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Adamantane-Based Oxacyclophanes Containing Pyrazines: Synthesis, Crystal Structure, and Self-Assembly Behavior

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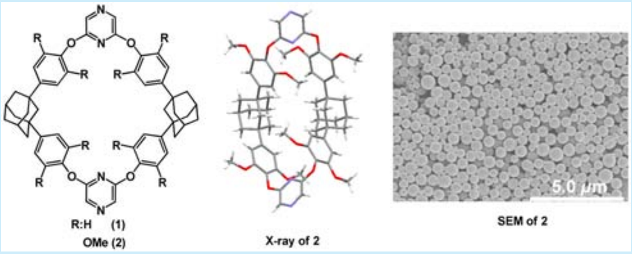
Supporting Information

ABSTRACT: Two adamantane-based oxacyclophanes were synthesized by the S_NAr reaction of bis-phenol derivatives based on adamantane with 2,6-dichloropyrazine. Their crystal structures had distorted or twisted 1,3-alternate conformations. The oxacyclophanes indicated no formation of spherical aggregates in acetone. However, addition of water into the solution caused the generation of hollow spherical aggregates with a multilayer membrane. Over time, the hollow spheres were induced into fibrous and network assemblies, which were eventually transformed into single crystals.



Oxacalixarenes and oxacyclophanes are a new class of host molecules, where aromatic units are alternately connected with oxygen atoms.[1−3] When compared with methylene-bridged macrocycles such as calixarenes, resorcinarenes, cyclotriveratrylenes, pyrogallolarenes, and pillararenes,[4−8] oxacalixarenes and oxacyclophanes have unique synthetic and structural features, owing to two or three different aromatic moieties being easily introduced in the macrocyclic frameworks. These macrocycles have various sizes, shapes, conformations, and cavities, which exhibit potential applications in the selective recognition of anions and organic molecules.[9,10] Oxacalixarenes and oxacyclophanes composed of a number of dihydroxybenzene derivatives and nitrogen heterocycles were reported by the Katz, Dehaen, and Wang groups. Larger aromatic moieties, such as naphthalene, triptycene, tetraphenylethylene, and terphenylene derivatives, have been used to construct large-sized oxacalixarenes and oxacyclophanes.[11] However, the preparation of the macrocyclic compounds containing aliphatic moieties in their backbones remains largely unexplored. Adamantane derivatives are versatile building blocks as an aliphatic unit in oxacyclophanes, which are spherical and have bulky skeletons. Oxacyclophanes containing adamantane moieties may possess intriguing and attractive molecular structures and find use as host−guest systems.

Recently, self-assembled nanostructures, such as spheres, tubes, and fibers derived from several macrocyclic compounds, have attracted attention in the areas of materials science and supramolecular chemistry.[12−14] The oxacyclophane-based nanoarchitectures, including vesicle and network structures, have been reported;[11c,15] however, their dynamic behavior is quite restricted. Adamantane-based oxacyclophanes are valuable candidates for the creation of supramolecular nanostructures. We have demonstrated that hydrophobic tetrapodal adamantanes are fabricated to form hollow spherical structures in organic solvents, and the adamantane moieties play a critical role in the self-assembly.[16] Further, we observed a concentration-dependent morphological change. Herein, we report the synthesis of two adamantane-based oxacyclophanes, which are composed of two disubstituted adamantane bearing benzene derivatives and two pyrazine moieties linked with oxygen atoms. Single-crystal X-ray analysis revealed distorted or twisted 1,3-alternate conformations in the backbone of the macrocycles. The adamantane-based oxacyclophane was self-assembled into hollow spherical aggregates in a mixture of acetone and water. Over time, the hollow spheres were induced into fibrous and network aggregates, which were eventually transformed into single crystals.

We synthesized two adamantane-based oxacyclophanes (**1**, **2**) by the nucleophilic aromatic substitution (S_NAr) reactions of bisphenol derivatives based on adamantane with 2,6-dichloropyrazine. We previously showed the preparation of a series of adamantane-based macrocycles, where two disubstituted adamantanes containing phenol derivatives were connected with a diyne derivative as a spacer.[17] We chose disubstituted adamantanes possessing phenol (**4**) and dimethoxyphenol (**5**) as nucleophilic reagents. 2,6-Dichloropyrazine was selected as an electrophilic compound, which has been used in the production of several oxacalixarenes. The adamantane-based oxacyclophanes consist of hydrophobic aromatic and aliphatic portions and polar aromatic moieties and therefore possess an amphiphilic property which can be induced into the oxacyclophane-based nanoma-

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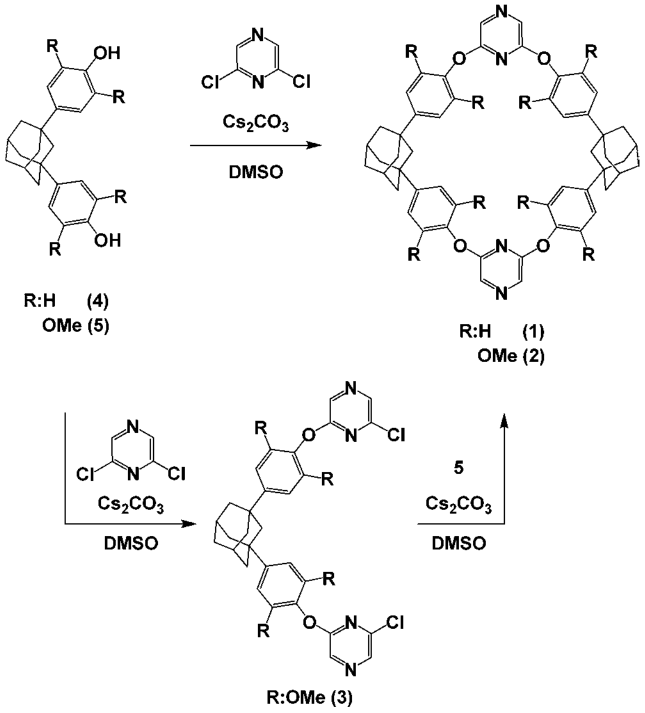
terials. Two oxacyclophanes were synthesized by a one-step nucleophilic reaction according to Scheme 1. First, the reaction of **4** with 2,6-dichloropyrazine with 1:1 stoichiometry in the presence of cesium carbonate afforded macrocycle **1** in 53% yield. Similarly, the macrocycle **2** from **5** was obtained in a low yield (6%). We synthesized the macrocycle **2** by a two-step reaction. The reaction of **5** and an excess of 2,6-dichloropyrazine gave compound **3** in 91% yield. The reaction of **3** with **5** at a ratio of 1:1 afforded macrocycle **2** in 7% yield. The compound **5** gave multiple decomposed products under this condition. Thus, macrocycle **2** was prepared with 1:5 stoichiometry in 30% yield. The compounds **1**−**3** were characterized by NMR spectroscopy and mass spectrometry.

Scheme 1. Synthetic Procedure of Two Adamantane-Based Oxacyclophanes



Single crystals **1a** of macrocycle **1** were obtained from vapor diffusion of 1,4-dioxane into a chloroform solution of **1**. X-ray crystallographic analysis revealed that the macrocyclic framework had a distorted 1,3-alternate conformation in the solid state (Figure 1), which is similar to that of previously reported oxacalixarenes.[1,2,11] The centroid−centroid distances between each aromatic and aliphatic parts are 13.99 Å for pyrazine rings, 5.19 and 5.35 Å for two pairs of benzene rings, and 6.33 Å for adamantane moieties. The angles between the ring planes of the benzene moieties are 57.25 and 70.14°.

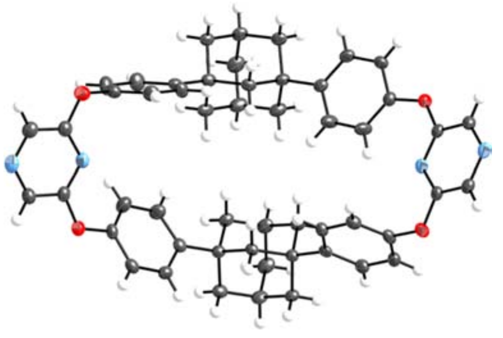


Figure 1. Crystal structure of **1a** represented as a thermal ellipsoid model.

We obtained single crystals **2a** of macrocycle **2** from vapor diffusion of hexane into a chloroform solution of **2**. As depicted in Figure 2, a macrocyclic framework adopted a twisted 1,3-alternate conformation,[18] which is different from that of macrocycle **1** in the crystal **1a** owing to the steric hindrance of the methoxy groups. The centroid−centroid distances between each aromatic and aliphatic parts are 14.31 Å for the pyrazine rings, 4.88 and 5.05 Å for the two pairs of benzene rings bearing methoxy groups, and 6.57 Å for the adamantane moieties. The benzene derivative parts were almost parallel, where the angles between ring planes of the benzene moieties bearing methoxy groups are 1.38 and 10.98°. The macrocyclic framework of **2** is twisted directly along the long axis of **2**. The macrocycle interacts with chloroform molecules through intermolecular CH/O and CH/π interactions.

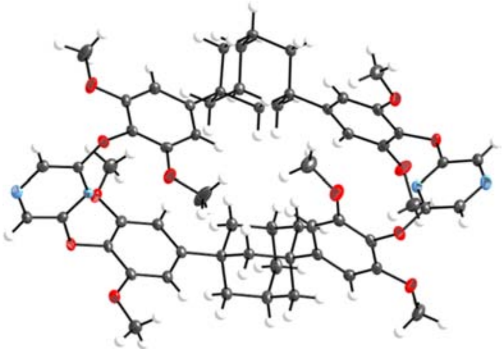


Figure 2. Crystal structure of **2a** represented as a thermal ellipsoid model. Chloroform molecules are omitted for clarity.

The aggregation behavior of adamantane-based oxacyclophanes has been examined in aqueous solution.[19] The macrocycle **2** was dissolved in acetone (1.0 mM) at 40 °C and allowed to stand for 5 days at 25 °C. The dynamic light scattering (DLS) and field-emission scanning electron microscopy (FE-SEM) studies showed no formation of spherical aggregates. Water was added into an acetone solution (H_2O/acetone = 1:4, v/v) of **2** (1.0 mM), and the solution was allowed to stand for 5 days at 25 °C. A DLS study at 25 °C gave a size distribution with an average diameter of 420 nm (Figure S1, Supporting Information). The spherical objects with a diameter of approximately 450 nm were confirmed by FE-SEM (Figures 3a and S2, Supporting Information). The SEM image indicated that the spherical aggregates are robust and stable because they keep their spherical shape without disruption despite being dried on a solid surface. The spherical structures were also supported by transmission electron microscopy (TEM) (Figure 3b), which exhibited obvious contrast between the outer and inner sides of the structures, evidencing the hollow natures of the spherical aggregates. The hollow spheres were composed of a multilayer membrane with a width of 40−70 nm. The single crystals **2b** from aqueous solution of **2** were generated after one month.

In the crystal structure of **2b**, the adamantane-based oxacyclophane **2** was in a twisted 1,3-alternate conformation (Figure S3, Supporting Information), which is similar to that of oxacyclophane in the crystal **2a**. The centroid−centroid

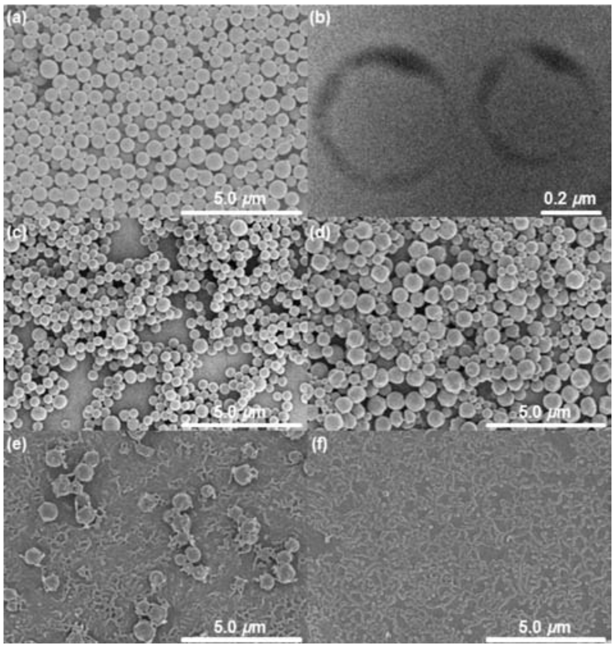


Figure 3. (a) SEM and (b) TEM images obtained from H_2O/acetone (1:4, v/v) mixture of **2** (1.0 mM) after 5 d. SEM images obtained from H_2O/acetone (2:3, v/v) mixture of **2** (0.6 mM) after (c) 0.25, (d) 1, (e) 6, and (f) 22 h.

distances between each aromatic and aliphatic parts are 14.13 Å for pyrazine rings, 5.06 and 5.26 Å for the two pairs of benzene rings bearing methoxy groups, and 6.41 Å for adamantane moieties. The angles between ring planes of the benzene parts with methoxy groups are 3.05 and 3.30°. Individual macrocycles were assembled into columnar structures (Figure 4a), which were produced into two- and three-dimensional networks via multiple CH/O, CH/N, and CH/π interactions between adamantane, dimethoxyphenyl, and pyrazine moieties (Figure 4b). Water molecules were included in the crystalline lattices, and the water molecule interacted with the nitrogen atoms of the pyrazine moieties in the oxacyclophane **2** via hydrogen bonds.

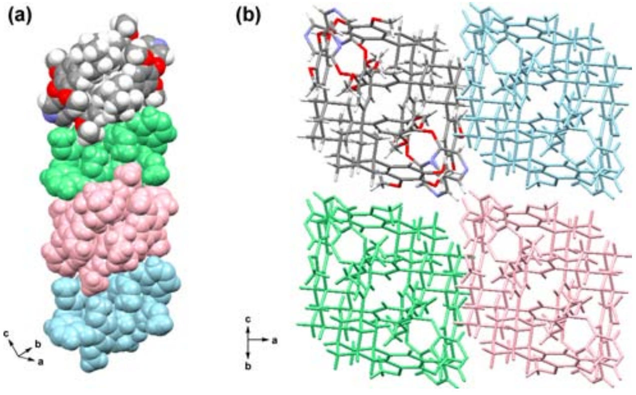


Figure 4. Packing diagram of crystal **2b**. (a) Side view of columnar structure and (b) top view of network structures. Acetone and water molecules were omitted for clarity.

From these results, the spherical assemblies may result from the two- and three-dimensional alignments of the columnar structures of macrocycle **2** (Figure 5).[20] The polar pyrazine moieties in the macrocyclic framework were exposed at the outside of the spherical aggregates, while the nonpolar aliphatic adamantane units were located on the inside of the multilayer membrane to escape the polar external environments. The driving forces for the generation of spherical aggregates were attributed to the hydrophobic interactions in the aqueous solution.

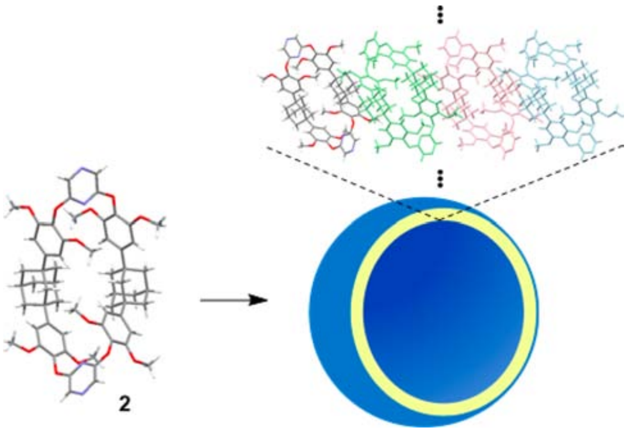


Figure 5. Schematic representation of the self-assembly of hollow spherical aggregates with a multilayer membrane from the oxacyclophane **2**.

It is noteworthy that the transformation from the spherical assemblies into single crystals in an aqueous solution of macrocycle **2** denotes a phase transition from the solution into the solids via hollow spheres. To elucidate this phenomenon in detail, we examined the influence of the polarity of the aqueous solution on crystal formation. Single crystals were generated after 2 days in H_2O/acetone (3:7, v/v) mixture and after 2 h in H_2O/acetone (2:3, v/v) mixture of **2** (1.0 mM). Further, in an aqueous solution (2:3, v/v) of **2** (0.6 mM) with a lower concentration, single crystals were observed after 22 h. These findings show that the rate of crystal formation is elevated according to the increase of the polarity in a mixed solution and the concentration of **2**. We monitored the morphological changes and the crystallization process as a function of time by SEM. In a H_2O/acetone (2:3, v/v) mixture of **2** (0.6 mM), the sizes of spherical assemblies were approximately 400 nm without other morphological aggregates after 0.25 h (Figure 3c). A fusion phenomenon between the spherical aggregates was partly observed (Figure S4, Supporting Information). Sphere formation triggered by the addition of water is attributed to the hydrophobic interaction of the amphiphilic nature of **2** and hydrogen bonds between the nitrogen atoms of pyrazine moieties in **2** and water molecules as observed in the crystal structure. After 1 h, spherical aggregates indicated a hubbly surface (Figure 3d), which partially formed into their fused aggregates (Figure S5, Supporting Information). Over time, fused aggregates of the spheres such as fibrous and network structures with a width of 100−180 nm were observed and gradually increased with the decrease of spherical aggregates, showing the morphological changes (Figure 3e). After 22 h, in the early stage after crystal occurrence of **2**, network structures were mainly observed (Figure 3f) in addition to plate-shaped crystals, indicating the phase transition of single crystals via network aggregates. Therefore, the addition of water into the acetone solution promoted the generation of spherical, fibrous, and network aggregates, which were eventually transformed into single crystals. These results provide evidence for a morphological change and phase transition occurring from the solution into a solid.

In summary, we succeeded in the synthesis and structural analysis of two adamantane-based oxacyclophanes having distorted or twisted 1,3-alternate conformations. The addition of water into an acetone solution of the adamantane-based oxacyclophane triggered the production of spherical, fibrous, and network aggregates and ultimately single crystals. The adamantane derivatives were unique building blocks for the construction of oxacyclophanes to exploit the self-assembled nanostructures owing to their bulky skeleton and aliphatic nature. The study on the development of adamantane-based oxacyclophanes incorporating other aromatic moieties and their aggregation phenomenon is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data, DLS data, SEM and TEM images, crystal data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data were deposited with the Cambridge Crystallographic Data Centre as CCDC 1035797−1035799.

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Notes

The authors declare no competing financial interest.

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