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Micrometer-sized rodlike structure formed by the secondary assembly of cyclodextrin nanotube

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Abstract

In this work, we report the observation on the self-assembly of β-CD nanotube induced by 2-phenyl-5-(4-diphenylyl)1,3,4-oxadiazole (PBD) molecule with fluorescence microscopy and transmission electron microscopy (TEM). Micrometer-sized rodlike structure is formed by the secondary assembly of cyclodextrin nanotube driven by the inter-nanotubular hydrogen bonding. The effects of pH value, urea, DMF and NaCl on the formation of the rodlike structure are investigated. Dynamic light scattering (DLS) is applied to further characterize the formation of the PBD–β-CD nanotube. The effect of light scattering on the measurement of fluorescence anisotropy of PBD in the aqueous solutions of β-CD is corrected. A new mechanism of cyclodextrin aggregation is proposed for this system.

Keywords: Cyclodextrin nanotube; Secondary assembly; Hydrogen bonding; Transmission electron microscopy (TEM); Dynamic light scattering (DLS); Micrometer-sized rod

1. Introduction

Supramolecular assemblies including rotaxanes and catenanes have generated various applications in nanoscience as contributing to advances in molecular electronics and the construction of artificial molecular machines [1–3]. Cyclodextrin (CD) nanotube as another important type of supramolecular assembly in cyclodextrin chemistry has intrigued chemists increasing interest in recent years due to their potential to serve as molecular devices as well as functional materials [4–14]. In crystal structure, either cyclodextrin itself or some inclusion complexes of cyclodextrin are known to be arranged within the crystal lattice in one of two modes as cage-type and channel-type structures [15–19]. For the cage-type structure, two different categories are encountered depending on the packing of the CD molecules. In one, CDs are packed crosswise in herringbone fashion, and in another, the packing model is reminiscent of bricks in a wall [17]. But the secondary assembly behavior of cyclodextrin nanotube is rarely reported [5].

In this work, we report the observation on the self-assembly of β-CD nanotube induced by PBD molecule (see Fig. 1) with fluorescence microscopy and TEM. We find that micrometer-sized rodlike structure is formed by the secondary assembly of cyclodextrin nanotube. DLS result indicates that the single nanotube does exist in the solution after being treated with the 0.2-μm filter. Agbaria and Gill reported that some oxazole molecules including PBD can form inclusion complexes with γ-CD at lower concentrations and these inclusion complexes can form extended nanotubes at relatively high concentrations [7]. In our previous work [9], we further studied the interactions of PBD with α-, β- and γ-CDs. The results showed that α-CD can form a simple inclusion complex with PBD in a stoichiometry of 1:2 (guest:host). β-CD can form

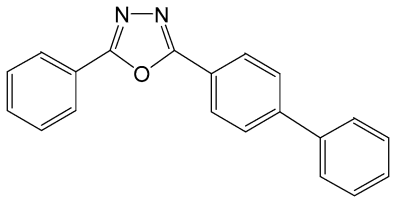

Fig. 1. Molecular structure of PBD.

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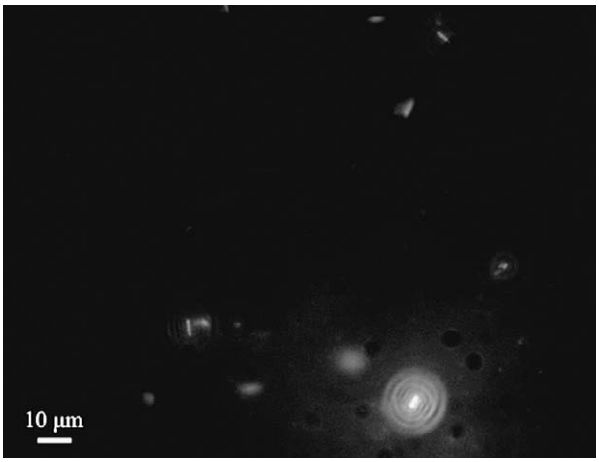

Fig. 2. Fluorescence image of the micrometer-sized rodlike structure of PBD–β-CD nanotube aggregates. [PBD] = 1×10^{-5} M, [β-CD] = 10 mM.

(see Fig. 3b). Fig. 3c provides important information about the dimensions of the rods, that is, the section of the rod is approximately oblong and the thickness of the rod is about 40 nm. The mechanism by which the small cyclodextrin nanotubes stack in such a highly organized way intrigues our great interest. Research concerning this kind of cyclodextrin nanotube induced by small molecule has confirmed that besides hydrophobic interaction and van der Waals interaction, hydrogen bonding between the hydroxyl groups of neighboring cyclodextrin is necessary to the formation of the nanotubular structure [5b,9,12]. Since the pK_a value of β-CD is 12.20, hydroxyl groups of β-CD will turn to negative oxygenic ions at pH higher than 12.20 [30]. Under this condition, the destruction of hydrogen bonding between neighboring β-CDs would lead to the collapse of the nanotubular structure [5b,9,12]. In case of the PBD–β-CD system, when adjusting pH value to 13.0, we find the turbid solution becomes transparent completely. Subsequently, no

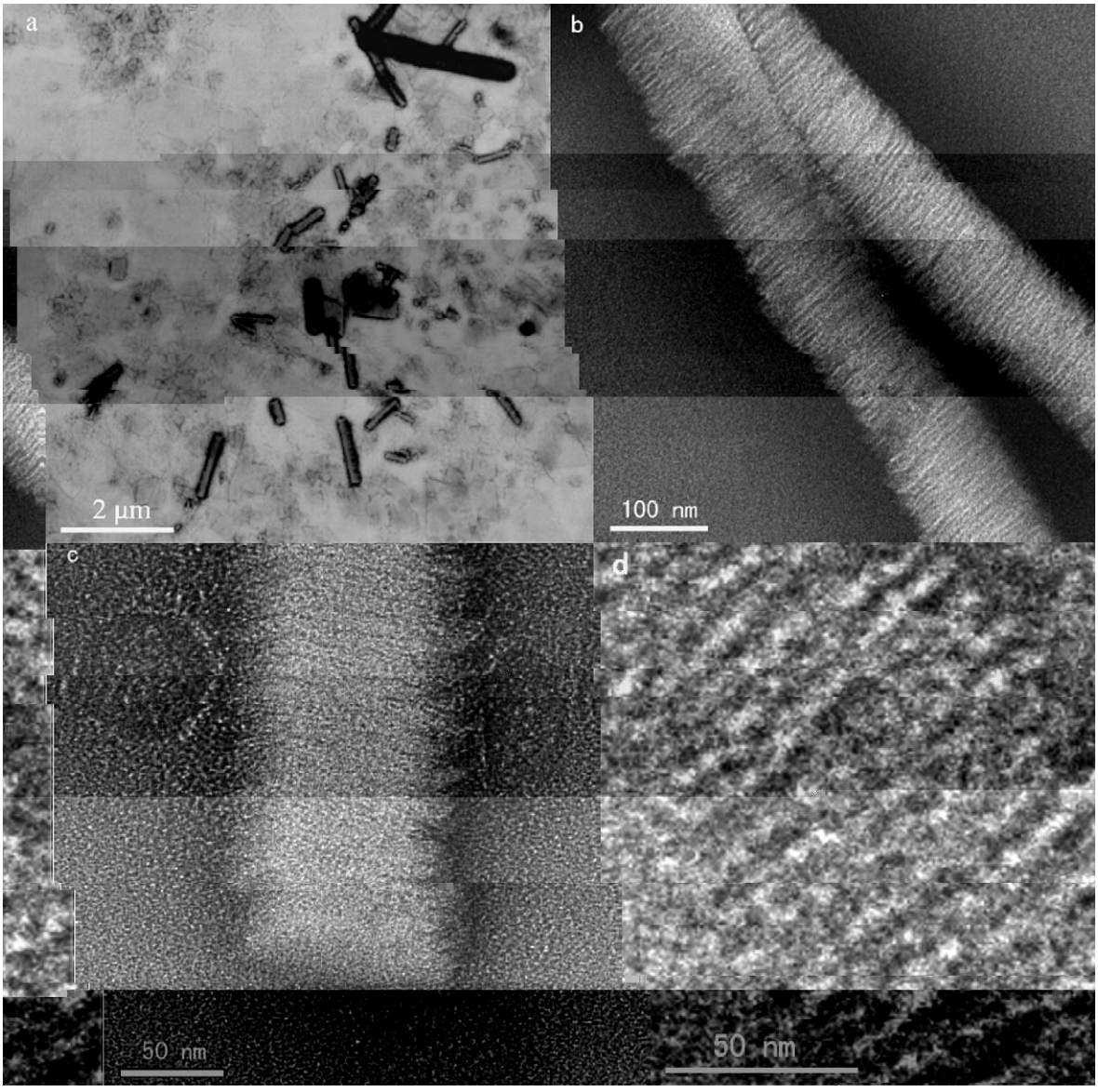

Fig. 3. TEM (a) and high-resolution TEM (b) micrographs of the micrometer-sized rodlike structure of PBD–β-CD nanotube; high-resolution TEM micrographs of the section (c) and the surface (d) of the rod. [PBD] = 1×10^{-5} M, [β-CD] = 10 mM.

rodlike structures except spherical ones are observed by TEM (see Fig. 4b). Analogous importance of hydrogen bonding has been reflected in the process of an amphiphilic hyperbranched copolymer assembling to a macroscopic multiwalled tube with millimeter in diameter, centimeter in length and 400 nm in thickness [31]. Self-aggregation phenomenon of cyclodextrin itself in the absence of small molecule has been investigated by

Table 1
Mean hydrodynamic radius (R_h), correlative intensity (I) and mass (M) contributions of various components in the aqueous solutions of CDs and PBD-CDs treated with 0.2-μm filters. [PBD] = 1×10^{-5} M, [CD] = 10 mM

Sample	R_{h1} (nm)	I_1 (%)	M_1 (%)	R_{h2} (nm)	I_2 (%)	M_2 (%)	R_{h3} (nm)	I_3 (%)	M_3 (%)
α-CD[a]	0.6 ± 0.1	6.68	99.9989	–	–	–	64.4 ± 0.5	93.32	0.0011
PBD–α-CD	0.7 ± 0.1	7.10	99.9989	–	–	–	74.4 ± 0.3	92.90	0.0011
β-CD[a]	0.8 ± 0.1	14.02	99.9998	–	–	–	114.7 ± 0.4	85.98	0.0002
PBD–β-CD	0.9 ± 0.2	15.55	99.9947	11.2 ± 0.2	1.51	0.0050	109.4 ± 0.3	82.94	0.0003
γ-CD[a]	0.7 ± 0.2	3.19	99.9977	–	–	–	76.7 ± 0.5	96.81	0.0023
PBD–γ-CD	0.8 ± 0.1	26.81	99.9989	11.2 ± 0.2	0.65	0.0009	84.8 ± 0.5	72.54	0.0002

[a] Taken from Ref. [12].

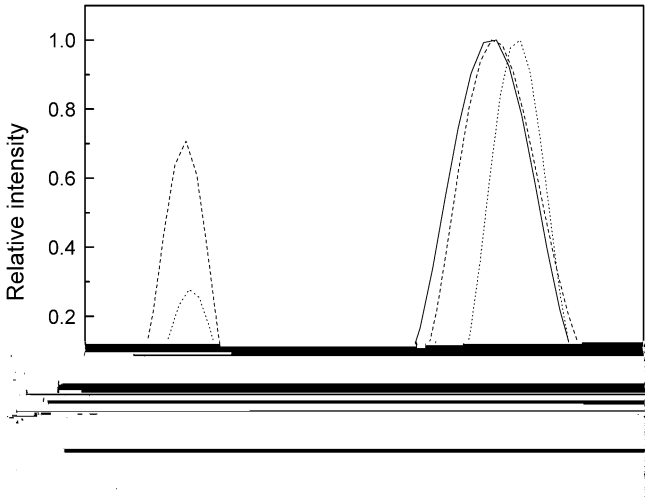

Fig. 5. DLS results of the aqueous solutions of PBD–α-CD (solid line), PBD–β-CD (dot line), PBD–γ-CD (dash line) treated with 0.2-μm filters. [PBD] = 1×10^{-5} M, [CD] = 10 mM.

in the systems of PBD–β-CD and PBD–γ-CD. We think that it corresponds to the size of nanotube other than monomeric and aggregated CDs. Analogous new peak appeared in the system of DPB–γ-CD was ascribed to the formation of DPB–γ-CD nanotube [12].

For the solution was treated with the 0.2-μm filter before the DLS measurement, the micrometer-sized rods or the secondary aggregations of PBD–β-CD nanotube as observed by TEM have been removed from the solution. Thus, the occurrence of the component with the hydrodynamic radius around 11 nm in the filtrate can be ascribed to the formation of single nanotube. Approximate calculation of mass contributions of all components can be carried out using the method suggested by Gonzalez-Gaitano et al. for spherical model [22] (see Table 1). The intensity contribution of cyclodextrin nanotube is very low, and the relative mass contribution is calculated to be 0.0050% (PBD–β-CD) and 0.0009% (PBD–γ-CD). It should be pointed out that the occurrence of the new peak does not come from mathematical artifact though its relative intensity and mass contributions are low. In our previous work, we discussed this point in detail [12]. Herein, the small mass quantity of the single PBD–β-CD nanotube in the filtrate indicates that it is greatly inclined to assemble further driven by the inter-nanotubular hydrogen bonding. It can be inferred that the formation of the micrometer-sized rod is stepwise, that is, the single nanotube is formed first and then it aggregates further to form the micrometer-sized rod.

3.4. Corrected fluorescence anisotropy in turbid solution

The artificial decrease in fluorescence anisotropy caused by light scattering has been described by Teale [24]. Approximate expression for the fractional decrease in anisotropy is

$$\left(r' - r_{obs}\right)/r' = (\quad (2)$$

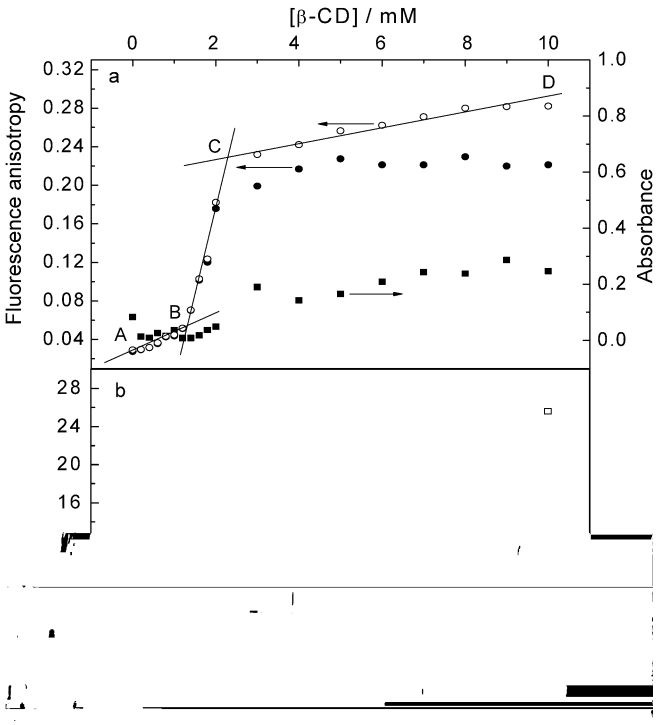

Fig. 6. (a) Absorbance value (filled square), corrected (open circle) and observed (filled circle) fluorescence anisotropy of PBD (1×10^{-5} M) in aqueous solutions of β-CD at various concentrations; (b) Estimated number of β-CD units in a single nanotube from corrected (□) and observed (■) anisotropy values.

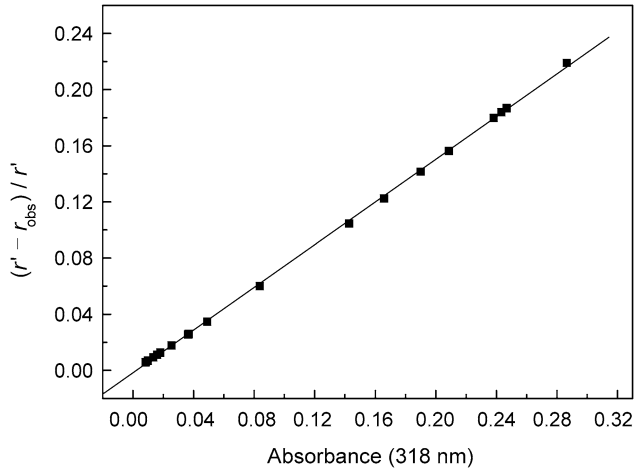

Fig. 7. Dependence of $(r' - r_{obs})/r'$ of PBD vs absorbance in aqueous solutions of β-CD at various concentrations.

But this value is smaller than that theoretically predicted by Teale as 2.303. Similar phenomenon was observed by Lentz et al. in membranes where the estimated K value ranged from 0.15 to 1.77 [25]. The reason concerning the difference between the measured and predicted K values was discussed by Lentz et al. Three possible factors were given. First of all, the apparent turbidity determined with the absorption spectrophotometers is lower than that with the proper light scattering instrument [25]. Secondly, the K value 2.303 predicted theoretically by Teale is approximate and would not be expected to agree well with any system exactly [25]. Thirdly, deviations of the experimental K value from the predicted value may reflect scattering birefringence that was not taken into account by Teale's treatment of simple, isotropic scattering [25]. Thus, such factors may coexist in our system, too.

The actual anisotropy values corrected by Eq. (2) accompanying the observed values are illustrated in Fig. 6a, which indicates that the error of anisotropy measurement affected by light scattering can be neglected at the concentrations of β-CD lower than 2 mM, whereas it increases at higher concentrations and cannot be neglected.

The fact that the formation of the micrometer-sized rod is stepwise is also exhibited in the relationship between fluorescence anisotropy and the concentration of β-CD. As illustrated in Fig. 6a, we draw three lines to represent three stages of the interactions between PBD and β-CD, i.e., A to B, B to C and C to D. They correspond to the stages of the formation of 1:1 (guest:host) inclusion complex, single nanotube and micrometer-sized rod, respectively.

The relative size of the PBD–β-CD nanotube can be estimated with the equation derived from the combination of the Perrin and Einstein equations [5b,9,12],

$$r_2(r_0 - r_1)/r_1(r_0 - r_2) = V_2/V_1, \tag{4}$$

where r_0 is the maximum value of anisotropy for a certain probe in a frozen state in which it cannot undergo rotational diffusion. For PBD, the measured value of r_0 is 0.271 in the vitrified solution of glycerol. r_1 and r_2 are the values of the fluorescence anisotropy measured in two different systems, V_1 and V_2 are the effective volumes of these two systems.

Introducing the r_1 value of 1:1 PBD–β-CD complex ([PBD] $= 4 \times 10^{-8}$ M, [β-CD] = 10 M, $r_1 = 0.051$), the value of V_2/V_1 is equal to the number of β-CD unit of a single nanotube at length dimension. Thus, we think that this estimation can be applied reasonably in the stage from B to C only in our case [5b]. After C, the single nanotubes begin to further assemble to large-sized rods. Since the assembly of nanotubes in a rod is toward three-dimensional, above method of estimation would need further correction in complicated situation. In our previous work, we did not realize the stage of the secondary assembly and gave the estimated numbers in all concentrations [9]. In Fig. 6b we estimate the number of the β-CD unit of a single nanotube over the stage from B to C. It can be seen that the number of β-CD unit estimated by the corrected anisotropy reaches 27, larger than the value of 12 estimated from the observed anisotropy. This strongly indicates that the effect of light scattering cannot be neglected in such system.

3.5. Structural feature

The density of β-CD at various concentrations in water was measured and their relationship was showed in Fig. 8. The density of the filtrate of the PBD (10^{-5} M)–β-CD (10 mM) mixture by the 0.2 μm filter was estimated to be 6.15 mM (see the open circle in Fig. 8). On the other hand, the measured fluorescence intensity of the same filtrate was very weak (figure not shown) suggesting that only very small percent of PBD molecules are

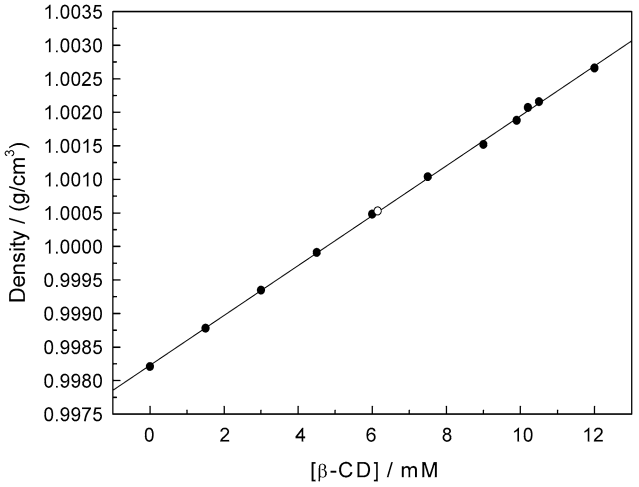

Fig. 8. The density of β-CD at various concentrations (●) and of the filtrate of PBD (10^{-5} M)–β-CD (10 mM) (○).

left. On the basis of above results, one can infer that in the secondary assembly of the nanotube, most of them are empty, not occupied by PBD molecules. The structural feature of the secondary assembly reported here is much different from that of β-CD observed by Bonini et al. [38]. This phenomenon actually means a new aggregation mechanism of β-CD, that is, the nanotube of β-CD occupied by PBD molecule acted as a center for the aggregation of β-CD to form the empty nanotube. The occupied and empty nanotubes must make up of the micrometer-sized rods together. If only occupied ones existing, the amount of β-CD in the filtered rods would not exceed so largely to that of PBD molecule. On the other hand, if only empty ones existing, imaging rods cannot be observed with fluorescence microscopy for pure β-CD is nonfluoresent.

Ohira et al. observed the nanotube structures constructed from α-, β-, and γ-CDs by potential-controlled adsorption on Au(111) surface with STM [39]. As mentioned, the balance of adsorption–desorption equilibrium of CD and the formation of nanotubular structures of CDs are dependent on the electrode potential. It was pointed out that the dominant driving forces for the formation of the tubular structure are the intermolecular hydrogen bonds between hydroxyl groups on the same rims of CD molecules. This viewpoint is supported by the fact that the AISO (adsorption-induced self-organization) potential range for α-CD was positive relative to those for β- and γ-CDs, which is attributable to the much smaller ring size of α-CD [39].

At present time, we are not sure whether the low temperature condition in the Cryo-TEM experiment as reported in the literature [38] will help induce the formation of the linear assembly of β-CD to a certain extent. Actually, it is a very normal phenomenon for cyclodextrin itself and some inclusion complexes of cyclodextrins to assemble in crystal lattice [17].

In conclusion, it is the PBD molecule that induces the formation of β-CD nanotube and its secondary assembly. The dominant driving force for the formation of β-CD nanotubes is the hydrogen-bonding between hydroxyl groups of β-CD molecules as well as the hydrophobic interaction between PBD and β-CD, while the driving force for the secondary assembly should be mainly the hydrogen bonding. This force can effectively promote the self-assembly of CD molecules to a linear structure only when a stimulus, e.g., controlled potential, low temperature and the inducing of small molecules with proper length and rigidity, well strengthens it in the local region.

The geometries of the 1:1 inclusion complex and nanotube between PBD and β-CD can be inferred from geometrical complementarity between the sizes of the inner β-CD cavity and the PBD molecule. It is the combining contributions of bridge connection of PBD molecule and hydrogen-bonding between hydroxyl groups of adjacent β-CD molecules that promote the formation of nanotube. We have tried to discuss the geometries of the 1:1 inclusion complex and the nanotube from the point of geometrical complementarity and a proposed structural motif was described in the previous work [9]. Similar experimental results were observed in the interaction between DPH (1,6-diphenyl-1,3,5-hexatriene) and β-CD [5b]. We used molecular mechanic calculations and molecular dynamic simulations to predict the theoretical models of cyclodextrin nanotube induced by DPH molecule and the results showed that the β-CD molecules in the DPH–β-CD nanotube were arranged in head-to-head/tail-to-tail manner [11]. This is also the structural motif suggested in the crystal of cyclodextrin and its inclusion complex [17]. However, Miyake et al. found two types of CD arrangements in the case of α-CD-PEG polyrotaxane, corresponding to head-to-head/tail-to-tail and head-to-tail configurations, and suggested that the averaging content of head-to-tail configuration was about 20% [40]. Thus, the exact arrangements of β-CD molecules in the PBD–β-CD nanotube would be complicated and we are uncertain the manner as the head-to-head/tail-to-tail or the head-to-tail without the further proof.

4. Conclusion

The micrometer-sized rod formed by the secondary assembly of β-CD nanotube induced by PBD molecule is observed with fluorescence microscopy and transmission electron microscopy (TEM). It can be inferred from the results of DLS and fluorescence anisotropy that the formation of micrometer-sized rod is stepwise. The effect of light scattering on the measurement of fluorescence anisotropy of PBD in the solutions of β-CD is corrected and the results show that such an effect cannot be neglected in this system. We propose a new aggregation mechanism that the nanotube of β-CD occupied by PBD molecule acted as a center for the aggregation of β-CD to form the empty nanotube.

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