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# Self-Assembly of Gels through Molecular Recognition of Cyclodextrins: Shape Selectivity for Linear and Cyclic Guest Molecules

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Ⓢ Supporting Information

## INTRODUCTION

Since the 1970s, much attention has been attracted to molecular recognition,[1] host−guest chemistry,[2] and supramolecular complexes.[3] Recently, interests in the field of self-organization of molecules[4] have been extending to those in supramolecular polymers[5] and materials.[6] Although there have been numerous studies on the self-assembly and self-organization of molecules,[7] there are few on macroscopic scale self-assembly. Self-assembly with macroscopic dimensions has been reported using macroscopic interactions such as hydrophile−lipophile balance,[8] capillary effects,[9] magnetic interactions,[10] and electrostatic interactions.[11] However, the self-assembly of macroscopic materials through molecular recognition is one of the biggest challenges. If molecular recognition works on the macroscopic scale, then macroscopic self-assembly based on molecular recognition may allow a variety of architectures and functions to be realized in a manner similar to living things and, thus, significantly broadening the field of materials science. Previously, we have reported on macroscopic self-assembly through molecular recognition using polyacrylamide gels containing host molecules or guest molecules.[12] A $\beta$-cyclodextrin ($\beta$-CD)-gel, for example, bound an adamantane gel strongly to give a combined gel. $\beta$-CD-gel bound to *tert*-butyl-gel, but not to *n*-butyl-gel.

Herein we demonstrated that molecular recognition of CDs for linear and cyclic guest moieties attached to the gels could lead to the specific assembly of gels, which are on the millimeter/centimeter scale. α-CD-gel bound a gel containing linear alkyl groups to give an association, although α-CD-gel did not bind a cyclic alkyl-gel at all. In contrast, $\beta$-CD- or $\gamma$-CD-gel bound the cyclic alkyl-gel strongly, although it did not bind the linear alkyl-gel. This is the first example to visualize specific molecular recognition of CDs for linear and cyclic alkyl guests on a macroscopic scale. The assembly of host-gels with guest-gels was found to be reversible. The mechanical strength of the assembled gel could be regulated by the mole content of guest moiety in the guest gels.

## MATERIALS AND METHODS

Cyclodextrins (α-, $\beta$-, and $\gamma$-CDs) were obtained from Junsei Chemical Co., Ltd. (Tokyo, Japan). $NaHCO_3$, NaOH, acetone, methanol, triethylamine, THF, chloroform, dimethyl sulfoxide (DMSO), 2,2′-azobis(isobutyronitrile) (AIBN), ammonium peroxodisulfate (APS), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and *N,N′*-methylenebis(acrylamide) were obtained from Nacalai Tesque Inc. (Kyoto, Japan). *n*-Hexyl acrylate, cyclohexyl acrylate, *n*-dodecylamine, and cyclododecylamine were obtained from Tokyo Kasei Co., Ltd. (Tokyo, Japan). Acrylamide and *n*-dodecyl acrylate were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). CDs were recrystallized twice from distilled water. The other materials were used without further purification. Mono-6-deoxy-6-amino-CDs were prepared according to the literature reported by Toda et al.[13]

Acrylamido-α-CD and acrylamido $\beta$-CD were prepared according to the literature previously reported by our group.[12] Acrylamido-$\gamma$-CD was synthesized by coupling of acryloyl chloride with 6-amino-$\gamma$-CD (see Supporting Information). CD-gels were prepared by copolymerization of acrylamide (6.1 mmol), 6-acrylamido-CD (CD = α-/$\beta$-/$\gamma$-CD, respectively, 0.31 mmol) and *N,N′*-methylenebis(acrylamide) (0.12 mmol) by radical polymerization initiated by a redox pair of APS and TMEDA in water. Guest-gels were prepared by copolymerization of acrylamide, acrylate, or acrylamide derivative bearing a guest moiety and *N,N′*-methylenebis(acrylamide) by radical polymerization using AIBN in DMSO at 63 °C (see Supporting Information). An acrylamide gel bearing neither CDs nor guest moieties was also prepared as a blank-gel in a similar manner.

Water-soluble guest polymers bearing guest moieties were also prepared by copolymerization of acrylamide (31 mmol) and alkyl acrylate or alkylacrylamide (1.6 mmol) by a radical polymerization using AIBN (0.04 mmol) in DMSO at 60 °C. These soluble guest polymers bearing *n*-hexyl, cyclohexyl, *n*-dodecyl, and cyclododecyl groups were used for the measurements of $^1$H NMR to determine the apparent association constants ($K_a$)[14] for the complexation of CDs with these guests.

$^1$H NMR spectra were recorded at 500 MHz with a JEOL ECA-500 NMR spectrometer. Chemical shifts were referenced to the solvent values ($\delta$ 2.49 ppm for DMSO, $\delta$ 4.79 ppm for

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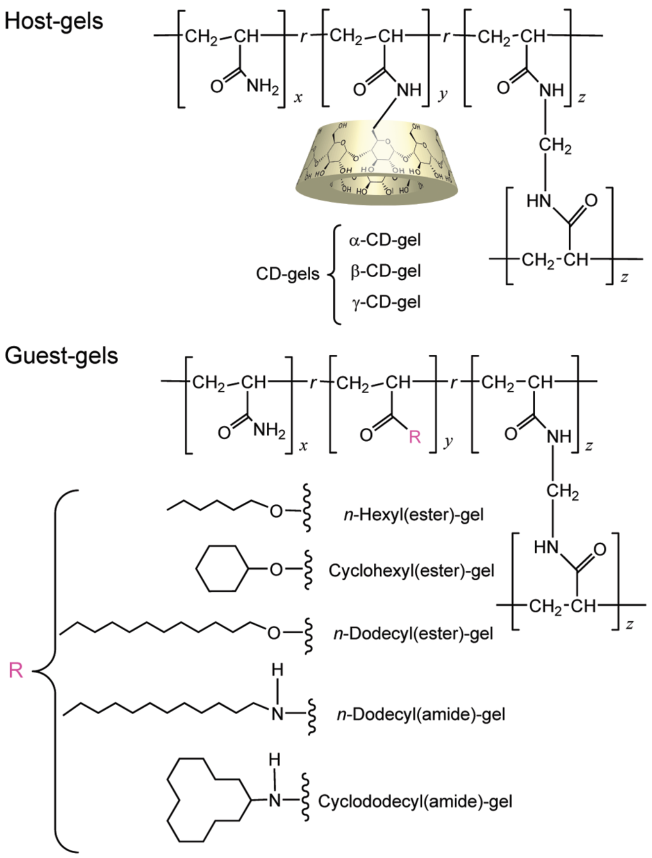
**Chart 1. Chemical Structures of Host-Gels (α-, *β*-, and *γ*-CD-Gels) and Guest-Gels (*n*-Hexyl-, Cyclohexyl-, *n*-Dodecyl-, and Cyclododecyl-Gels)[a]**



[a]The molar ratio of acrylamide, host- or guest-modified acrylate and acrylamide, and *N,N'*-methylenebis(acrylamide) is shown as *x*, *y*, and *z*. Host-gels with a mol % *x*/*y*/*z* of 93/5.0/2.0 were used. In this study, guest-gels (hexyl- and dodecyl-gels) with different mol % content (*y*) of alkyl groups were prepared. The mol % of *z* was set at 2.0 for all host and guest gels. The character *r* in the main chain of polymers indicates that each monomer was copolymerized randomly.

HOD, and $\delta$ 7.25 ppm for $CDCl_3$). Mechanical properties of gel-assemblies were measured by the mechanical tension testing system (Rheoner, RE-33005, Yamaden Ltd.). Host-gel and guest-gel were pushed together to contact with each other. The samples of 1 × 1 cm length were measured with a speed of 0.1 mm/s at room temperature.

Macroscopic self-assembly between host gels and guest gels was performed in water. Pieces of CD-gels and guest-gels were stained by soaking these gels into the solutions of dyes; α-CD-gel (blue, FD&C Blue No. 1 (brilliant blue FCF)), *β*-CD-gel and *γ*-CD-gel (red, FD&C Red No. 3 (erythrosine)), *n*-hexyl-gel and *n*-dodecyl-gel (yellow, FD&C Yellow No. 5 (tartrazine)), cyclohexyl-gel and cyclododecyl-gel (green, malachite green). Each gel was placed in a Petri dish, followed by adding 5 mL of water and shaking (EYELA CM-1000) for a few minutes at room temperature.

## ■ RESULTS AND DISCUSSION

In this study, we chose polyacrylamide gels as a scaffold for host and guest moieties because there is little interaction between polyacrylamide gels and other molecules, for example, proteins, polysaccharides, and DNA as shown that they are used as bases for electrophoresis, gel filtration, and sequencing of DNA. We selected *n*-hexyl and *n*-dodecyl groups as a linear guest moiety and cyclohexyl and cyclododecyl as a cyclic one (Chart 1). All the gels were prepared by radical copolymerization under conventional conditions. These gels were stained by dyes which have no influence on the association between CDs and guest moieties in the gels.

When a piece of α-CD-gel was brought into contact with a piece of *n*-hexyl(ester)-gel, the α-CD-gel adhered to the *n*-hexyl(ester)-gel to form a combined gel. In contrast, *β*-CD-gel did not form an aggregate with *n*-hexyl(ester)-gel. On mixing and shaking pieces of cyclohexyl(ester)-gel, α-CD-gel, and *β*-CD-gel in water, cyclohexyl(ester)-gel bound *β*-CD-gel in a minute; however, no adhesion occurred with α-CD-gel. A mixture of pieces of α-CD-gel, *β*-CD-gel, *n*-hexyl(ester)-gel, and cyclohexyl(ester)-gel exhibited excellent selectivity only by mixing and shaking in water; α-CD-gel specifically adhered to *n*-hexyl(ester)-gel and *β*-CD-gel selectively bound cyclohexyl(ester)-gel to form macroscopic self-assemblies (Figure 1). The estimated $K_a$ values for pairs of α-CD/*n*-hexyl(ester)[14] and α-CD/cyclohexyl(ester) were 290 and 87 $M^{-1}$, respectively. The $K_a$ values for the complexes of *β*-CD with *n*-hexyl group or cyclohexyl group were 90 and 160 $M^{-1}$, respectively. Pairings of α-CD-gel with *n*-hexyl(ester)-gel and *β*-CD-gel with cyclohexyl(ester)-gel, which have higher affinities among these four possible pairs, occurred without any cross-pairing. The assembly of CD-gels with hexyl(ester)-gels was perfectly selective (all or nothing) and reproducible. The binding of host-gel to guest-gel is thought to occur through the desired multivalent host–guest interactions. In control experiments, a pair of α-CD-gel/α-CD-gel, *β*-CD-gel/*β*-CD-gel, *n*-hexyl(ester)-gel/*n*-hexyl(ester)-gel, and cyclohexyl(ester)-gel/cyclohexyl(ester)-gel did not stick together. Pieces of blank-gel did not stick together or form aggregates with these CD-gels or guest-gels.

Competitive experiments indicated that the self-assembly of host-/guest-gels was based on molecular recognition of CDs. *n*-Hexyl(ester)-gel did not form an assembly with α-CD-gel in aqueous solutions containing excess α-CD. The addition of *n*-hexyl alcohol as a soluble competitive guest to the assembly of α-CD-gel with *n*-hexyl(ester)-gel caused the dissociation of gels. The interaction between *β*-CD-gel and cyclohexyl(ester)-gel was also found to be controllable by the addition of a soluble competitive host (*β*-CD) or guest (cyclohexyl alcohol). Dissociation of gels from the assembly by the addition of competitive guests and readhesion of host- and guest-gels after washing gels with water could be observed as shown in Figure S3 of the Supporting Information. The assembly of gels was reversible and reproducible.

As a guest gel bearing a longer alkyl chain, *n*-dodecyl(ester)-gel was prepared. When *n*-dodecyl(ester)-gel was mixed and shaken with α-CD-gel, adhesion of these gels immediately occurred. On the other hand, *β*- or *γ*-CD-gel did not bind *n*-dodecyl(ester)-gel. Selective binding of α-CD-gel to *n*-alkyl-gels was confirmed in this system. The values of $K_a$ for the soluble *n*-dodecyl(ester)-polymer with α-, *β*-, or *γ*-CD were 1200, 580, and 29 $M^{-1}$, respectively. α-CD was found to have the highest affinity to *n*-dodecyl(ester)-polymer among these CDs, and it resulted in the selective adhesion of α-CD-gel to *n*-dodecyl(ester)-gel. Although the value of $K_a$ for *β*-CD with *n*-dodecyl(ester)-polymer was relatively large (580 $M^{-1}$), *β*-CD-gel did not bind *n*-dodecyl(ester)-gel.

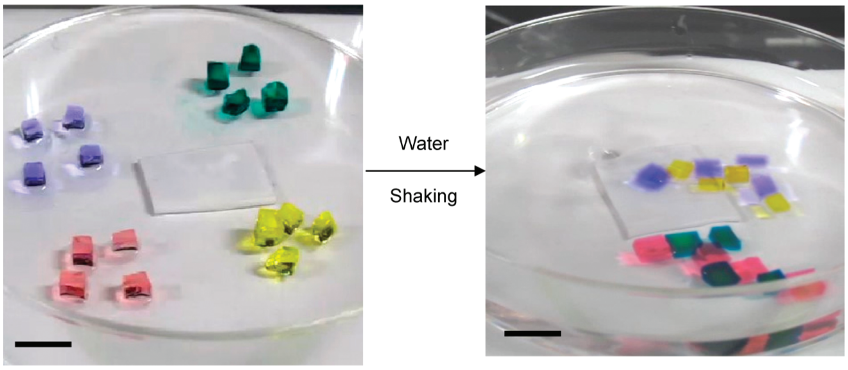


**Figure 1.** Selective assembly of host-gels with guest-gels. Host-gels (α-CD-gel (blue) and *β*-CD-gel (red)) and guest-gels (*n*-hexyl(ester)-gel (yellow) and cyclohexyl(ester)-gel (green)) were placed in a Petri dish. Adding water and shaking for a few minutes led to the selective formation of alternating self-assemblies of α-CD-gel/*n*-hexyl(ester)-gel and *β*-CD-gel/cyclohexyl(ester)-gel. The scale bar corresponds to 1.0 cm.

**Table 1. Physical Properties of Macroscopic Self-Assemblies between Host-Gels and Guest-Gels and the Apparent Association Constants ($K_a$) of CDs with Guest Moieties in the Soluble Guest Polymers**

| host-gel | guest-gel | assembly[a] | $K_a$/M$^{-1}$ [b] | stress/Pa[c] |
|---|---|---|---|---|
| α-CD-gel | *n*-hexyl(ester)-gel(5.0) | A | 290 | 1700 ± 280 |
| *β*-CD-gel | *n*-hexyl(ester)-gel(5.0) | N | 90 | |
| α-CD-gel | cyclohexyl(ester)-gel(5.0) | N | 87 | |
| *β*-CD-gel | cyclohexyl(ester)-gel(5.0) | A | 160 | 6670 ± 170 |
| α-CD-gel | *n*-dodecyl(ester)-gel(1.0) | A | 1200 | 1450 ± 390 |
| *β*-CD-gel | *n*-dodecyl(ester)-gel(1.0) | N | 580 | |
| *γ*-CD-gel | *n*-dodecyl(ester)-gel(1.0) | N | 29 | |
| α-CD-gel | *n*-dodecyl(amide)-gel(0.5) | A | 330 | 1570 ± 50 |
| α-CD-gel | *n*-dodecyl(amide)-gel(1.0) | A | 330 | 5500 ± 540 |
| *β*-CD-gel | *n*-dodecyl(amide)-gel(0.5) | N | 160 | |
| *γ*-CD-gel | *n*-dodecyl(amide)-gel(0.5) | N | | |
| α-CD-gel | cyclododecyl(amide)-gel(2.0) | N | 32 | |
| *β*-CD-gel | cyclododecyl(amide)-gel(2.0) | A | 84 | 1170 ± 210 |
| *γ*-CD-gel | cyclododecyl(amide)-gel(0.5) | A | 310 | 730 ± 60 |
| *γ*-CD-gel | cyclododecyl(amide)-gel(2.0) | A | 310 | 4370 ± 90 |

[a] Interactions between host-gels and guest-gels; assembled (A), no interactions (N) were observed in water. [b] Association constants ($K_a$) were determined by Benesi–Hildebrand plots of the chemical shifts of the peaks in the $^1$H NMR spectra of soluble guest polymers with CDs. Error, within ±10%. [c] Physical properties of assemblies of gels obtained by materials tension testing machines. Table S1 of the Supporting Information includes the strain values of these systems.

The interactions of CD-gels with *n*-dodecyl(amide)-gel, which *n*-dodecyl group was introduced to the polymer backbone via amide bond, were also examined. The same results were obtained as the *n*-dodecyl(ester)-gel system; *n*-dodecyl(amide)-gel bound to α-CD-gel, but not to *β*-CD-gel or *γ*-CD-gel. The stress at rupture of the assembly of α-CD-gel with *n*-dodecyl(amide)-gel was measured by using a creep meter. When the mol % content of *n*-dodecyl moiety was set at 0.5, the stress value of α-CD-gel/*n*-dodecyl(amide)-gel(0.5) was 1570 Pa. With 1.0 mol % of *n*-dodecyl unit, *n*-dodecyl(amide)-gel(1.0), it was estimated to be 5500 Pa (Table 1). The stress values on the assembly of α-CD-gel with *n*-dodecyl(amide)-gel increased with increasing the content of *n*-dodecyl moiety in the guest-gel. The addition of an aqueous solution of sodium dodecyl sulfate (SDS, 3.0%) led to the separation of assembled gels, suggesting that SDS inhibited the association of gels by blocking the binding sites on the host gel.

Cyclododecyl(amide)-gels were prepared to investigate the selectivity of CD-gels. Similar to the cyclohexyl(ester)-gel system, cyclododecyl(amide)-gel bound *β*-CD-gel, but not to α-CD-gel. *γ*-CD-gel also formed the assembly with this guest gel. The stress values of the *γ*-CD-gel/cyclododecyl(amide)-gel increased with increasing the content of guest moiety in the cyclododecyl(amide)-gel, 730 Pa at 0.5 mol % and 4370 Pa at 2.0 mol %.

Interestingly, *β*-CD-gel bound cyclododecyl(amide)-gel strongly, although $K_a$ of the complex of *β*-CD with cyclododecyl(amide)-polymer (84 M$^{-1}$) was smaller than that with the *n*-dodecyl(amide)-polymer (160 M$^{-1}$). It is indicated that the binding property of *β*-CD to the *n*-dodecyl-polymers in homogeneous solutions is not reflected as the selective adhesion of *β*-CD-gel to *n*-dodecyl-gels. *n*-Dodecyl groups in the gels might have some interactions each other to give some aggregates. α-CD is suggested to have an ability to loosen the aggregation and to bind the group, but *β*-CD does not have such ability.

As we described above, *n*-dodecyl(ester)-gel adhered to α-CD-gel ($K_a$ = 1200 M$^{-1}$), but not to *γ*-CD-gel (29 M$^{-1}$). On the other hand, cyclododecyl(amide)-gel adhered to *γ*-CD-gel ($K_a$ = 310 M$^{-1}$), but not to α-CD-gel (32 M$^{-1}$). When a mixture of pieces of α-CD-gel, *γ*-CD-gel, *n*-dodecyl(ester)-gel, and cyclododecyl(amide)-gel was shaken in water, α-CD-gel bound *n*-dodecyl(ester)-gel, and *γ*-CD-gel bound cyclododecyl(amide)-gel as shown in Figure 2. CD-gels exhibited excellent selectivity to the corresponding guest-gels.

The same tendency was observed in the hexyl-gel and dodecyl-gel systems; i.e., α-CD-gel formed an assembly with the linear guest-gels, and a gel modified with larger CDs (*β*-CD or *γ*-CD) adhered to the cyclic guest-gels. The linear *n*-hexyl and *n*-dodecyl groups are indicated to fit well in the α-CD cavity, while the bulky cyclohexyl and cyclododecyl groups fit well in larger *β*- or *γ*-CD cavity, respectively (Figure 3).

In conclusion, we successfully prepared assembly of gels without any cross-pairing by utilizing shape-selective molecular recognition of CDs for the linear and cyclic guest molecules attached to the gels. α-CD-gel selectively adhered to the guest-gels bearing *n*-alkyl groups. *β*-CD-gel or *γ*-CD-gel could form assemblies with cycloalkyl-gels, not with *n*-alkyl-gels. The interaction between CD-gel and alkyl-gel was found to be reversible by adding or removing a soluble competitive guest. The stress

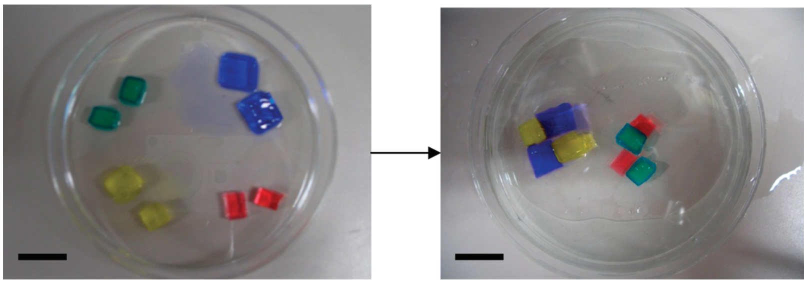


**Figure 2.** Self-assembly between host-gels (α-CD-gel (blue) and γ-CD-gel (red)) and guest-gels (*n*-dodecyl(ester)-gel (yellow) and cyclododecyl-(amide)-gel (green)). The scale bar indicates 1.0 cm.

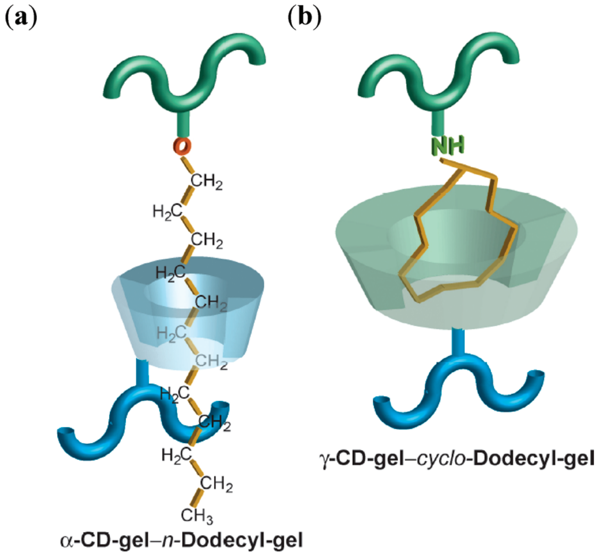


**Figure 3.** Schematic representation of the complexes of CDs with dodecyl guests attached to a gel. α-CD forms an inclusion complex with *n*-dodecyl group (a). The larger γ-CD recognizes the wider cyclododecyl group (b).

values on the assembly of host/guest-gels increased with increasing the contents of guest moieties in the guest-gels, indicating that the mechanical strength at the interface between host-gel and guest-gel could be regulated. Detailed investigation of the adhesion mechanism of CDs to guest moieties at the interface of gels is in progress.

## ASSOCIATED CONTENT

**Ⓢ Supporting Information.** Detailed experimental procedures, synthesis of water-soluble guest polymers and guest-gels, physical property of gels, and some photographs of self-assembly of gels. This material is available free of charge via the Internet at http://pubs.acs.org.

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