Gel Nanocubes

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Nano- and Microsized Cubic Gel Particles from Cyclodextrin Metal–Organic Frameworks**

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The bottom-up control of the three-dimensional shapes of objects in a wide range of sizes, from nanometer to millimeter, has attracted attention in diverse fields.[1,2] For instance, metal nanocrystals having various shapes, such as spherical, cubic, hexagonal plate, and octahedral, have been extensively investigated owing to interest in crystal growth[3] and the control of catalytic activities.[4] Among the inorganic metal oxides and minerals, for example, the crystallization and morphology control of $CaCO_3$ have been of interest for decades, with relation to biomineralization, to produce the more complex structures that living organisms produce.[5] More recently, sol–gel polymerization using the surface of supramolecular assemblies as templates has been extensively investigated for the fabrication of various well-defined nano- and microsized objects such as mesoporous silica,[6] hollow tubes,[7] and helical ribbon structures.[8] In spite of diverse approaches for controlling the sizes and shapes of inorganic materials in the micro and nanometer ranges, less attention has been paid to organic network polymers, because the network polymers are generally not moldable nor can be processed after formation of the networks as they are insoluble in all solvents and have no observed melting points. As a bottom-up approach, emulsion polymerization using micelles and vesicles as templates produce spherical particles,[9] hollow spherical particles,[10] and a layer structure,[11] whereas the top-down approaches, nanoimprint lithography[12] with photoresist and three-dimensional microfabrication by two-photon laser chemistry,[13] have been reported for controlling the network polymers to form complex objects in the micro- and nanometer ranges. Thus, a bottom-up approach for other polyhedral objects of organic network polymers in these regions has never been shown. Herein, we focused on the fabrication of nano- and microsized cubic gel particles (CGPs) from metal–organic frameworks (MOFs)[14] as a template with a cubic shape, that is, a bottom-up approach.

MOFs are crystalline materials consisting of organic linkers with bridging organic ligands and metal ions and have been of considerable interest as functional nanoporous materials for gas storage,[15] separation,[16] catalysis,[17] and drug delivery.[18] Generally, MOFs yield uniform polyhedral crystals with sharp edges and flat surfaces from hydrothermal reactions, and their sizes range from nanometers to millimeters. These well-defined shapes are dependent on the combinations of the organic linkers and the metal ions, however, prediction of the structure of the crystal system from its components remains a great challenge. Experiments to understand the crystallization processes of MOFs will enable us to partially control their sizes and shapes by controlling the recrystallization conditions.[19] This prompted us to fabricate a polyhedral polymer network in a wide range of sizes using a cross-linking reaction inside the MOFs. In a previous report, we demonstrated the formation of a polymer gel from a MOF by cross-linking of the organic linkers in the crystalline state of the MOF using an in situ click reaction of the azide-modified MOF, with external multifunctional cross-linkers with four acetylene moieties.[20] However, control over the size of the crystals was not successful, thus only millimeter-sized polymer gels were prepared. Herein, we demonstrate control over the crystal size of a cyclodextrin MOF (CD-MOF)[21] and cross-linking of the hydroxy and alkoxide groups of γ-CD to form network polymer particles with well-defined polyhedral shapes in the range of several hundred nanometers to millimeters (Figure 1). The facile synthetic route used herein and abundant starting materials for the CD-MOF allowed us to explore further recrystallization conditions and cross-linking in a wide range of sizes.

According to a previously reported method, the CD-MOF was prepared by reacting γ-CD with 8.0 equiv. of KOH in aqueous solution, followed by vapor diffusion of MeOH into the solution.[21a] Optical micrographs and scanning electron microscopic (SEM) images of the crystals illustrated that they were well-defined cubic crystals with 40–500 μm on a side as shown in Figure 2 a,b. To create much smaller CD-MOF crystals, we added a modified mother liquor with cetyltrimethylammonium bromide (CTAB) and controlled the incubation time.[19a] As shown in Table 1, the mother liquor was prepared by incubation of γ-CD and 8.0 equiv. of KOH in water under MeOH vapor for the first crystal-growth stage.

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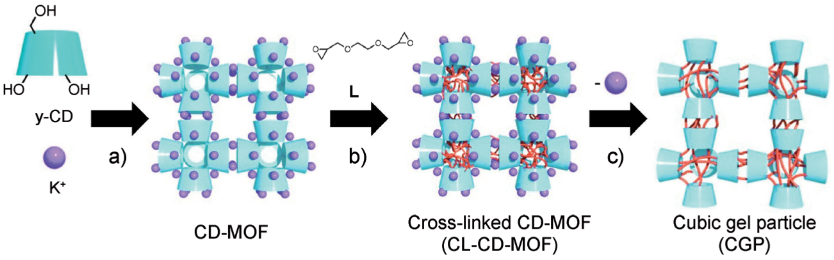

Figure 1. Schematic illustration of the synthesis of cubic gel particles. a) crystallization, b) cross-linking reaction, and c) removal of coordinated metal ions.

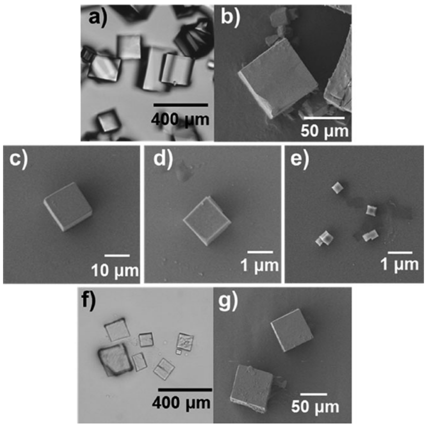

Figure 2. a) Optical microphotograph and b) SEM image of CD-MOF. SEM images of c) CD-MOF-Micro1, d) CD-MOF-Micro2, and e) CD-MOF-Nano. f) Optical microphotograph and g) SEM image of CL-CD-MOF.

Table 1: Preparation conditions for different-sized CD-MOFs.

Sample	First crystal-growth time[a]	Second crystal-growth time[b]	MeOH[c] [mL]	CTAB [mg]
CD-MOF[21]	24 h	–	–	–
CD-MOF-Micro1	26 h	3 h	–	40
CD-MOF-Micro2	26 h	3 h	0.050	40
CD-MOF-Nano	32 h	3 h	5.0	40

[a] Under MeOH vapor conditions. [b] After addition of MeOH and CTAB. [c] Amount of MeOH added to the mother liquor.

After removal of the newly formed CD-MOF by decantation or filtration, CTAB was added to the supernatant. For the CD-MOF-Micro2 and CD-MOF-Nano samples, a small amount of methanol was added as a poor solvent for the CD-MOF. The solution was incubated again at room temperature for several hours for the second crystal-growth stage. The crystals formed were collected by centrifugation after repeated washing with EtOH. SEM observations of the CD-MOFs formed by this process clearly indicated that they were uniform cubic crystals with different sizes, approximately 10 μm for CD-MOF-Micro1, 1 μm for CD-MOF-Micro2, and 200–300 nm for CD-MOF-Nano, as shown in Figure 2c–e. These crystals were used for the cross-linking reaction without further purification.

The cross-linking reaction of the γ-CDs in the CD-MOF prepared by the standard diffusion method was carried out by treatment with ethylene glycol diglycidyl ether (**L**), which has two epoxy groups to cross-link between the hydroxy groups of each γ-CD in the CD-MOF pores (Figure 1). After incubation of the cubic crystals in an EtOH solution of **L** at 65 °C for three days, the cross-linked CD-MOF (CL-CD-MOF; Figure 2 f,g) was formed. To degrade the coordination bonds and remove the potassium ions and unreacted **L**, the resulting polymer gels were repeatedly soaked in a mixed solvent (EtOH/H_2O = 1:1 (v/v)) and H_2O. The unmodified CD-MOFs dissolved within one minute in water (Supporting Information, Figure S1), but following the cross-linking reaction, the resulting CL-CD-MOFs were practically insoluble and swelled in H_2O, as shown in Figure 3 a. The original cubic shape of the CD-MOF was retained even after the cross-linking and degradation process. However, the sizes of the cubes were expanded by 1.37 times the original CL-CD-MOF length. Thus, the degree of swelling (Q) is defined as $Q = (L_{\mathrm{CGP}}/L_{\mathrm{CL\text{-}CD\text{-}MOF}})^3$, where L is the length of CGP in water and CL-CD-MOF in ethanol, and was found to be $Q = 2.57$. Intriguingly, SEM observations illustrated that the cubic shape of the CD-MOF was reflected in the cubic shape of the polymer gels, even after drying under a high vacuum (Figure 3 b).

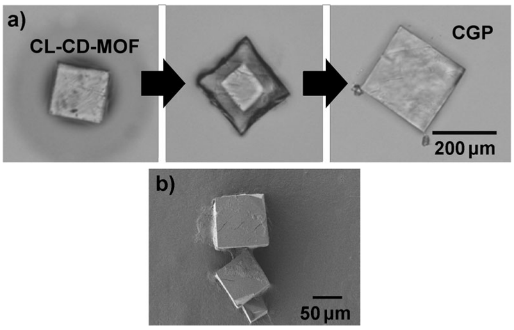

Figure 3. a) Preparation of a CGP from CL-CD-MOF by removal of coordinating potassium ions. b) SEM image of CGP.

The CGPs were characterized by their IR spectra, elemental analysis, X-ray powder diffraction (XRPD), and thermogravimetric (TG) analyses. The IR spectra showed a stretching band (2870–2920 $\mathrm{cm^{-1}}$) derived from the $-(CH_2)-$ group in **L**, which increases with the increasing **L** content. The absorption derived from the C–O–C stretching vibration (1020–1150 $\mathrm{cm^{-1}}$) for the free γ-CD was a sharp peak, while that of the immobilized γ-CD was broad because of the cross-linking (Figure S2).[22] Elemental analysis revealed that one unit of CD-MOF was modified with 16.02 molecules of **L**. These results confirmed that **L** reacted in the nanopores of the CD-MOF and acted as a cross-linker between the CDs in the CD-MOF. To study the crystallinity of CL-CD-MOF and CGP, we performed XRPD analysis. As shown in Figure 4a, the XRPD patterns illustrated that CL-CD-MOF was a crystalline material similar to CD-MOF. For CGP, no apparent diffraction peaks were observed, indicating that CL-CD-MOF became amorphous after swelling, like a polymer gel (Figure 4a). Furthermore, the thermal stabilities and guest inclusion properties of CD-MOF, CL-CD-MOF, and CGP after being immersed in EtOH or H_2O for 6 h were estimated by TG analysis as shown in Figure 4b. The pyrolysis temperatures of CD-MOF, CL-CD-MOF, and CGP were determined to be 298.7 °C, 325.5 °C, and 356.4 °C, respectively (Figure S3 and Table S1). The thermal stability was improved by cross-linking the γ-CD units. For evaluation of the inclusion abilities of CD-MOF, CL-CD-MOF, and CGP, we estimated the weight loss upon heating as the vaporization of included EtOH. The number of included EtOH molecules per unit structure was determined to be 91.0 for CD-MOF and 7.4 for CL-CD-MOF. This suggested that the nanopores of CL-CD-MOF were mostly filled with reacted **L** following the cross-linking reaction. Besides, CGP could include 16.1 EtOH molecules and 263.8 H_2O molecules per unit. For EtOH, the amount of the guest included in the CGP slightly increased compared to the CL-CD-MOF owing to a slight expansion of the network constructed from the γ-CD and **L**. Moreover, the entrapment of a large amount of water in the CGP was attributed to swelling of the CGP because of its good compatibility with water. The degree of swelling was estimated from the change in size and it agreed with this value. These results indicated that the cross-linking reaction of **L** induced the network formation. These behaviors were similar to those of the cross-linking of the azide-modifed isoreticular MOF (IRMOF) by the click reaction with external cross-linkers.[20] The cross-linking reaction proceeded between the epoxy group of **L** and the hydroxy groups of each γ-CD in the CD-MOF pores. Cross-linking between the organic linkers provided an insoluble polymer network, whereas imperfections in the cross-linking did not allow for a crystalline organic network polymer similar to a covalent organic framework (COF) to form,[23] but instead gave amorphous polymer networks that can swell by soaking in the solvent.

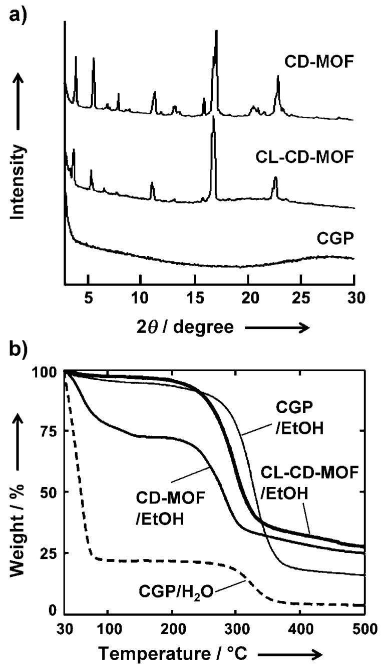

Figure 4. a) XRPD patterns of CD-MOF (upper), CL-CD-MOF (middle), and CGP (lower). b) Thermogravimetric analysis of CD-MOF including EtOH as a guest, CL-CD-MOF including EtOH as a guest, and CGP including EtOH or water (dashed) as a guest.

CD-MOF-Micro1, CD-MOF-Micro2, and CD-MOF-Nano were cross-linked by a similar procedure, but differed in their isolation of the product by centrifugation of the precipitate. The XRPD patterns showed that the cross-linking reaction proceeded while retaining the crystal shape, and CGP-Micro1, CGP-Micro2, and CGP-Nano were amorphous (Figure S4, S5). CGP, CGP-Micro1, CGP-Micro2, and CGP-Nano were insoluble after treatment in H_2O. SEM images showed that CGP-Micro1, CGP-Micro2, and CGP-Nano retained their cubic shapes as shown in Figure 5. This indicated that a similar cross-linking reaction occurred between the epoxy group of **L** and the hydroxy group of each γ-CD in the micro- and nanosized CD-MOF pores. We found from the SEM images that the average size of the CD-MOF-Nano and CGP-Nano cubes was around 338 ± 76 nm and 328 ± 80 nm, respectively (Figure S6). These results demonstrated that the CGP-Micro1, CGP-Micro2, and CGP-Nano were successfully prepared with the same size and shape as the corresponding CD-MOF (Figure S6 and Table S2). Therefore, the size variation of the CD-MOFs from nanometers to millimeters enabled us to control the size and shape of the CGP.

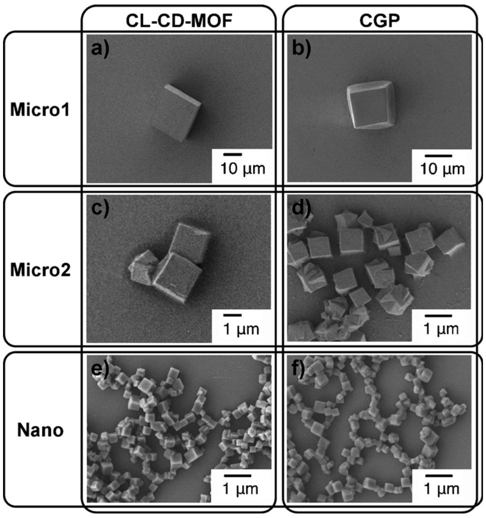

Figure 5. SEM images of a) CL-CD-MOF-Micro1, b) CGP-Micro1, c) CL-CD-MOF-Micro2, d) CGP-Micro2, e) CL-CD-MOF-Nano, and f) CGP-Nano.

In summary, we fabricated uniform cubic gel particles with well-defined edges and square faces using internal cross-linking of the CD-MOF crystals followed by loss of coordinating metal ions. The cubic gel particles retained the shape and size of the original CD-MOF crystals, indicating that by controlling the recrystallization conditions a wide range of sizes of CGPs, from millimeters to nanometers, can be produced. Moreover, using MOF crystals as templates for the CGPs should enable us to prepare a wide variety of polyhedral gel particles from the MOF crystals with controlled polyhedral shapes. Therefore, this method can open a new horizon for the preparation of micro- and nanosized polyhedral polymer gels with well-defined shapes and sizes. These gels could provide mesoscopic building blocks with a soft interface for constructing complex architectures by self-organization, or be used in biomedical applications such as drug carriers and cell-support materials. Studies of the internal cross-linking of MOF crystals with other organic linkers and metal ions to produce polyhedral gel particles with shapes other than spheres and cubes are currently ongoing.

Experimental Section

Preparation of CD-MOF, CD-MOF-Micro, and CD-MOF-Nano: γ-CD (163 mg, 0.126 mmol) was dissolved in aq. KOH (200 mM, 5.0 mL) in a glass tube. The solution was filtered through a 13 mm syringe filter (0.45 μm PTFE membrane) into a glass tube. MeOH was allowed to vapor-diffuse into the solution at the temperature (25 °C) of the first crystal-growth time. 5 mL of the solution was transferred to another glass tube containing CTAB (40 mg, 0.110 mmol). When the CTAB had thoroughly dissolved, the solution was incubated at the temperature (25 °C) of the second crystal-growth time. A tube of the turbid solution (500 μL) was centrifuged at 500 rpm for 3 min and the supernatant was removed. CD-MOF-Micro and CD-MOF-Nano were redispersed and washed in 1.0 mL of EtOH.

Preparation of CL-CD-MOF: Ethylene glycol diglycidyl ether/EtOH solution (5 mL, 1.5 M) containing CD-MOFs were heated to 65 °C in an oven for 3 days. The solution was added to a tube, centrifuged at 500 rpm for 3 min and the supernatant removed. CL-CD-MOFs were obtained and repeatedly washed with EtOH.

Preparation of CGP: CL-CD-MOF was immersed in an excess of mixed solvent (EtOH/H_2O = 1:1 (*v*/*v*)) and H_2O, sequentially.

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