Hydrogels

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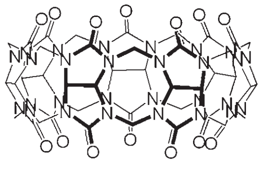
Cucurbit[7]uril: A Simple Macrocyclic, pH-Triggered Hydrogelator Exhibiting Guest-Induced Stimuli-Responsive Behavior**

*Ilha Hwang, Woo Sung Jeon, Hee-Joon Kim, Dongwoo Kim, Hyunuk Kim, Narayanan Selvapalam, Norifumi Fujita, Seiji Shinkai, and Kimoon Kim**

Small organic molecule gelators have received much attention in recent years because of their potential applications in many areas, including materials science, biomedical fields, separation technology, cosmetics, and food science.[1] In particular, hydrogelators are of special interest as they offer great promise in tissue engineering and drug-delivery systems.[2,3] Furthermore, hydrogels that are responsive to external stimuli such as heat, light, and chemicals may be useful for applications such as sensing and the controlled release of drugs.[4] Therefore, the design and discovery of novel hydrogelators, particularly those that yield stimuli-responsive hydrogels, has been a subject of intense research. Despite extensive studies, however, the design of a small molecule that self-assembles into fibrous structures in aqueous solvents and disassembles in response to external stimuli still poses a challenge. In principle, one can design stimuli-responsive hydrogels by incorporating a receptor unit that responds to a specific external stimulus into a well-known gel-forming unit. More specifically, one may design a stimuli-responsive hydrogel based on a macrocyclic cavitand such as a cyclodextrin or calixarene by taking advantage of their well-established host–guest chemistry. Nevertheless, 1) there are only a few examples[5] of gelators based on macrocyclic cavitands, 2) they all gel only organic solvents with only one exception,[5e] and 3) controlling gelation by host–guest interactions has been seldom reported.[5d]

Cucurbit[*n*]urils (CB[*n*], $n = 5$–10), a family of cavitands comprising *n* glycoluril units, have a variable-sized cavity that is accessible through two identical carbonyl-fringed portals.[6] Their rigid, highly symmetrical structures with hydrophilic portals and a hydrophobic cavity lead to unique recognition properties unmatched by other families of macrocyclic cavitands.[7] In particular, the ureido carbonyl groups at the portals serve as a binding site for various cations, including protons. Unlike other family members, CB[7], whose cavity size is comparable to that of β-cyclodextrin, has modest solubility in water. We and others reported its usual host–guest behavior,[8] including its exceptionally high binding affinity (binding constant as high as $10^{12}\,\text{M}^{-1}$).[8i,j] Herein we report the unexpected hydrogel formation of CB[7] without any modification of its periphery. Furthermore, the gel is not only sensitive to external stimuli but also shows unprecedented guest-induced stimuli-responsive behavior.



CB[7]

Slow cooling of a warm solution of CB[7] (3–5 wt.%) dissolved in a diluted mineral acid such as sulfuric acid to room temperature leads to gelation of the solution.[9] No other member of the CB family induces gelation of any solvents. The gelation is largely affected by the pH value of the solution. The pH dependence of the CB[7] gel formation has been investigated with a CB[7] (3 wt.%) solution in dilute sulfuric acid by monitoring its transmittance at 600 nm (see the Supporting Information). The optimum pH value for the gel formation ranges between 0 and 2; below pH 0, the solution remains transparent upon cooling, and, above pH 2, CB[7] precipitates out. The pK_a value of CB[7] is measured to be 2.2,[10] which suggests that the complexation of protons (hydronium ion) to the CB[7] portals is important for the hydrogel formation. A large shift in the C=O stretching band of CB[7] upon hydrogel formation (1729 vs. 1712 cm^{-1} in the solid and gel states, respectively) is consistent with the complexation of hydronium ions to the carbonyl groups in the gel state. Moreover, the gelation is suppressed in the presence of alkali-metal ions, such as Na^+ or K^+, which are known to bind to CB[*n*] portals. For example, upon addition

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[*] I. Hwang, Dr. W. S. Jeon, Dr. H.-J. Kim,[+] Dr. D. Kim, H. Kim,
Dr. N. Selvapalam, Prof. Dr. K. Kim
National Creative Research Initiative Center for Smart
Supramolecules and
Department of Chemistry
Pohang University of Science and Technology
San 31 Hyoja-dong, Pohang 790-784 (Republic of Korea)
Fax: (+82) 54-279-8129
E-mail: kkim@postech.ac.kr
Homepage: http://css.postech.ac.kr
Dr. N. Fujita, Prof. Dr. S. Shinkai
Department of Chemistry & Biochemistry
Graduated School of Engineering, Kyushu University
744 Moto-oka, Nishi-ku, Fukuoka 819-0395 (Japan)

[+] Current address: Department of Applied Chemistry, Kumoh National Institute of Technology, 1 Yangho-dong, Gumi 730-701, Republic of Korea

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

of two equivalents of Na_2SO_4 or K_2SO_4, CB[7] gel slowly turns into a transparent fluid, which is presumably due to the coordination of metal ions to the CB[7] portals.[7] This result also supports the supposition that the complexation of hydronium ions to the CB[7] portals is essential for the gel formation.

The thermoreversible gel–sol transition of CB[7] gel was studied with a solution containing 3 wt.% CB[7] in 0.5 N sulfuric acid by monitoring its transmittance at 600 nm. A sharp sol-to-gel transition was observed upon cooling to around 42 °C, whereas a slow gel-to-sol transition was observed over a temperature range of 43–57 °C upon heating (see the Supporting Information).

The morphology of CB[7] gel was investigated by AFM. The AFM images of the gel show long fibrous gel networks with fiber lengths of several tens of micrometers (Figure 1 a). A magnified image (Figure 1 b) of a fiber reveals that it consists of a bundle of fibrils, which can also be seen in Figure 1 c. The height of a thin fibril is as small as 1.2 nm (Figure 1 c and d), which is comparable to the size of CB[7] (equatorial width 16.0 Å, height 9.1 Å, including van der Waals radii). These results suggest that the fibril is composed of one-molecule-thick arrays of CB[7].

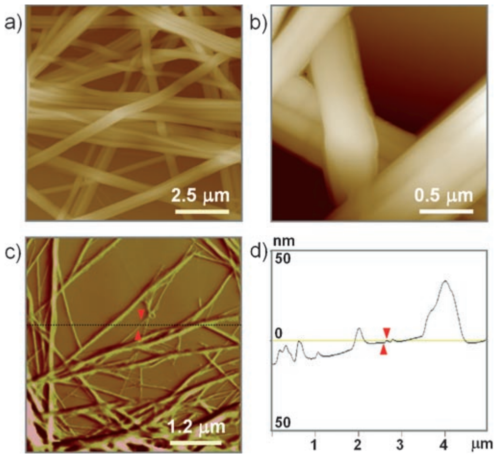


Figure 1. AFM images of CB[7] gel: a) A large-area image showing the fibrous structure of CB[7] gel on a mica substrate. b) A magnified image of a thick fiber revealing a bundle of fine fibrils. c) An amplitude image of CB[7] gel on another mica substrate. d) A height profile (measured from a height image; see the Supporting Information) along the dotted line in Figure 1 c reveals that the height of a thin fibril is approximately 1.2 nm (marked).

The small-angle X-ray scattering (SAXS) data of a CB[7] gel (3 wt.% in dilute sulfuric acid) obtained at 25 °C by using synchrotron radiation ($\lambda = 1.54019$ Å) show two peaks at $2\theta = 0.83$ and 1.68° (Supporting Information), which can be assigned as (100) and (200) reflections, respectively, of a layer structure and suggest the presence of a subunit in the gel with a regular spacing of 11 nm. The peaks disappear upon heating of the gel to 45 °C and reappear upon cooling of the gel to 25 °C. Furthermore, the arc in the 2D SAXS data of an aligned sample recorded at 25 °C (Supporting Information) indicates that the subunits are one-dimensionally aligned along the fibrils when they assembled.

To gain an insight into the molecular organization that leads to the gel formation, we determined the X-ray crystal structure of needle-shaped crystals grown from a solution similar to the one from which the CB[7] hydrogel is formed, but with a lower concentration of CB[7] (ca. 1 wt %).[11] A close inspection of the crystal structure reveals that CB[7] molecules, each of which encapsulates an acetone molecule inside the cavity,[12] are packed in a herringbone structure along the *a* axis (Figure 2 a). On the *ab* plane, each CB[7] molecule interacts with six neighboring CB[7] molecules directly through extensive C–H···O hydrogen bonds, and indirectly through mediating water/hydronium ions (see the dotted lines in Figure 2 a). Furthermore, the channels between the zigzagged CB[7] columns along the *b* axis are filled with water/hydronium ions and sulfate ions to form an extensive hydrogen-bonding network (Figure 2 b). A similar packing pattern of CB[7] molecules and water/hydronium ions was observed in another X-ray crystal structure of CB[7].[6b] Thus, the driving force for the aggregation of CB[7] leading to a hydrogel appears to be the strong interactions between CB[7] portals and water/hydronium ions, and between the CB[7] molecules themselves. This is a rare example of a single-crystal X-ray structure revealing the organization of hydrogelators and their interactions with gelling solvents.[13]

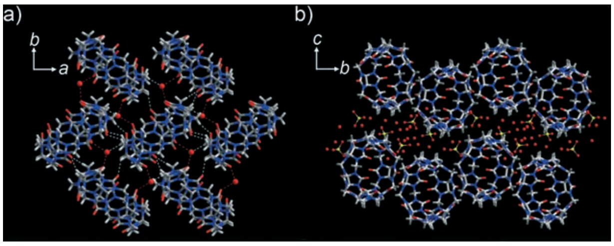
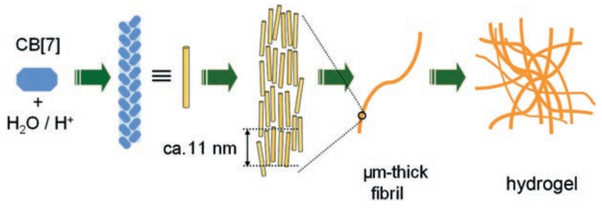


Figure 2. X-ray crystal structure of CB[7]. Color codes: gray C, blue N, red O, yellow S, white H. Encapsulated acetone molecules are omitted for clarity. a) Organization of CB[7] molecules on the *ab* plane. An extensive hydrogen-bonding network is presented with dotted lines (white: C–H···O hydrogen bonding, red: O–H···O hydrogen bonding). b) A packing diagram on the *bc* plane. The channels between the zigzagged CB[7] columns along the *b* axis are filled with water/hydronium ions and sulfate ions to form an extensive hydrogen-bonding network.

On the basis of these data, a hierarchical structure of the fibrous network in CB[7] gel is proposed as in Scheme 1. Besides the C–H···O hydrogen bonds between CB[7] molecules, water molecules and/or hydronium ions act as a "glue" to bind CB[7] molecules to form an approximately 11-nm-long secondary building unit (although its exact nature is not clear), which assembles into a long fibril. The latter in turn bundles into a thick fiber, which forms a fibrous network leading to a gel.

The guest-induced stimuli-responsive behavior of CB[7] gel was investigated in the presence of a small amount of 4,4′-diaminostilbene dihydrochoride (**1**) as a guest. Both *trans* and



Scheme 1. Schematic representation of the hierarchical assembly of CB[7] gel.

cis isomers of **1** are known to form stable 1:1 inclusion complexes with CB[7] (**1**$\subset$CB[7]), and their interconversion has been studied.[8f] Slow cooling of a hot $1.0\,\text{N}$ H_2SO_4 solution containing 5 wt.% CB[7] and 0.1 equivalent of *trans*-**1** produces a gel. When the gel is irradiated with UV light (365 nm) for 2 h, the white gel turns into a yellow sol (Figure 3a). Heating the yellow sol at 60 °C for 12 h followed by slow cooling to room temperature regenerates a pale-yellow gel. This procedure can be repeated many times with alternating UV irradiation and heat treatment, as illustrated in Figure 3b. The reversible gel–sol transition is presumably induced by a large structural change in **1**$\subset$CB[7] associated with the *trans–cis* isomerization of the guest. In *trans*-**1**$\subset$CB[7], only part of the guest is included in the host cavity: one ammonium terminus of the guest interacts with one of the host portals while the other terminus sticks out of the host. In contrast, in *cis*-**1**$\subset$CB[7], the C-shaped guest fits well in the cavity of CB[7], and both ammonium termini of the guest interact with the host portals.[8f] The complete blocking of the host portals with the guest ammonium groups in *cis*-**1**$\subset$CB[7] may interrupt the hydrogen-bonding network formed by water/hydronium ions and CB[7], and thereby suppress the gel formation. To the best of our knowledge, this is the first example of a guest-induced stimuli-responsive system based on low-molecular-weight hydrogelators.[14]

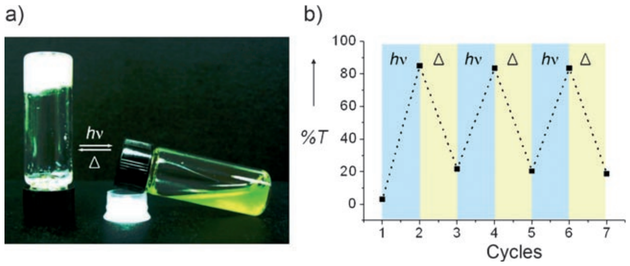


Figure 3. Guest-induced stimuli-responsive behavior of CB[7] gel: a) Photographs of CB[7] (5 wt.%) gel containing 0.1 equivalent of *trans*-**1** before (left) and after (right) UV irradiation (365 nm) for 2 h. b) Change in transmittance (600 nm) of CB[7] gel shown in (a) with alternating UV irradiation and heat treatment.

In conclusion, CB[7] forms a hydrogel without modification of its periphery; such a simple macrocycle has never been thought to be a hydrogelator. The gelation is thermoreversible, sensitive to pH, and inhibited by the presence of alkali-metal ions. The driving force for gelation appears to be the propensity of CB[7] to aggregate through strong interactions between CB[7] portals and hydronium ions as well as between CB[7] molecules themselves. As no other member of the CB family gel any solvents (although it is not clear why this is the case), this study confirms that a subtle balance between hydrophilicity and hydrophobicity of a molecule is important in gelation. Unlike other stimuli-responsive gels in which the stimuli-responsive behavior originates from conformational or configurational changes of gelators themselves, the CB[7] hydrogel shows a guest-induced stimuli-responsive sol–gel transition. By choosing the appropriate guest molecules, one may be able to design various stimuli-responsive gel systems based on the intriguing host–guest chemistry of CB[7] and the properties of the included guest molecules.

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