

Probing into the Supramolecular Driving Force of an Amphiphilic β -Cyclodextrin Dimer in Various Solvents: Host–Guest Recognition or Hydrophilic–Hydrophobic Interaction?

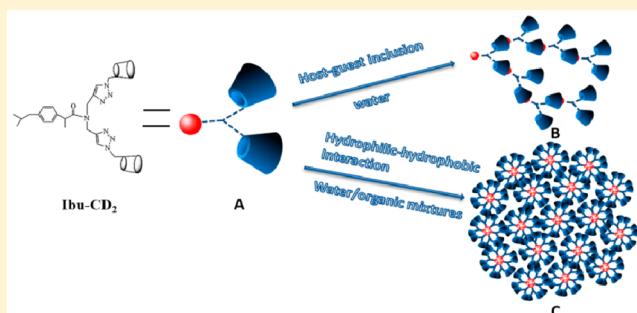
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S Supporting Information

ABSTRACT: Tuning of the morphology and size of supramolecular self-assemblies is of theoretical and practical significance. To date, supramolecular driving forces in different solvents remain unclear. In this study, we first synthesized an amphiphilic β -cyclodextrin (β -CD) dimer that consists of one hydrophobic ibuprofen (Ibu) and two hydrophilic β -CD moieties (i.e., Ibu-CD₂). Ibu-CD₂ possesses double supramolecular driving forces, namely, the host–guest recognition and hydrophilic–hydrophobic interaction. The host–guest interaction of Ibu-CD₂ induced the formation of branched supramolecular polymers (SPs) in pure water, whereas the hydrophilic–hydrophobic interaction generated spherical or irregular micelles in water/organic mixtures. The SP size increased with the increase in Ibu-CD₂ concentration in pure water. By contrast, the size of micelles decreased with the increase in volume ratio of water in mixtures.



INTRODUCTION

Supramolecular chemistry deals with the manipulation of intermolecular noncovalent interaction and is a new branch of chemistry that has attracted research interests.^{1–8} Noncovalent interactions, such as hydrogen bonding, π – π stacking, metal–ligand interactions, host–guest recognitions, and hydrophilic–hydrophobic interactions as well as a combination of these interactions, have been used to construct different supramolecular structures.^{9–13} Among these interactions, host–guest intermolecular recognition and hydrophilic–hydrophobic interaction are considered important driving forces in supramolecular chemistry. Host–guest intermolecular recognition covers the selective binding of a guest molecule by a host, which can be used to construct supramolecular polymers (SPs) with various chain topologies, including linear,^{14,15} star-shaped,¹⁶ hyperbranched,^{17–23} dendronized,²⁴ and cyclic structures.²⁵ Hydrophilic–hydrophobic interaction mainly facilitates noncovalent self-assembly of monomeric units into larger structures, including aggregates, micelles, and particles.^{26–35}

In host–guest recognition systems, cyclodextrin (CD) is a common host unit that can form inclusion complexes with the whole molecule or rather some nonpolar parts in its hydrophobic cavity through molecular recognition.¹⁸ Several groups have synthesized SPs through the host–guest complexation of various functionalized CD monomers.^{14–25} For

example, Yuan's group discovered that polystyrene (PS)- β -CD and poly(ethylene oxide)-ferrocene (PEO-Fc) can orthogonally self-assemble into a supramolecular diblock copolymers in aqueous solutions based on the terminal host–guest interactions.¹⁴ Gao et al. also found that the nanowires can be formed by the host–guest inclusion interaction with the β -CD-terminated polyrotaxanes and adamantyl-terminated PEG.¹⁵ Ritter et al. prepared AB-type β -CD-bearing Fc monomer (Fc- β -CD) via click reaction, and the host–guest inclusion between CD and Fc led to ring-like structures.²⁵ In particular, bifunctional CD derivatives were used to prepare branched SPs. Zhou and Zhu et al. reported a novel class of photoreversible hyperbranched SPs through the host–guest complexation of azobenzene dimer as A₂ monomer and β -CD trimer as B₃ monomer.¹⁸ However, the host–guest interaction from the CD cavity is regarded as the only supramolecular driving force in the above examples. As a result, SPs are the only product under this kind of supramolecular interaction, although they possess different topological structures.

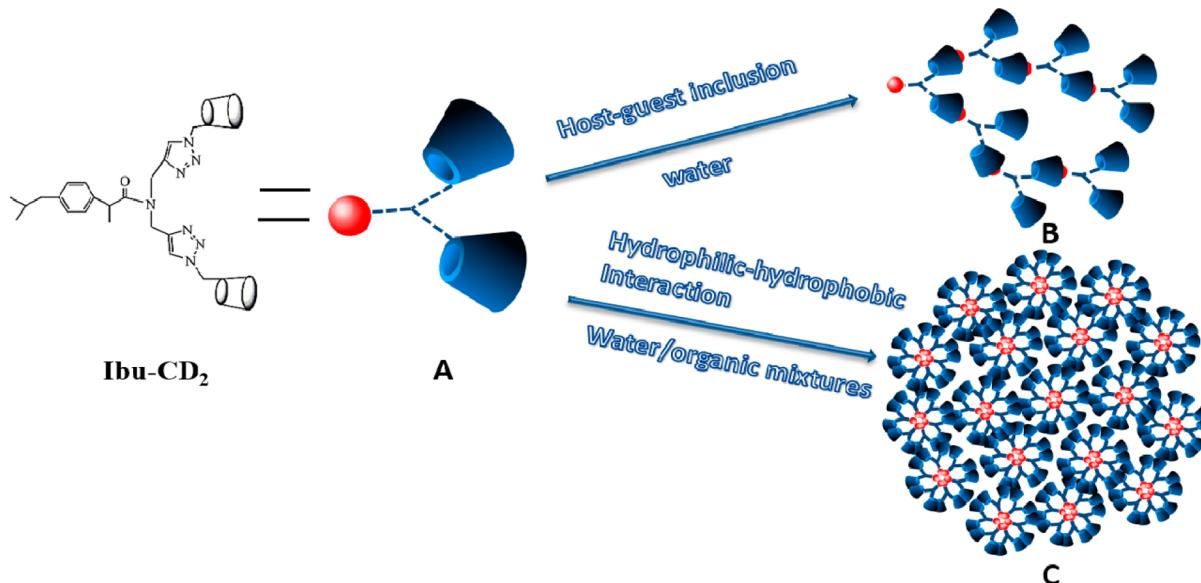
Considering the special requirements of different fields, we introduced another driving force (i.e., hydrophilic–hydrophobic interaction) into the CD monomer by constructing

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Scheme 1. Possible Supramolecular Interactions of Ibu-CD₂ in Varied Solvents: (A) Chemical Structure of Ibu-CD₂; (A–B) Ibu-CD₂ Forms Branched SPs in Pure Water Based on the Host–Guest Recognitions of Two β-CD Cavities and the Hydrophobic Group in Ibu Molecule; (A–C) Ibu-CD₂ Self-Assembled into Micelles in Water/Organic Mixed Solvents Based on Hydrophilic–Hydrophobic Interactions of Two Hydrophilic β-CD Units and One Hydrophobic Ibu Moiety



amphiphilic molecular structure to obtain various supramolecular self-assemblies. CD is a hydrophilic moiety of amphiphilic polymers and is known to induce self-assembly of nanostructures in aqueous solutions.^{36,37} Borsali et al. prepared PS chains end-functionalized with β-CD; in addition, this polymer could form the stable β-CD self-assemblies that consist of a dense hydrophobic PS core and a thin hydrophilic β-CD shell in water.³⁶ Therefore, the amphiphilic β-CD monomer, which simultaneously possesses double supramolecular driving forces including host–guest recognition and hydrophilic–hydrophobic interaction, is known to possibly display various supramolecular self-assemblies under suitable solution conditions.

On the basis of the above considerations and our previous work on the SP construction,^{38,39} we first designed and synthesized an AB₂ type amphiphilic β-CD monomer through the click reaction; this monomer consists of one ibuprofen (Ibu) and two β-CD moieties (i.e., Ibu-CD₂; Scheme 1A). Given this special structure, two β-CD cavities can interact with the hydrophobic group in Ibu molecule based on the host–guest recognitions.⁴⁰ Meanwhile, hydrophilic–hydrophobic interactions also exist because of a combination of two hydrophilic β-CD units and one hydrophobic Ibu moiety in the aqueous solution. We found that Ibu-CD₂ formed branched SPs in pure water, whereas this substance self-assembled into different morphological micelles in water/organic solvents. Furthermore, the size of SPs is dependent on the Ibu-CD₂ concentration in pure water, whereas the size of micelles is dependent on the amount of organic solvent in mixed solvents.

EXPERIMENTAL SECTION

Materials. Mono-6-deoxy-6-azido-β-CD (β -CD-N₃) was prepared according to literature.⁴¹ Alk-wang resin was prepared according to the literature⁴¹ Ibu (98%, Alfa Aesar), thionyl chloride (98%, Alfa Aesar), dipropargylamine (DPA, 99%, Syntechem), and Cu(Ph₃)₂Br (Acros, 99%) were all purchased

from the companies and used without further purification. Triethylamine was treated with calcium hydride and distilled before use. Tetrahydrofuran (THF) was treated with sodium hydride and distilled before use. N,N-Dimethylformamide (DMF) was dried with 3 Å grade molecular sieve before use.

Characterization. Fourier transform infrared (FT-IR) spectra were recorded on a NICOLET iS10 IR spectrometer. The ¹H NMR and ¹³C NMR spectra were obtained from a Bruker Avance 300 spectrometer (BrukerBioSpin, Switzerland), which operates at 300 MHz (1H) in DMSO-d₆. The molecular weight of the synthesized polymers was determined using a MADIL-TOF-MS. Furthermore, measurements were performed on a KratosAxima –CFR plus V2.3.2 with deionized water as the solvent.

Synthesis and characterization of Ibu-CD₂ can be found in the Supporting Information.

Construction of Branched SPs using Ibu-CD₂ as Monomer. In a typical experiment, a fixed amount of Ibu-CD₂ was directly dissolved in deionized water and stirred at room temperature. After stirring for another 24 h, the solution was treated by ultrasonic for 30 min. The concentrations of samples were set as 4, 7, and 10 mg/mL.

Preparation of Micelles Using Ibu-CD₂ as Starting Materials. In a typical experiment, a fixed amount of Ibu-CD₂ was directly dissolved in DMF and stirred for 1 h at room temperature. Afterward, fixed amount of deionized H₂O was added under stirring situation. After being stirred for another 12 h, the solution was treated by ultrasonic for 30 min. The volume ratios of DMF to H₂O were set as 3:1, 1:1, and 1:3 (monomer concentration: 10 mg/mL).

Investigation on the Morphology and Size of Supramolecular Self-Assemblies. The morphology of supramolecular self-assemblies was visualized using a Hitachi H-600 electron microscope at an acceleration voltage of 75 kV. Samples were prepared by placing 10 μL solution on copper grids, followed by staining with phosphotungstic acid. DLS measurements were carried out in a Malvern Zetasizer Nano ZS

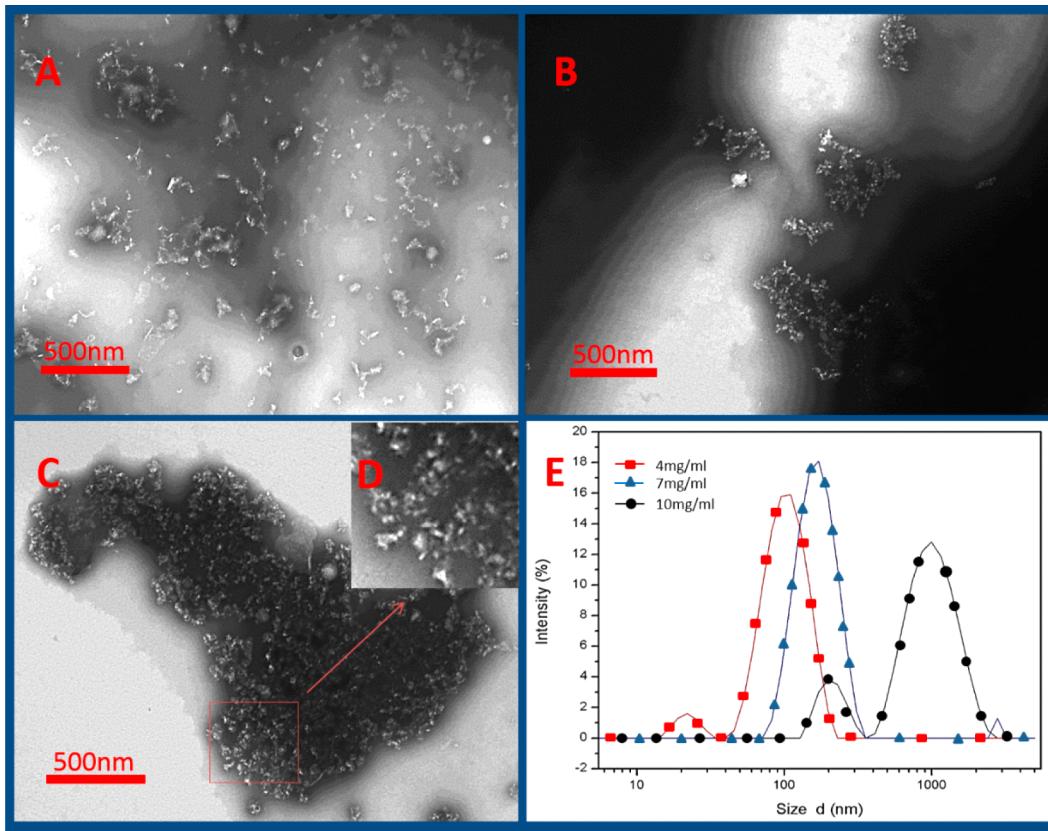


Figure 1. Typical TEM images (A–D) and size distributions (E) of Ibu-CD₂ in pure water (A, 4 mg/mL; B, 7 mg/mL; C, 10 mg/mL; the image D is the magnification of C). The samples were stained with phosphotungstic acid.

Table 1. Size and Morphology of Ibu-CD2 in Varied Solvents at 20 °C

ibu-CD ₂ concentration (mg/mL)	$D_{av,TEM}^a$ (nm)	D_z^b (nm)	PDI ^c	solvent systems	morphologies
4	155	180	0.331	H ₂ O	branched SPs
7	435	367	0.445	H ₂ O	branched SPs
10	1020	940	0.463	H ₂ O	branched SPs
10	393	626	0.215	DMF/H ₂ O = 3:1	spherical micelles
10	105	266	0.324	DMF/H ₂ O = 1:1	spherical micelles
10	99	188	0.294	DMF/H ₂ O = 1:3	spherical micelles
10	80	157	0.168	DMSO/H ₂ O = 1:1	irregular micelles
10	395	651	0.362	THF/H ₂ O = 1:1	irregular micelles

^aAverage diameter determined by TEM. ^bZ-average diameter determined by DLS. ^cPolydispersity of particles diameter determined by DLS.

dynamic light scattering instrument. The light source was a He–Ne laser operating at 632 nm. The dust was eliminated by filtering the sample solutions with a pore size of 0.45 μm. Sample solutions with a concentration of 1 mg/mL were placed in the cell for at least 5 min prior to the measurement to allow for thermal equilibration. The 2D ¹H NMR ROESY spectra were recorded on a Bruker-Avance III NMR spectrometer (400 MHz) with D₂O as solvent.

RESULTS AND DISCUSSION

The AB₂ monomer Ibu-CD₂ was first synthesized according to the routes depicted in Scheme S1. Ibuprofen acid chloride (Ibu-Cl) was synthesized by acylation reaction of ibuprofen with thionyl chloride in refluxing condition. Subsequently, two alkyne units were introduced by the reaction of acyl chloride and amido in the presence of triethylamine, which is denoted as Ibu-DPA, to enhance the reactivity of Ibu-Cl. Considering that click chemistry is a highly selective and effective synthetic

method with mild and clean conditions,³⁷ Ibu-CD₂ was finally synthesized by the click reaction between Ibu-DPA and an excess of β-CD-N₃ using the organosoluble Cu(Ph₃)₃Br as the catalyst. On the basis of the FTIR spectrum of Ibu-CD₂ in Figure S1(b), the disappearance of absorption peaks of azido group at 2096 cm⁻¹ and alkynyl group at 2102 cm⁻¹ confirmed the occurrence of click reaction. Furthermore, in the ¹H NMR spectrum of Ibu-CD₂ (Figure S2(IV)), characteristic signals for β-CD at δ = 4.45, 4.8, 5.7 and protons for 1,2,3-triazole ring at δ = 7.82 appeared, which further indicated the occurrence of 1,3-dipolar cycloaddition reaction. This result is also supported by the ¹³C NMR spectrum of Ibu-CD₂ (Figure S3). Figure S4 shows that the molecular weight of Ibu-CD₂ measured by MALDI-TOF-MS was 2602.93. This value was in accordance with the theoretical value (calculated for [M + H]⁺: 2601.93). Therefore, Ibu-CD₂ has been successfully obtained.

The supramolecular behavior of Ibu-CD₂ in pure water was first carefully examined using transmission electron microscopy

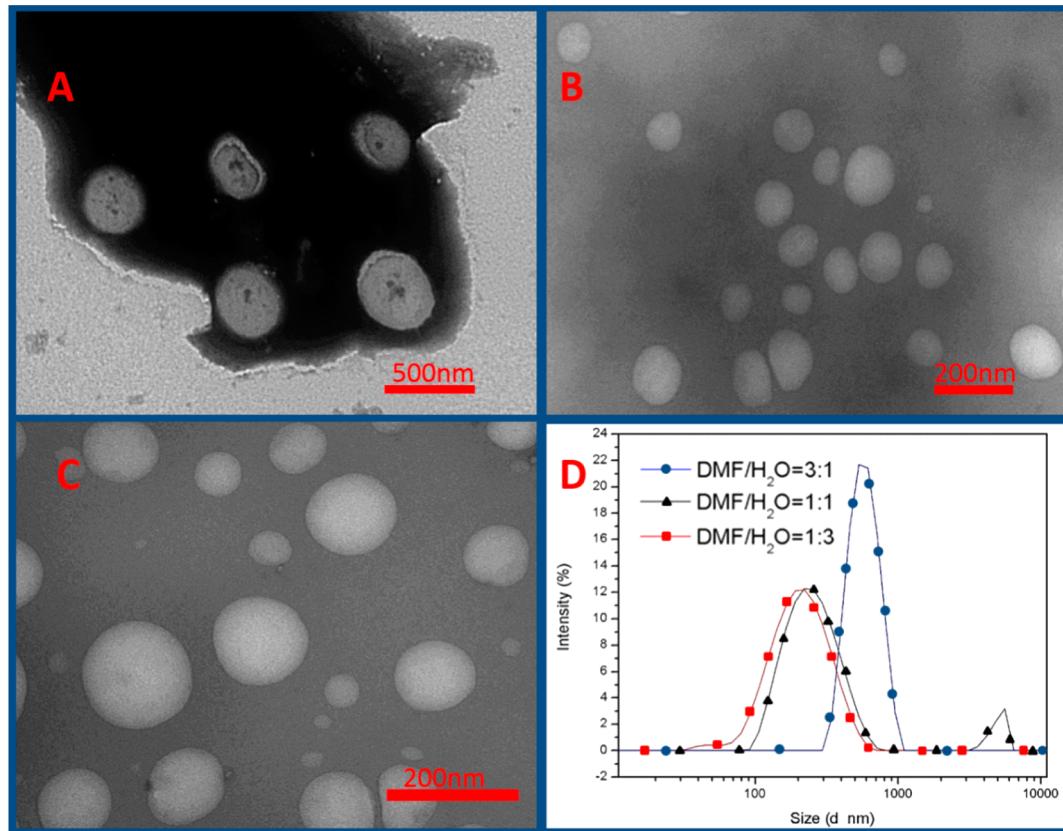


Figure 2. Typical TEM images (A–C) and size distributions (D) of Ibu-CD₂ in DMF/H₂O mixed solvents (A, $V_{\text{DMF}}/V_{\text{H}_2\text{O}} = 3:1$; B, 1:1; C, 1:3). All samples were stained with phosphotungstic acid.

(TEM) and dynamic light scattering (DLS) measurements. As seen from the TEM image results (Figure 1A–C), a branched SP was gradually formed by increasing the Ibu-CD₂ concentration from 4 mg/mL to 10 mg/mL. The similar morphology was also observed for hyperbranched SPs from the host–guest complexation of azobenzene dimer and β -CD trimmer.¹⁸ As shown in Figure 1E and Table 1, the D_z values of SPs increased from 180 to 940 nm with increased Ibu-CD₂ concentration from 4 mg/mL to 10 mg/mL. Thus, TEM and DLS results indicated that Ibu-CD₂ in pure water formed a branched SP morphology, which was dependent on the Ibu-CD₂ concentration. Accurate test of the size of branched SP is extremely difficult because of the irregular morphology shown in Figure 1.

To determine whether or not the morphology of branched SPs could be changed when mixed solvents were used instead of pure water, we adopted different mixed solvent systems, namely, DMF/H₂O, DMSO/H₂O, and THF/H₂O as solvents for Ibu-CD₂. The Ibu-CD₂ morphology in DMF/H₂O solvents ($V_{\text{DMF}}/V_{\text{H}_2\text{O}}$ is equal to 3:1, 1:1, and 1:3, respectively) with fixed monomer concentration was observed by TEM images. As shown in Figure 2A–C, spherical micelles were formed in DMF/H₂O solutions. On the contrary, no branched SP structure was found compared to the TEM images of Ibu-CD₂ in pure water (Figure 1A to Figure 1C). The average diameter (D_{av} , TEM) of these micelles decreased from 393 to 99 nm when the H₂O volume ratio was increased (Table 1). DLS results in Figure 2D also proved micelle formation. The D_z values of micelles under different volume ratios of DMF to H₂O (3:1, 1:1, and 1:3) were 626, 266, and 188 nm,

respectively. These results agreed with that of TEM results. In addition, similar micelles were found in DMSO/H₂O and THF/H₂O mixed solvents (Figure S4). The related TEM and DLS results are listed in Table 1. Compared with DMF/H₂O mixed solvents, the irregular micellar morphologies were found in DMSO/H₂O and THF/H₂O systems. This difference may be attributed to the solubility and polarity of different solvents to Ibu-CD₂. The above results implied that the Ibu-CD₂ in mixed solvents could self-assemble into micellar morphology, and the ratio of mixed solvents had a pronounced effect on the size and morphology of micelles.

We have determined the influence of different solvent systems on the self-assembly morphology of Ibu-CD₂ based on the above results. Moreover, determining which driving force determined the final morphology of Ibu-CD₂ self-assemblies in pure water and mixed solvents is necessary. For the pure water system, the formation of branched SPs is mainly driven by the host–guest interaction of Ibu-CD₂ monomer (Scheme 1A to Scheme 1B). In general, inclusion complexation can occur between Ibu and β -CD in pure water, with a high inclusion constant of 8740 M⁻¹ according to literature.⁴⁰ Thus, covalently linked double- β -CD units drive one Ibu molecule into their cavities, which further results in the formation of branched SPs. For the mixed solvent systems, the self-assembled micelles may be generated by the hydrophilic–hydrophobic interaction of Ibu-CD₂ in mixed solvents based on its amphiphilic property (Scheme 1A–C). In general, the organic solvent can influence or tune the morphology of the assemblies. In the current study, an increase in the DMF content in mixed solvents can weaken the host–guest interaction of Ibu-CD₂. Therefore, DMF

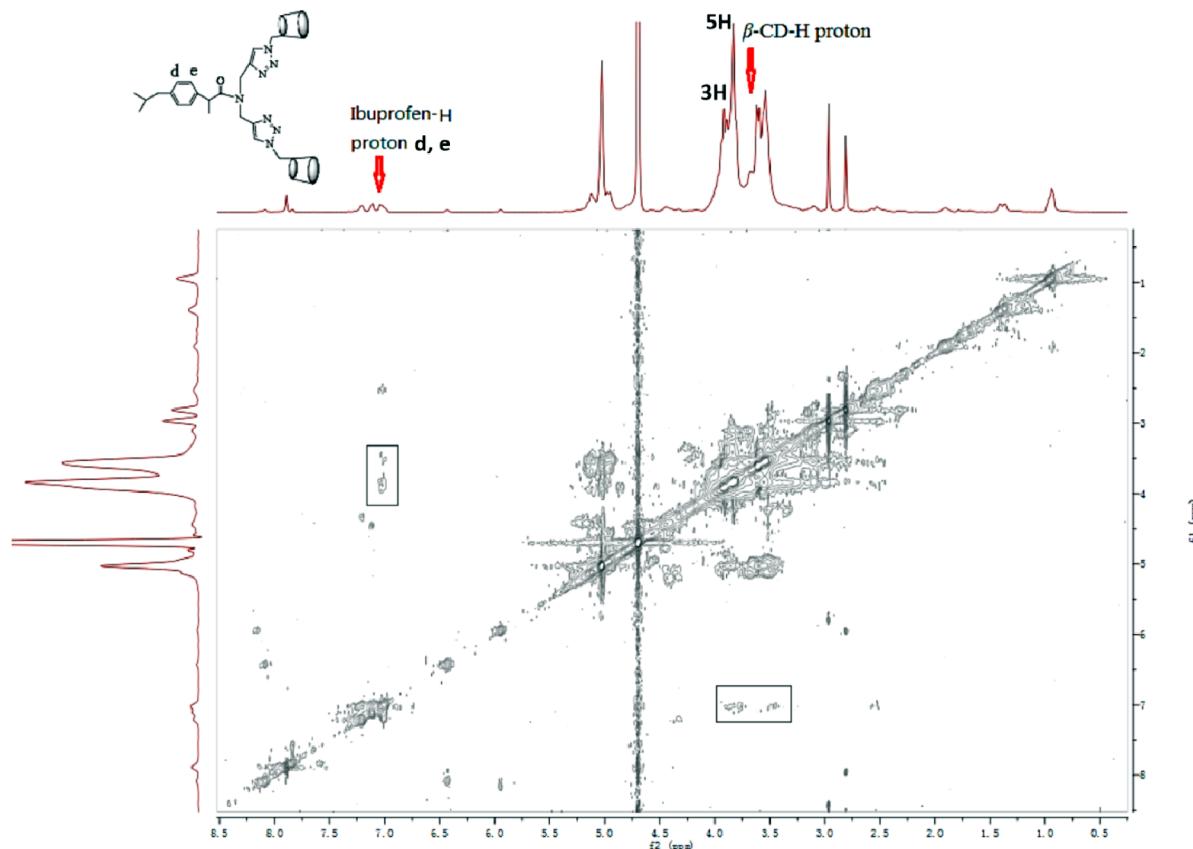


Figure 3. 2D NOESY ¹H NMR spectra of Ibu-CD₂ in D₂O (4 mg/mL).

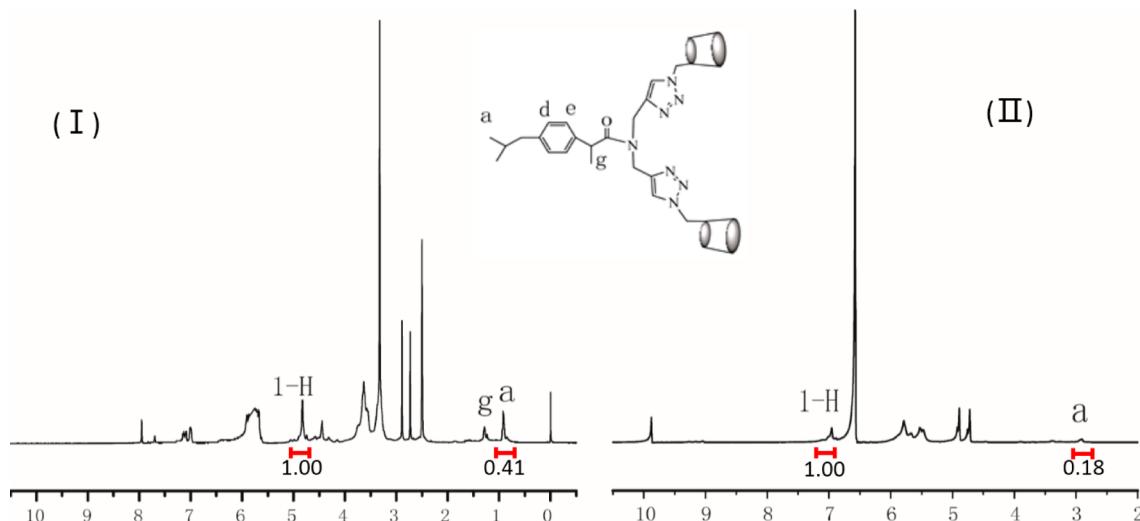


Figure 4. ¹H NMR spectrum of Ibu-CD₂ in DMF-*d*₇ (I) and DMF-*d*₇/D₂O (II).

dissolves the Ibu moiety attached on Ibu-CD₂ better than that those of water molecules; this condition leads to the weak host–guest interactions between β-CD units and Ibu moiety. In this case, the hydrophilic–hydrophobic interaction plays an important role in the self-assembly process of Ibu-CD₂ as the main driving force, instead of the host–guest interaction. As a result, the self-assembly morphology of Ibu-CD₂ changed from branched SPs to spherical micelles. Large micelles may have been formed by the secondary aggregation of small micelles; a similar result has been found by Huang et al.⁴¹ On the basis of

the above analysis, possible supramolecular interactions of Ibu-CD₂ in various solvents are proposed in Scheme 1.

The host–guest inclusion interaction of Ibu-CD₂ in pure water was further confirmed using the 2D ¹H NMR NOESY spectra (Figure 3). The cross-peak interactions between β-CD and Ibu protons reflected the interactions between 3-H and 5-H in β-CD with the d, e protons in Ibu. The notations used were n-H for β-CD protons, and d and e for Ibu protons; n was the carbon number. This result provided strong evidence that SPs were formed via the intermolecular complexation between

one Ibu moiety and two β -CD units of Ibu-CD₂. This result was in agreement with that obtained by Rossi et al.⁴⁰ for the host–guest interaction of Ibu and β -CD monomer.

The hydrophilic–hydrophobic interaction of Ibu-CD₂ in DMF-*d*₇/D₂O was further explored by the ¹H NMR analysis. Compared with the ¹H NMR spectrum of Ibu-CD₂ in DMF-*d*₇ (Figure 4I), the weakening of Ibu signals (such as a) in DMF-*d*₇/D₂O (Figure 4II) indicated that the core layer of micelles were mainly formed by the hydrophobic Ibu moiety. Furthermore, the 1-H ratio in β -CD to a in Ibu was 5.56, which is larger than that of the ratio value (2.43) in DMF-*d*₇. This finding may be attributed to the shield of the “core” part according to the literature.⁴² In addition, the intensities of proton peaks of hydrophilic β -CD in Figure 4I did not considerably changed compared with those of Figure 4II. Thus, hydrophobic Ibu would self-assemble to form the “core”, whereas the hydrophilic β -CD formed the “shell” layer of the micelles in DMF-*d*₇/D₂O mixed solvents. These results further implied the existence of the hydrophilic–hydrophobic interaction.

CONCLUSIONS

An AB₂ type amphiphilic β -CD dimer (Ibu-CD₂) was synthesized. Ibu-CD₂ simultaneously possesses two kinds of supramolecular driving forces, and it can form different supramolecular self-assemblies in various solvents. Branched supramolecular polymers (SPs) were formed in pure water through the host–guest interaction, whereas spherical or irregular micelles were formed in water/organic mixtures based on the hydrophilic–hydrophobic interaction. The size of SPs increased with the increase in Ibu-CD₂ concentration, and the micelle size decreased with the increase in volume ratio of water in mixtures. The idea of combining two kinds of supramolecular driving forces into one functional small molecule presents a convenient and effective way to control the morphology and size of supramolecular self-assemblies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.jpcb.Sb05317](https://doi.org/10.1021/acs.jpcb.Sb05317).

Synthesis and characterization of Ibu-CD₂ and self-assembly in DMSO/H₂O or THF/H₂O with TEM images ([PDF](#))

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Notes

The authors declare no competing financial interest.

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