Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202301582
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Aggregation Behavior of Cyclodextrin-Based [3]Rotaxanes

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Abstract: The aggregation of a cyclodextrin (CD)-based [3]rotaxane has been observed and analyzed in detail for the first time in this work. Although the hexagonal packing aggregation of CD-based polyrotaxane is a well known phenomenon, corresponding studies in terms of rotaxanes without any polymer structure have not been conducted so far, probably owing to the difficulty of the molecular design. We synthesized a series of [3]rotaxane species by using a urea-end-capping method and evaluated their aggregation behavior by XRD and SEM measurements. [3]Rotaxane species containing native CD rings showed clear signals assigned to the hexagonal packing by XRD measurement as did polyrotaxane; this proved their aggregation capability. Because the corresponding per-acetylated derivatives did not show this aggregation behavior, the driving force of this aggregation was suggested to be hydrogen bond formation among CD units. The effect of axle end structures and partial acetylation of CDs were also studied.

Introduction

Rotaxane species are widely studied owing to the high mobility of their mechanically interlocked components.[1] For example, a variety of elaborate structural regulation systems have been developed via a rotaxane framework in low-molecular-weight systems, while they have been also studied in materials applications such as stimuli responsive polymers.[2,3] Owing to their unique dynamic character, several studies on rotaxanes have naturally focused on how to control or make the best use of their mobility.[1–3] Meanwhile, cyclodextrin (CD)-based polyrotaxane is well known to form a hexagonally packed aggregation structure under appropriate conditions, which is derived from the formation of hydrogen bonds among the CD units.[4,5] This aggregation of polyrotaxane is expected to be developed into a diverse range of applications, such as biocompatible materials, sensing materials, or 3D printing inks, thanks to the biological compatibility of CD and the unique function of the inclusion complex structure.[4,5] However, as polyrotaxane has limitations on its molecular design owing to the difficulty of maintaining the inclusion complex structure during the synthesis and the fundamental difficulty of modifying polymer species, its application would lack versatility. For example, the development of a fusion material with a polyrotaxane structure is still not so easy owing to the above synthetic difficulties, although it would be scientifically and industrially highly interesting. In many cases poly(ethylene oxide) (PEO) has to be used as the polymer axle unit in polyrotaxane synthesis, thus introducing this framework without PEO is still challenging.[1]

To solve this synthetic issue, we considered the following strategy; dividing the polyrotaxane into a [3]rotaxane that does not have any polymer structure, and using it as the building block to construct the aggregation framework (Figure 1). As [3]rotaxane does not have any polymer structure, its molecular design becomes much more flexible than that of polyrotaxane species, which enables modification by general organic reactions. Here, the direction of the ring units on [3]rotaxane is important, because the head-to-head repeating unit in polyrotaxane is considered to be necessary to form hydrogen bonding to construct an aggregation structure.[1a,4,5] To synthesize a head-to-head structured α-CD-based [3]rotaxane framework, the urea-end-capping method developed by Takata and co-workers proved to be very useful, because of its facile high yield synthesis and flexible molecular design afterwards.[6] Moreover, modification of hydroxy groups on CD of [3]rotaxane is easily conducted on this framework, opening the avenue to a further systematic analysis depending on the effect of modification ratio of CD in terms of the aggregation behavior. Considering the above, in this study, we investigated the aggregation behavior of CD-based [3]rotaxane species mainly by powder XRD (PXRD) measurement. As a result, a hexagonal packing type aggregation of [3]rotaxane was observed similar to polyrotaxane species, although it has only two CD units per molecule. As encouraged by the initial observation of the

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202301582

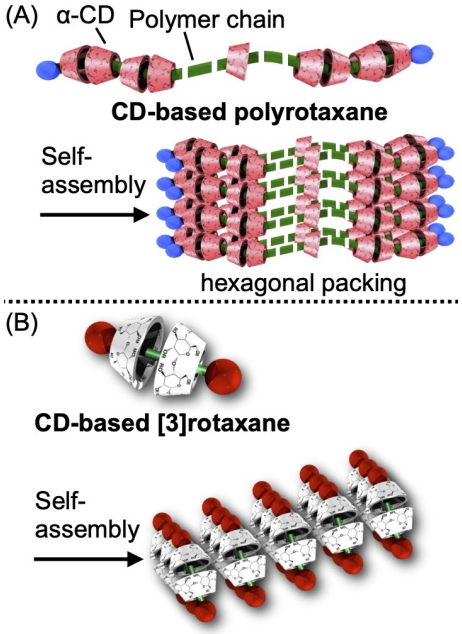
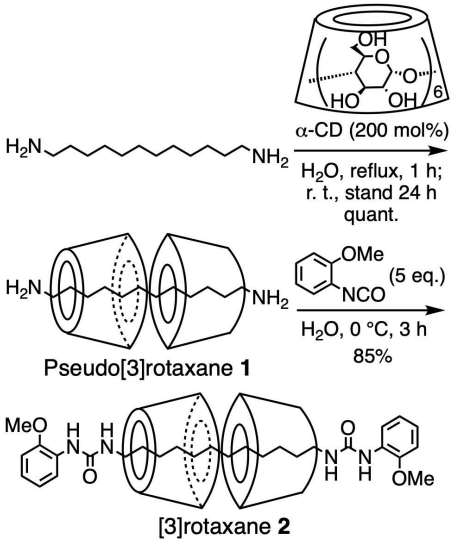


Figure 1. Schematic illustration of A) aggregation of polyrotaxane species (conventional study) and B) aggregation of [3]rotaxane species (this study).



Scheme 1. Synthesis of [3]rotaxane **2**.

aggregate formation, further experiments were carried out to clarify a more detailed view of the mechanism of this aggregation behavior.

Results and Discussion

As previously reported, the aggregation of polyrotaxane species was induced by hydrogen bond formation among CD units. In this regard, Kwak and co-workers reported that dispersion of polyrotaxane into a certain solvent drastically affected this aggregation behavior, because this solvent treatment involved hydrogen bond formation process.[5b] In their polyrotaxane system composed of α-CD and poly(caprplactone) (PCL), THF effectively induced aggregate formation. Considering the above, such solvent effect was also evaluated in this study.

[3]Rotaxane species were easily synthesized by previously established method (Scheme 1).[6] Namely, the inclusion complex was formed by mixing 1,12-diaminododecane and α-CD in water, and the successive end-capping reaction by the excess of substituted phenyl isocyanate species afforded corresponding [3]rotaxane. Afterwards, the axle end structure could be modified by bromination with *N*-bromosuccinimide and successive transition metal-catalyzed cross-coupling reaction such as Suzuki reaction.[6] Notably, the reported yield of the rotaxanation step for [3]rotaxane **2** was 64%, which was already quite high compared with other rotaxane syntheses, but simple extension of the reaction time from 1 to 3 h increased this yield to 85%. Because all the ingredients of this rotaxane synthesis were commercially available and the purification was only by simple precipitation without a chromatographic purification process, this facile preparation protocol supported an advantage of this molecular design for further development. Moreover, substituted phenyl isocyanate species, which are used as an end-cap reagent in this synthesis, are accessible via the reported facile synthesis[6,8] in addition to the commercially compounds, could also contribute the flexible molecular design.

α-CD-pseudopolyrotaxane consisted of α-CD and PEO, which was synthesized by a standard protocol,[9] α-CD, and [3]rotaxane **3** were evaluated by PXRD (Figure 2). Here for the sample preparation, α-CD was dispersed in THF or acetone, and both pseudopolyrotaxane and [3]rotaxane **3** were prepared in THF or water respectively to evaluate the solvent effect. As a result, α-CD and pseudopolyrotaxane showed a reasonable XRD profile consistent with previous reports.[5] Namely, the XRD profile of the former was consisted of many small peaks which indicated the microcrystal structures, while the characteristic peaks of the latter at $2\theta = 12.8°$ (110), 16.1° (201), 19.6° (210), and 22.4° (300) were in good agreement with the hexagonal lattice with unit cell parameters $a = b = 13.65$ Å and $c = 16.4$ Å, as the head-to-head and tail-to-tail repeating inclusion structure.[5] Moreover, the peak at 11.9° was assigned as the (001) plane of the hexagonal unit cell $a = b = 13.65$ Å and $c = 7.43$ Å, which derived from the partial formation of the head-to-tail repeating inclusion structure, as same as the previous report.[5a] Here, XRD profiles of pseudopolyrotaxane after THF or water treatment were observed as almost the same, indicating that the previously mentioned solvent effect did not have much of an effect. Meanwhile, [3]rotaxane **3** treated with THF clearly showed XRD peaks at $2\theta = 12.8°$ (110), 19.6° (210), and 22.4° (300) resulting from the hexagonal unit cell. As [3]rotaxane **3** treated with water showed broader patterns compared with the THF-treated sample, THF induced the aggregate formation in this case (Figure 2B). Herein, it was clarified that the [3]rotaxane framework also formed hexagonally aligned structures similar to polyrotaxane species, although there were only two CD units

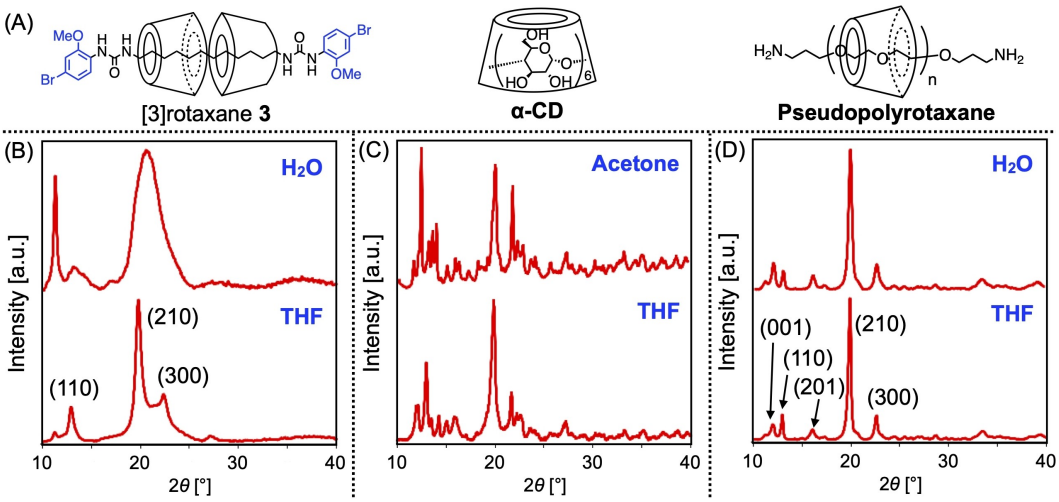


Figure 2. A) Chemical structures of [3]rotaxane **3**, α-CD, and pseudopolyrotaxane. Powder XRD profiles of B) [3]rotaxane **3** treated with H_2O (top) or THF (bottom), C) α-CD treated with acetone (top) or THF (bottom), and D) pseudopolyrotaxane treated with H_2O (top) or THF (bottom).

included in one molecule. Meanwhile, the peaks of pseudopolyrotaxane were observed sharper than those of [3]rotaxane **3**, indicating a higher crystallinity of the former. Because [3]-rotaxane **3** does not have a long polymer chain axle, the structural regularity along the axle unit would be smaller than that of polyrotaxane, could induce the sharper profile of the latter. However, as encouraged by this observation, further details of this aggregation behavior were studied. Here, as the axle end moiety of [3]rotaxane **2** is relatively small and it might slightly decompose the inclusion complex structure in the solvent treatment process via deslipping reaction which is often observed on the size-complementary rotaxane species,[2c] XRD measurement of [3]rotaxane **2** was not conducted.

[3]Rotaxane **3** was treated with other solvents (acetone, CH_2Cl_2, EtOAc, *n*-hexane, MeOH, EtOH, *i*PrOH, *n*BuOH, and hexan-1-ol) and analyzed by XRD.[7] As a result, while acetone treatment resulted in a similar XRD profile to THF, other non-polar organic solvents induced broad signals, meaning that they did not promote the hexagonal alignment formation. Meanwhile, alcohol solvents induced clear signals similar to those recorded after treatment with THF and acetone, although the peaks were slightly broader and noisier. This observation suggested that a certain polarity of the solvent is required to induce the formation of the hexagonal aggregation, provably for supporting the intermolecular interaction among CD units. From this solvent study, THF and acetone were revealed to induce the aggregation more effectively than other solvents. Besides the solvent effects, heat treatment might also affect the aggregation behavior as observed on polyrotaxane species.[10] However, heating [3]rotaxane species could induce the decomposition of the inclusion complex structure as previously reported.[3m] Therefore, heat treatment was not conducted in this study.

Next, to evaluate the effect of the axle end structure on this phenomena, [3]rotaxane **4**, **5**, and pseudo[3]rotaxane **1** were evaluated (Figure 3). These samples were synthesized in a similar manner to [3]rotaxane **2**.[6] As a result, [3]rotaxane **4** and **5** showed similar profiles to [3]rotaxane **3**, thus suggesting the occurrence of the same aggregation phenomena. Meanwhile, pseudo[3]rotaxane **1** showed sharper signals than [3]rotaxane species, and it was rather similar to the profile of pseudopolyrotaxane (Figure 2D). This difference in (pseudo) [3]rotaxane system between with an end-cap structure and without, might be explained as following. As the end-cap moieties in these [3]rotaxane species do not contribute strongly to the aggregate formation, species without an end-cap structure would exhibit a stronger driving force for aggregation per volume. Therefore, different profiles were observed between [3]rotaxane and pseudo[3]rotaxane. In the case of (pseudo)polyrotaxane system, the contribution of axle end moieties was so small that the existence of the bulky end-cap moiety would not affect that much on this aggregate formation, resulting in the well ordered hexagonal alignment in both cases.[9]

To evaluate further details of this axle end effect, SEM measurements were carried on [3]rotaxane **3** and **5** (Figure 4). Compared with the previous report where a certain smooth surface had been observed with the inclusion complex of α-CD and PCL, surface images observed here were generally rough.[5b] As mentioned by the same reference, a smooth surface was built only when polyrotaxane formed quite high order of aggregation structure, indicating the aggregation observed here would be of lower order than the reported system. However, compared with the surface of [3]rotaxane **3** (Figure 4A and B) and **5** (Figure 4C and D), the latter was rougher. This was probably because the bulkier axle end structure on [3]rotaxane **5** would have prevented the aggregate formation to some extent. These results revealed that the axle end structure also affected this aggregate formation, meaning properly designed axle end structure can enable a fine tuning. As previously mentioned, this would not be the case on polyrotaxane system.

Because these [3]rotaxanes and α-CD could be easily acylated, peracetylated species were synthesized and evaluated.[7]

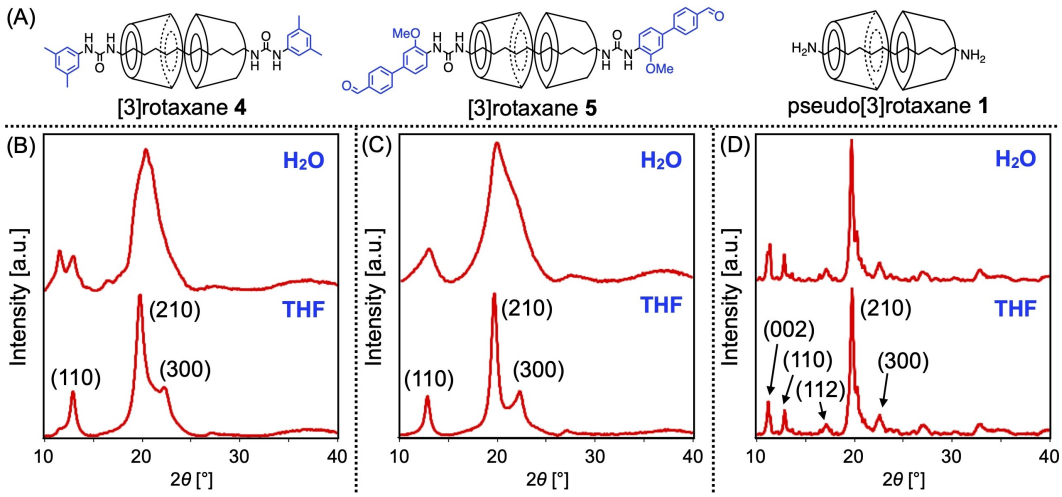


Figure 3. A) Chemical structures of [3]rotaxanes **4** and **5** as well as pseudo[3]rotaxane **1**. Powder XRD profiles of B) **4**, C) **5**, and D) **1** treated with H_2O (top) or THF (bottom).

As expected, peracetylated species showed only broad amorphous halos on the XRD profiles, clearly suggesting the necessity of the existence of the hydroxy groups to induce aggregation. Since these [3]rotaxane species have 36 hydroxy groups in one molecule, partial modification would enable to control the aggregation property.

To test this, partially acetylated species were synthesized and evaluated (Scheme 2). Here, peracetylated [3]rotaxane **6** was partially de-acetylated to prepare samples, because the de-acetylation of per acetylated CD derivatives were more easily controllable than partial acetylation.[6] Here, basic aqueous solution was used as the de-acetylation reagent, and the reaction ratio was controlled by reaction condition.[7] By doing so, two partially acetylated [3]rotaxanes were obtained. In ^{1}H NMR spectra, de-acetylated samples did not show the simple sum of the signals of [3]rotaxane **3** and [3]rotaxane **6**, but showed other types of signals, suggesting that the partial deacetylation occurred successfully (Figure 5). Here, signals from acetyl groups were clearly observed around 2 ppm in each compound. Therefore, the acetylation ratio were calculated by integration of this region, and were determined as 33% for [3]rotaxane **Ac33** and 64% for [3]rotaxane **Ac64**, respectively. One of the most popular modifications of CD derivatives other than acetylation is methylation, which could be also conducted as a partial modification.[2b,c] However, methylated hydroxy groups on CD are difficult to demethylate. As this partial acetylation is easily conducted and de-acetylated, this modification method could be a useful tool to control the hydrophilicity and the solubility of CD derivatives.

[3]Rotaxanes **Ac33** and **Ac64** were evaluated by XRD like all other samples (Figure 6). Interestingly, THF-treated samples showed broader profiles than water-treated ones in this case, which was opposite to the results obtained for native CD-based species. Although water-treated [3]rotaxane **Ac33** and **Ac64** showed broader profiles than that of THF-treated [3]rotaxane having native CD rings for example [3]rotaxane **3** (Figure 2B), the

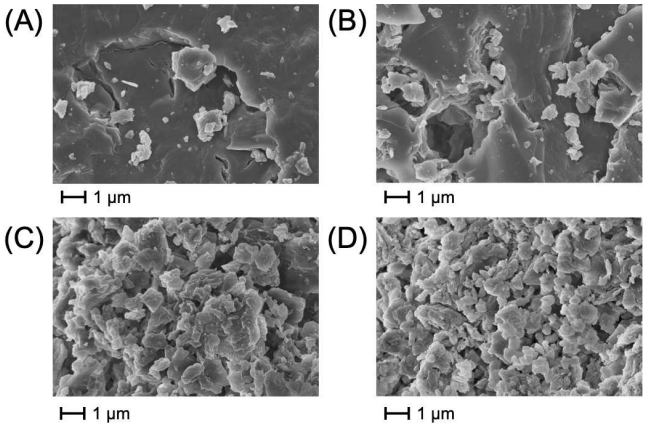
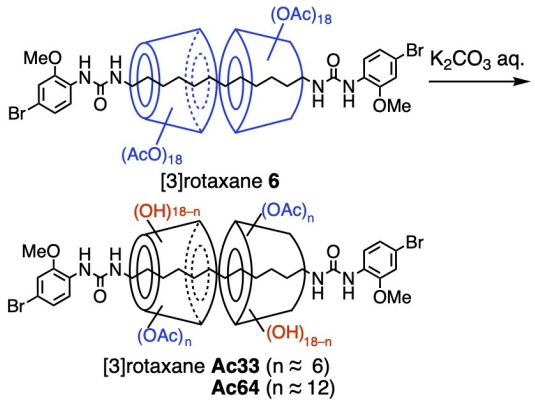


Figure 4. SEM images (x 30000) of A) [3]rotaxane **3** treated with THF; B) [3]rotaxane **3** treated with acetone; C) [3]rotaxane **5** treated with THF; D) [3]rotaxane **5** treated with acetone.



Scheme 2. Partial de-acetylation of [3]rotaxane **6**.

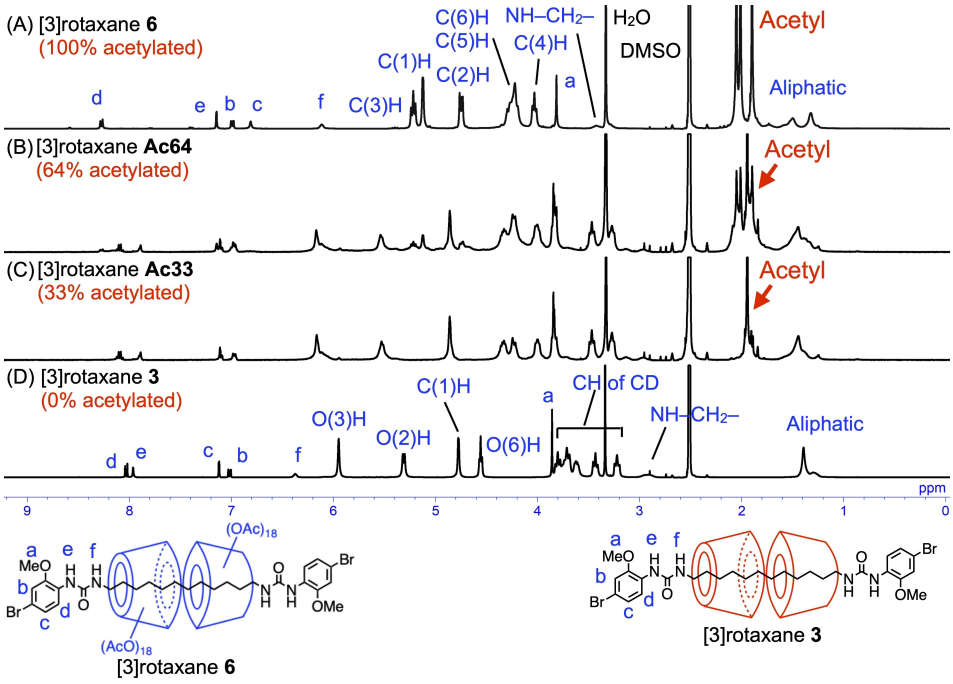


Figure 5. ^{1}H NMR spectra of A) [3]rotaxane **6**, B) [3]rotaxane **Ac64**, C) [3]rotaxane **Ac33**, and D) [3]rotaxane **3** (400 MHz, [D_6]DMSO, 298 K).

XRD peaks at $2\theta = 12.8°$ (110), 19.6° (210), and 22.4° (300) resulting from the hexagonal unit cell were detected on the XRD profile of [3]rotaxane **Ac33** (Figure 6B). In the case of [3]rotaxane **Ac64**, XRD peaks at $2\theta = 12.8°$ (110) and 19.6° (210) were still detectable, while a peak at $2\theta = 22.4°$ (300) became vague (Figure 6C). These profiles indicated the aggregate formation not by THF but by water-treated samples. These results can be explained by the interaction among CD or end-cap moieties and solvent as follows. In the case of native CD-based [3]rotaxane in H_2O, CD units could move on alkyl chain and end-cap moieties owing to the hydrophobic interaction (Figure 7A). Therefore, the locations of two CD units have a certain dispersity on the entire axle unit, inducing no aggregation formation. Meanwhile, in THF, CD units are likely to stay on alkyl chain and not on end-cap moieties, because the end-cap moieties have high affinity with THF and two CD units could form hydrogen bonding between themselves to reduce the exposure of OH groups in THF (Figure 7C). In that case, CD units on [3]rotaxanes could effectively form intermolecular hydrogen bonding to form aggregation. On the other hand, in the case of partially acetylated CD based [3]rotaxane in H_2O, CD units are not likely to move on end-cap moieties owing to the weakened hydrophobic interaction of them by the partial acetylation (Figure 7B). Therefore, CD units prefer to stay on alkyl chain with hydrogen bonding formation among them, inducing the aggregation as same as native CD-based [3]rotaxane in H_2O. However, since hydrogen bonding among partially acetylated CD units are weaker than native CD units, the aggregation of the former could have less regulated structure than the latter, resulted in the broader XRD pattern of the former. In THF, both partially

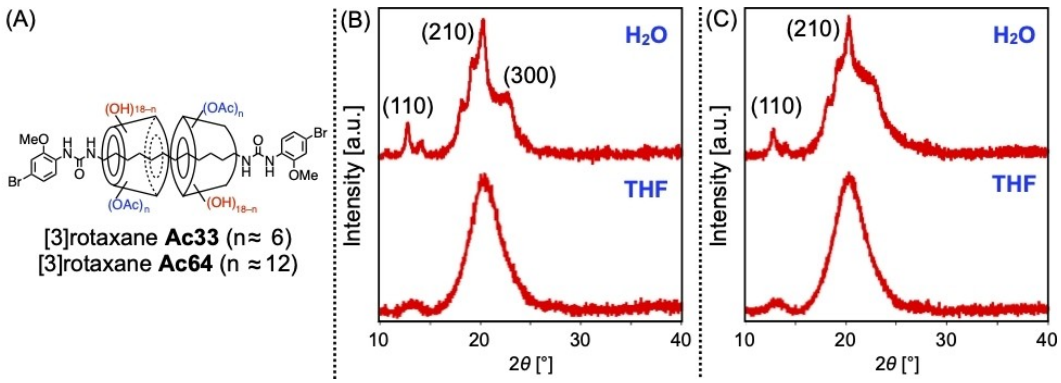


Figure 6. A) Chemical structures of [3]rotaxane **Ac33** and **Ac64**: powder XRD profiles of B) **Ac33** and C) **Ac64** treated with H_2O (top) or THF (bottom).

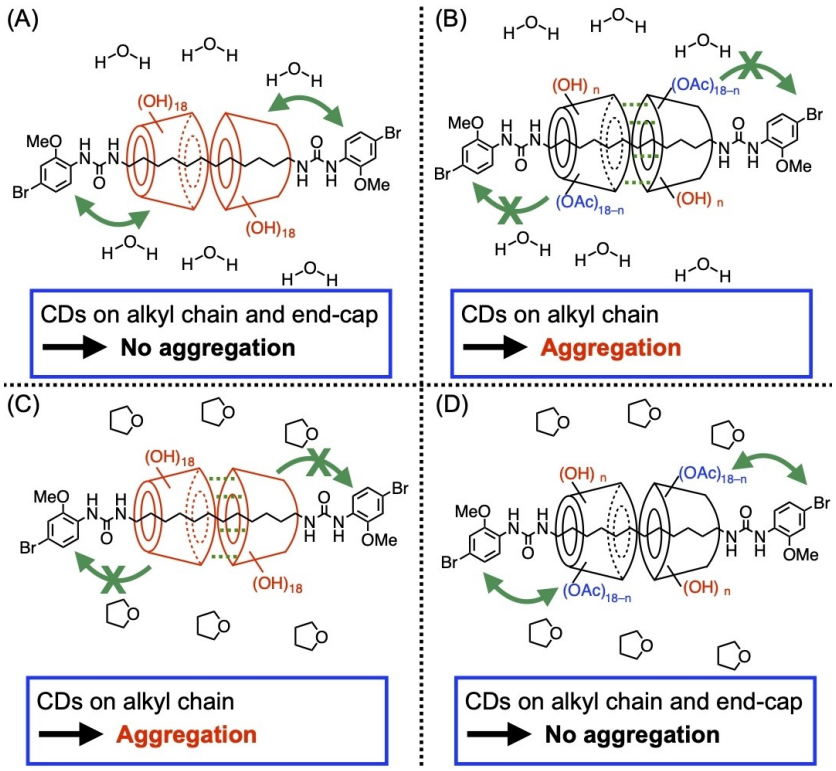


Figure 7. Schematic illustration of the plausible mechanism of the aggregation behavior of A) [3]rotaxane **3** treated with H_2O, B) [3]rotaxane **Ac33** or **Ac64** treated with H_2O, C) [3]rotaxane **3** treated with THF, and D) [3]rotaxane **Ac33** or **Ac64** treated with THF.

acetylated CD units and hydrophobic end-cap moieties have affinity on the solvent, inducing random distribution of CD units on the entire axle, inducing no aggregate formation (Figure 7D). Comparing [3]rotaxane **Ac33** and **Ac64**, the former had more hydroxy groups, resulting in a little sharper XRD profile of the former than the latter. Moreover, SEM images of peracetylated α-CD and [3]rotaxane **6** showed a particle type surface, while those of [3]rotaxane **Ac33** and **Ac64** did not show such particle images but rather similar patterns as native CD-based species.[7] These observation clearly indicated that partially acetylated species behave different from native CD based [3]rotaxanes and peracetylated species.

Because partially acetylated species could be easily de- or per-acetylated, partial acetylation would be an effective method to control the aggregation behavior of this [3]rotaxane framework, contributing the utility of this system when it comes to develop the further molecular design based on this aggregation of [3]rotaxane.

Conclusions

In this work, we have demonstrated that [3]rotaxane species were able to form a hexagonally aggregated structure in a similar manner with polyrotaxane, although it has only two CD units in one molecule. Moreover, it was clarified that this aggregation behavior was affected by the following three factors: dispersion in solvent, axle end structures, and degree of acetylation of CD units. Compared with polyrotaxane system, [3]rotaxane only has the strong driving force of self-assembly in the 2D region, not 3D, thus the choice of framework depends on the intended use. That [3]rotaxane species can be flexibly introduced into various types of architectures such as macromolecular[3]rotaxane or poly[3]rotaxane, indicates their potential application in materials as a new building block of self-assembling structures.

Experimental Section

General: ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance III Microbay spectrometer using deuteurated solvents, calibrated using residual undeuterated solvent or tetramethylsilane as the internal standard. Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectra were recorded on a Bruker Vertex 80 with a mid-wavelength to far infrared spectrum from 6000 to 50 cm^{-1}. X-ray diffraction (XRD) patterns were obtained at room temperature on Bruker D8 Advance diffractometer with a $Cu_{K\alpha}$ radiation source (wavelength = 0.154 nm). The supplied voltage and current were set to 40 kV and 40 mA, respectively. For XRD sample preparation, each compound was dispersed in a respective solvent for 24 h, the precipitate was collected by filtration, dried in vacuo to give solid samples. Powder samples were prepared by grinding solid samples by mortar. Powder samples were mounted on a sample holder and scanned at a rate of $2\theta = 0.33°\ min^{-1}$ between $2\theta = 10°$ and 40°. Scanning electron microscope (SEM) measurement was carried out by a Zeiss LEO 1530 with an accelerating voltage of 5 kV. The specimen were sputtered with a thin layer of Pt with a Leica EM ACE600 prior to observation.

α-Cyclodextrin (α-CD) was dried at 70 °C overnight under reduced pressure before use. Commercially available reagents and solvents were used without further purification unless otherwise noted.

Chemical synthesis: Chemical synthesis was carried out according to a standard procedure well described in previous reports.[6,9] Some representative syntheses are written below.

Synthesis of [3]rotaxane Ac33: K_2CO_3 aq. (K_2CO_3; 50 mg, 0.36 mmol, H_2O; 0.5 mL) was added to a solution of [3]rotaxane **6** (83 mg, 0.020 mmol) in mixed solvent (DMF; 0.75 mL, EtOH; 0.25 mL); the mixture was stirred at RT for 24 h. The resulting mixture was poured into water, the precipitate was collected and dried in vacuo to give the product (40 mg, 64%) as a white solid. The spectral analysis suggested the structure of the product as the [3]rotaxane having on average 33% acetylated α-CD, as described in the main manuscript; ^{1}H NMR (400 MHz, 298 K, [D$_6$]DMSO): δ = 8.15–8.04 (m, 2H), 7.97–7.85 (m, 2H), 7.15–6.93 (m, 4H), 6.35–5.89 (m, (14–2*n*/3)) H, O(3)H, –CO*NH*CH$_{2-}$), 5.53 (br, (12–2*n*/3)) H, O(2)H), 4.86 (br, 12H, C(1)H), 4.45–2.87 (m, (82–4n/3) H, (C(6)H, C(5)H, C(4)H of acetylated CD) + (C(6)H, C(5)H, C(4)H, C(3)H, C(2)H of native CD) + OMe + NH*CH*$_{2-}$), 2.12–1.75 (m, (6×*n*) H, Ac), 1.67–1.11 ppm (m, 20H, methylene); IR (ATR): ν = 3342, 2926, 1737, 1529, 1366, 1235, 1147, 1029, 948, 573 cm^{-1}.

Synthesis of [3]rotaxane Ac64: This synthesis was conducted as same as [3]rotaxane **Ac33** with another K_2CO_3 aq. (K_2CO_3; 25 mg, 0.18 mmol, H_2O; 0.5 mL), to give the product (51 mg, 68%) as a white solid. The spectral analysis suggested the structure of the product as the [3]rotaxne having on average 64% acetylated α-CD, as described in the main manuscript; ^{1}H NMR (400 MHz, 298 K, [D$_6$]DMSO): δ = 8.31–7.84 (m, 4H), 7.21–6.72 (m, 4H), 6.36–2.84 (m, (132–2*n*) H, CH of CD, OMe, NH*CH*$_{2-}$, –CO*NH*CH$_{2-}$), 2.28–1.04 ppm (m, ((6×*n*) + 20) H, Ac, methylene); IR (ATR): ν = 3359, 1739, 1525, 1367, 1230, 1148, 1025, 574 cm^{-1}.

Acknowledgements

This work was supported by JSPS KAKENHI (Japan) grant number JP20 J00360 (Y. A.). Samuel Struzek, Andrea De Giacinto, Braun Lukas, and Prof. Dr. Jan-Dierk Grunwaldt are gratefully acknowledged for their support in powder X-ray diffraction measurements. Volker Zibat is gratefully acknowledged for his support in SEM measurements. The authors acknowledge financial support from the Helmholtz Association. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interests.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cyclodextrins · hydrogen bonding · rotaxanes · self-assembly · solvent effects

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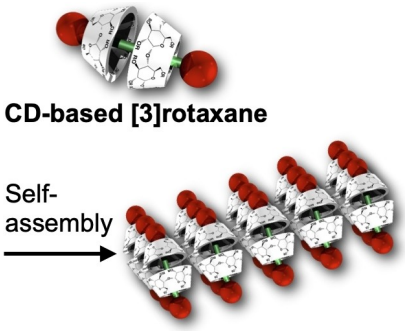
Manuscript received: May 18, 2023
Accepted manuscript online: June 5, 2023
Version of record online: ■■, ■■

RESEARCH ARTICLE

The aggregation of a cyclodextrin (CD)-based [3]rotaxane was first observed and analyzed in this work. It was clarified that [3]rotaxane forms a hexagonal packing type aggregation derived from hydrogen bond formation among CD units in a similar manner to polyrotaxane species. This aggregation could be controlled by solvent type on dispersion treatment, axle end structures, and modification of CD.



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Aggregation Behavior of Cyclodextrin-Based [3]Rotaxanes