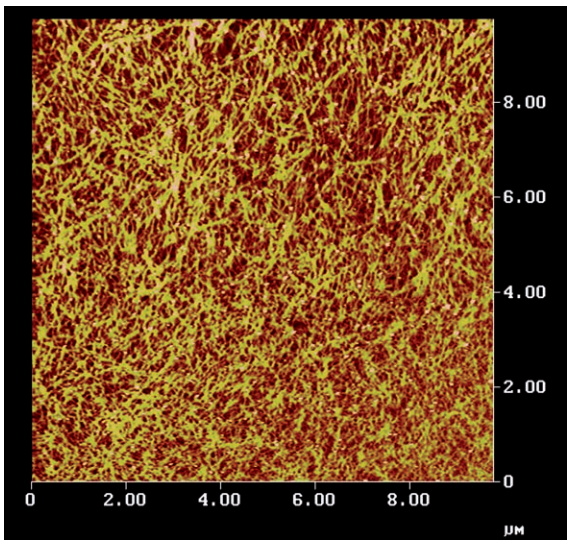

Figure 4. AFM image of **2** obtained from a 2 mM aqueous solution of **2** on a mica substrate.

hydrogen bonds between the neighboring fibrils are proposed to act as physical cross-linkers, and arise from the abundant OH groups on the CD ring. Therefore, the proposed mechanism for the supramolecular gelation is: firstly, supramolecular fibrils of the modified CD are formed by self-assembly through host–guest interactions, and then the formation of hydrogen bonds between the CDs results in cross-linking of the fibrils and leads to formation of the hydrogel.

Gel-to-sol transitions occurred on the addition of two equivalents of 1-adamantane carbonyl acid (AdCA) and 2 M urea as a strong guest compound and a denaturing reagent, respectively. The chemical-responsive properties of **2** were monitored by ^{1}H NMR and induced circular dichroism (ICD) spectroscopy (Figure 5). The observed ICD band in the 220–350 nm region of the spectrum is assigned to the circular dichroism band induced by the inclusion of the guest in the β-CD. The partial ^{1}H NMR spectrum of **2** in the presence of AdCA reveals that the proton signals of the guest are shifted downfield. The dispersed signals of the C(1)H protons are shifted to around $\delta = 5.1$ ppm. Furthermore, the ICD spectrum of **2** with AdCA shows that the ICD bands around 233 nm, 259 nm, and 313 nm are significantly weakened, and positive-to-negative changes occur around 282 nm and 353 nm. These changes suggest that the guest moieties were ejected from the CD cavities by AdCA which breaks the supramolecular polymers. Treatment of the hydrogel **2** with 2 M urea resulted in no or slight changes of the characteristic signals in both the ^{1}H NMR and ICD spectra, thus implying that urea acts as a denaturing agent, which only breaks the hydrogen bonds between the CDs. Addition of β-CD resulted in the formation of a precipitate instead of a hydrogel. The

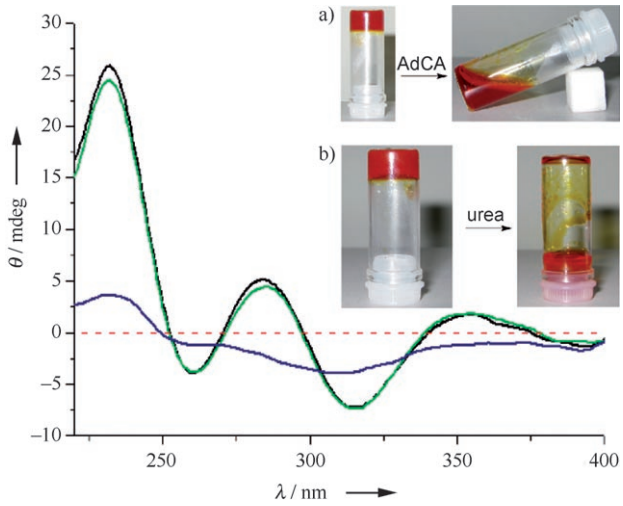

Figure 5. Circular dichroism spectra of 1 mM **2** (black line), in the presence of 2 M urea (green line), and in the presence of an excess of AdCA (blue line). The inset shows the gel-to-sol transition upon addition of a) 40 mM AdCA and b) 2 M urea to a 20 mM solution of **2**.

^{1}H NMR spectrum of **2** shows no change. However, the ICD bands at 220–250 and 295–340 nm decrease significantly with increasing β-CD concentrations (see the Supporting Information). Therefore, the destroyed hydrogel in the presence of β-CD should be ascribed to the complex formation of the native β-CD with compound **2**, which acts as a competitive host and shortens the length of the fibrils. All of the chemical-responsive experiments are in agreement and confirm the proposed mechanism.

In conclusion, a novel supramolecular hydrogel has been synthesized from a guest-modified cyclodextrin without a polymer backbone. The modified β-CD forms supramolecular fibrils through host–guest interactions, and then the formation of hydrogen bonds between the CDs results in cross-linking of the fibrils to give a hydrogel. Gel-to-sol transitions can be effected by adding a competitive guest or urea as a denaturing reagent. Thus, this system has potential applications in biomedical and material science.

Experimental Section

Materials: β-CD, sodium hydroxide (NaOH), and p-toluenesulfonyl chloride were obtained from Nacalai Tesque, Inc. 4-Aminocinnamic acid, 4-aminohydrocinnamic acid, sodium, 2,4,6-trinitrobenzene-1-sulfonate dehydrate (TNBS), and 1-adamantane carbonyl acid (AdCA) were obtained from Tokyo Chemical Industry, Co., Ltd. [D_6]DMSO and D_2O were purchased from Aldrich.

Measurements: The ^{1}H NMR spectra were recorded on a 400 MHz Joel Jnm Ex-270 spectrometer at 30 °C. Chemical shifts were referenced to the external standard in the solvent. 2D NMR (mixing time for the modified CDs and 1:1 complexes are 600 and 200 ms respectively) measurements were obtained at 400 MHz on a Varian Unity plus NMR spectrometer. FTIR measurements were performed on a Jasco FT/IR-410 spectrometer. KBr was used as the dispersant. Elemental analyses were recorded on an Elementar Vario EL-III instrument. The circular dichroism spectra and UV spectra were recorded on a Jasco J820 spectrometer in water with a 0.1-cm cell at room temperature. Positive-ion matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry experi-

ments were performed on a Shimadzu/Kratos Axima CFR V2.2.1 mass spectrometer. Vapor pressure osmometry measurements were recorded on a Knauer No. A0280 vapor osmometer at 40 °C. Aqueous NaCl solution and α-CD were used as the instrument standards.

Synthesis of **2**: AdCA (35.2 mg, 0.195 mmol) was added to a suspension of **1** (83.2 mg, 0.648 mmol) in H_2O (30 mL). After the mixture had been stirred for 12 h at room temperature, the suspension gradually became clear, and the precipitate was removed by filtration. Then, TNBS (39.0 mg, 0.111 mmol) was added, and the mixture stirred for one day. The obtained orange transparent solution was poured into acetone. The precipitate was isolated by filtration, washed with acetone, and dried under vacuum. Yield: 62 %. Positive ion MALDI-TOF MS: *m*/*z*: 1515.1 $[M+Na]^+$ (calcd: 1514); IR: $\tilde{\nu}$ = 3380, 2928, 1636, 1514, 1345, 1031 cm^{-1}; ^1H NMR (400 MHz, $[D_6]$DMSO): $\delta = 10.22$ (s, 1H, NH), 8.81 (brs, 2H, TNB), 7.61 (m, 3H, phenyl and CH=C), 7.05 (brs, 2H, phenyl), 6.59 (d, $J = 16.1$ Hz, 2H, CH=C), 5.77–5.64 (m, 14H, O(2)H and O(3)H of β-CD), 4.90–4.83 (m, 7H, C(1)H of β-CD), 4.50–4.25 (m, O(6)H and C(6′)H of β-CD), 3.92–3.16 ppm (m, overlaps with HOD); ^{13}C NMR (400 MHz, $[D_6]$DMSO): $\delta = 166.0$ (CO), 139.8, 139.6, 129.4, 129.35, 126.61, 126.56, 126.54 (C_{Ar}), 101.9 (C(1) of β-CD), 81.6 (C(4) of β-CD), 73.0 (C(3) of β-CD), 72.4 (C(2) of β-CD), 72.0 (C(5) of β-CD), 59.9 (C(6) of β-CD), 58.7 ppm (C(6′) of β-CD); elemental analysis calcd (%) for $C_{57}H_{78}O_{42}N_4 \cdot 9.5\,H_2O$: C 41.18, H 5.88, N 3.37; found: C 42.01, H 5.88, N 3.31.

Synthesis of **3**: TNBS (80.0 mg, 0.222 mmol) was added to a suspension of 6-AmHyCiO-β-CD (166 mg, 0.13 mmol) in H_2O (10 mL). The mixture was stirred for one day and the suspension gradually became clear. The solution was concentrated to 5 mL, and poured into acetone (50 mL). The resulting precipitate was washed 3 times with acetone, and dried under vacuum to give the crude product. Yield: 65 %. Positive ion MALDI-TOF MS: *m*/*z*: 1518.6 $[M+Na]^+$ (calcd: 1516); IR: $\tilde{\nu}$ = 3375, 2931, 1719, 1621, 1339, 1029 cm^{-1}; ^1H NMR (400 MHz, $[D_6]$DMSO): $\delta = 10.16$ (brs, 1H, CONH), 8.83 (brs, 2H, TNB), 7.16 (d, $J = 7.8$ Hz, 2H, phenyl), 6.98 (brs, 2H, phenyl), 5.77–5.64 (m, 14H, O(2)H and O(3)H of β-CD), 4.85–4.82 (m, 7H, C(1)H of β-CD), 4.44–4.28 (m, O(6)H and C(6′)H of β-CD), 3.84–3.16 (m, overlaps with HOD), 2.82 (t, $J = 7.3$ Hz, 2H, CH_2), 2.63 ppm (m, 2H, CH_2); ^{13}C NMR (400 MHz; $[D_6]$DMSO): δ = 171.8 (CO), 140.3, 138.7, 135.0, 129.2, 128.9, 127.6, 126.8, 121.1 (Ar), 101.9 (C(1) of β-CD), 81.6 (C(4) of β-CD), 73.0 (C(3) of β-CD), 72.4 (C(2) of β-CD), 72.0 (C(5) of β-CD), 59.9 (C(6) of β-CD), 57.2 (C(6′) of β-CD), 34.6 (C of CH_2), 29.6 ppm (CH_2); elemental analysis calcd (%) for $C_{57}H_{80}O_{42}N_4 \cdot 7.5\,H_2O$: C 42.04, H 5.88, N 3.44; found: C 42.10, H 5.83, N 3.39.

Received: March 3, 2007
Published online: May 25, 2007

Keywords: cyclodextrins · host–guest systems · hydrogels · self-assembly · supramolecular chemistry

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