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Assembly of Dumbbell- and Bola-Shaped Amphiphiles: Vesicles with Condensed Hydrophobic Domains or Blackberry-type Structures with Porous Surfaces?

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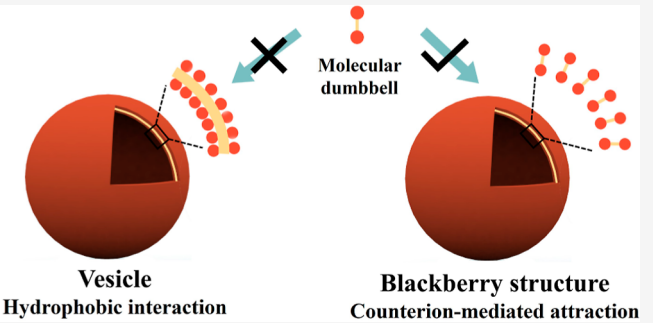
ABSTRACT: Dumbbell- and bola-shaped amphiphiles are commonly expected to self-assemble into vesicles with condensed hydrophobic domains due to the dominant hydrophobic interaction. In this work, we examined the assemblies of the dumbbell-shaped AC_{60}-AC_{60} amphiphile, with two carboxylic acid-functionalized fullerenes (AC_{60}) polar head groups linked by an organic tether, and found that they assemble into hollow, spherical blackberry-type structures with porous surfaces, judged by their smaller assemblies in organic solvents with higher polarity and in aqueous solutions with high pH. We attribute the formation of blackberry structures to the organic tether that may be too short to fill up a condensed hydrophobic domain, as confirmed by all-atom simulations. This is further proved by noticing that several bola-type macromolecules with hydrophilic polyethylene glycol (PEG) chain being the linker and no hydrophobic components, AC_{60}-PEG-AC_{60}, can also self-assemble into hollow, spherical assemblies and demonstrate similar pH response as the assemblies from AC_{60}-AC_{60} dumbbells. Therefore, we conclude that the driving force of the self-assembly for these dumbbell- or bola-shaped molecules is counterion-mediated attraction from the two AC_{60} head groups rather than the hydrophobic interaction due to the organic linkers. The so-formed blackberry structures here, as well-studied before in other systems, possess porous surfaces, making these charged amphiphiles a valuable model for designing stable nanocontainers with controllable porosity to the change of the environment.



1. INTRODUCTION

Vesicles, commonly formed by amphiphilic lipids, are hollow, spherical, shell-like supramolecular assemblies consisting of a condensed hydrophobic domain stabilized by hydrophilic layers on both sides. There are various categories of amphiphiles satisfying the packing parameter requirement in polar solvents, including conventional small-molecule surfactants,[1,2] giant surfactants,[3−5] block copolymers,[6,7] as well as supramolecular amphiphiles.[8−10] The assembled structures can be designed and regulated into well-defined macroscopic/microscopic structures with specific topology and properties, depending on the architectures and the properties, of the amphiphiles. This advances the development of stimuli-responsive amphiphilic materials.[11,12]

Dumbbell-shaped amphiphiles, formed by two solvophilic, bulky "head groups" connected by a short solvophobic linker, are a new type of surfactant.[13] Typically, the linker consists of an organic segment, while the "head groups" are composed of bulky inorganic or organic molecular clusters, such as polyoxometalate (POM), fullerene (C_{60}), polyhedral oligomeric silsesquioxane, and dendritic segments. When a long, hydrophobic chain serves as the linker, the amphiphiles are called bola amphiphiles.[14,15] The two polar head groups can be designed as identical or different, charged or uncharged, introducing more variety in their self-assembly features.[16−25] Symmetric dumbbell- and bola-shaped amphiphiles generally assemble into hollow spherical supramolecular structures, which are commonly expected to be amphiphilic vesicles.[16−18,20,24,26−28] Meanwhile, asymmetric molecules have been reported to form a diverse range of assembly structures, such as spherical and cylindrical micelles,[22] nanosheets and nanoribbons,[23] nanotubes,[25] nanorings,[21,29] and cubosomes,[30] depending on their specific molecular structures.

We have previously reported the self-assembly of some symmetric, charged, dumbbell-shaped inorganic−organic

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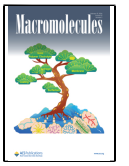

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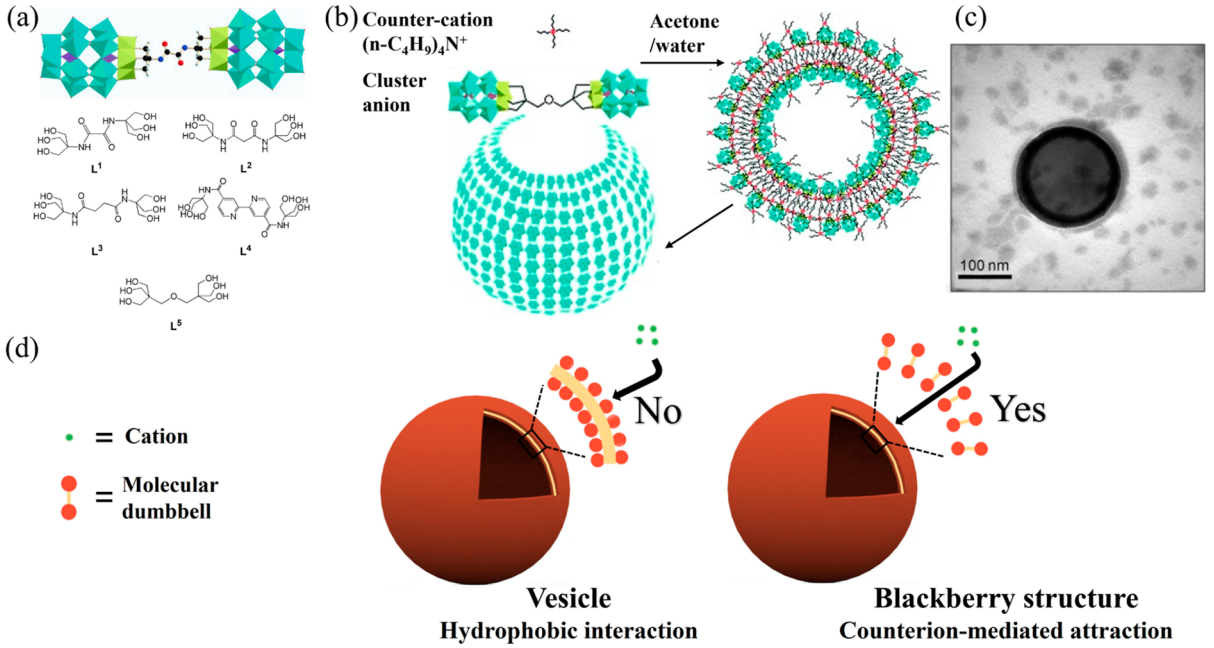

Figure 1. Self-assembly of dumbbell-shaped amphiphiles in solution. (a) Schematic representation of the molecular structure of the dumbbell-shaped anion and the structures of different linkers. (b) Schematic representation of the vesicle-like structure formed by the dumbbell-shaped anions shown in (a) and TBA^+ countercations. (c) TEM image of the assembly shown in (b) (© 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim). (d) Schematic representation showing the difference between vesicle and blackberry-type structure.

hybrid amphiphiles into hollow, spherical, vesicle-like structures (Figure 1a–c).[17,26] These dumbbells have negatively charged POMs as polar head groups and an organic tether in the middle. We hypothesized earlier that hydrophobic interaction dominated their self-assembly with the help of their organic counterions, tetrabutylammonium (TBA^+), which contributed their alkyl tails to help fill up the hydrophobic domain inside the vesicle surface since the short organic linkers may not be sufficient (Figure 1b). Work published by other groups also attributed hydrophobic interaction as the driving force of the assembly, and amphiphilic vesicles were assigned as the assembled structure.[27,31,32] For example, water-soluble pillar[n]arenes were used as macrocyclic hosts to construct bola-type supra-amphiphiles with a linear building block as the guest. These supra-amphiphiles can self-assemble into vesicles in water and demonstrate stimuli-responsiveness (e.g., pH, glutathione, and light), and therefore, these vesicles were developed into containers for drug delivery.[27,31]

However, another possibility exists that the assembled structures formed by the charged amphiphilic dumbbells might not be vesicles but blackberry-type structures. As shown in Figure 1d, blackberry-type structures possess similar overall morphology to vesicles; i.e., both are hollow, spherical supramolecular assemblies, whereas the driving forces and surface properties are entirely different. Blackberry structures are formed via counterion-mediated attraction among moderately charged nanoscale macroions, resulting in the porous surface of the assemblies.[33] Given the special dumbbell shape of these molecules, it is difficult to distinguish these two structures via direct laser light scattering or microscopic measurements as both models lead to very similar apparent assembly structures. However, it is critical to clarify the nature of these assemblies, which outlines their potential applications, given their completely different natures in surface porosity. A possible approach to examine the nature of these assemblies is revealed by their different responses to environmental changes due to their different driving forces[34] or their permeability to specific ions (Figure 1d).[35] A feasible way to distinguish vesicles and blackberry structures comes from the change in size in response to the change of their effective charges on their head groups as we demonstrated in this article. If the hydrophobic interaction is the dominant force, larger vesicle sizes (smaller curvature) should be preferred in more polar solvents with enhanced hydrophobic interaction. On the other hand, the counterion-mediated attraction will be weaker in a more polar solvent due to the stronger electrostatic repulsion between the large polar head groups, leading to a more significant interpolar head distance. This results in larger curvature and, thus, smaller sizes for the final assemblies, which is the trend for blackberry structures. More direct, convincing evidence will come by replacing the middle organic linker with hydrophilic polymer chains (such as polyethylene glycol, PEG). Then, the assemblies should not form if they are amphiphilic vesicles due to the lack of hydrophobic interaction, while blackberry-type structures will remain and might become even more favored in such a case.

To identify the nature of these assemblies formed by dumbbell-shaped amphiphiles, we designed and synthesized a new type of symmetric dumbbell-shaped amphiphile, AC_{60}-AC_{60}, with two AC_{60} polar head groups (carboxylic-acid functionalized fullerene) connected by a short organic tether. AC_{60}-AC_{60} has protons as counterions, excluding any counterion (TBA^+) contribution for forming the possible hydrophobic domain. It would be interesting to examine if this dumbbell-shaped molecule can still assemble into hollow, spherical structures given its limited hydrophobic domains and, if yes, which type of structure it would form. The nature of the resultant assemblies was examined by self-assembly studies in different organic solvents and aqueous solutions with different pH. A series of related bola macromolecules, AC_{60}-PEG-AC_{60},

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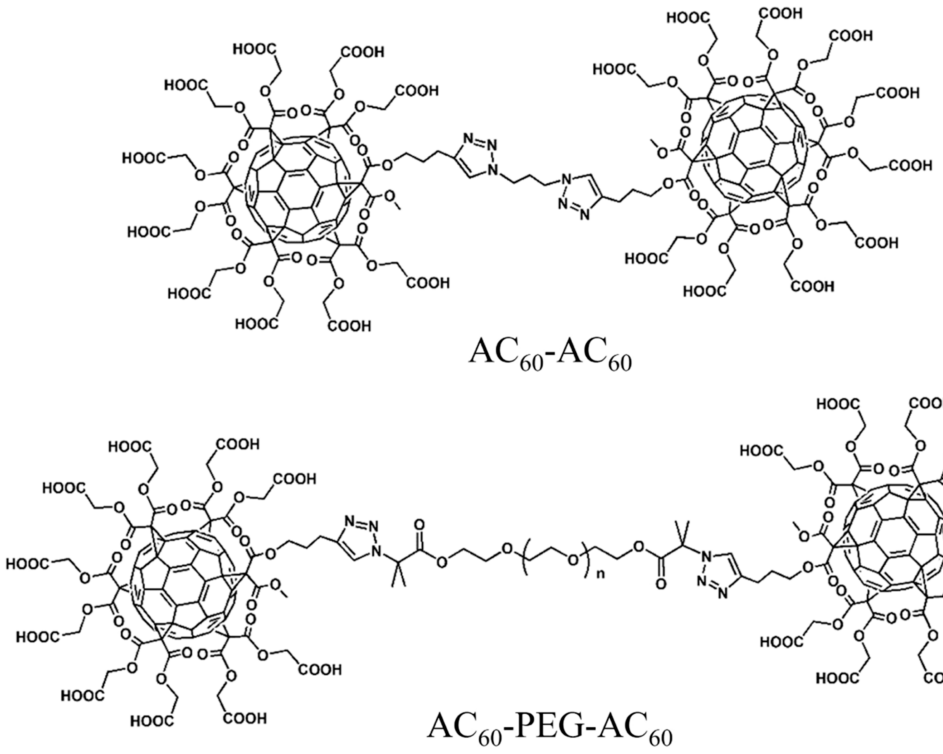
Scheme 1. Molecular Structures of the Dumbbell-Shaped Amphiphile, AC_{60}-AC_{60}, and Bola Macromolecules, AC_{60}-PEG-AC_{60}, where the Molecular Weights of PEG are 3k, 10k, and 20k corresponding to the Number of Repeat Units of 68, 227, and 455, Respectively



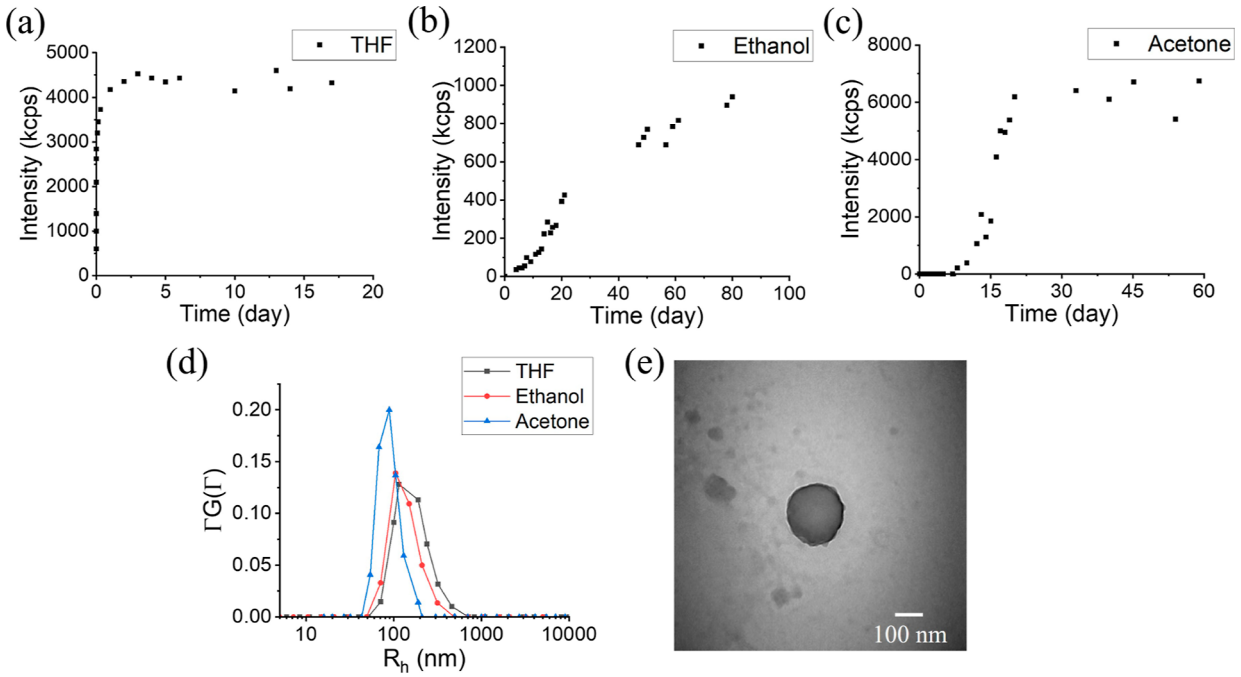


Figure 2. (a–c) Time-resolved SLS measurements of AC_{60}-AC_{60} in THF, ethanol, and acetone. (d) CONTIN analysis of the DLS data of 0.5 mg/mL AC_{60}-AC_{60} solutions in THF, ethanol, and acetone. (e) TEM image of the assembled structure of AC_{60}-AC_{60} in acetone (0.5 mg/mL).

with different polymer chain lengths, were also synthesized and studied as control groups to inspect any possible role played by the linker during self-assembly. The assembly mechanism will directly determine the surface porosity of these supramolecular structures and their consequent applications.

2. RESULTS AND DISCUSSION

2.1. Synthesis and Molecular Structure. The dumbbell-shaped amphiphile, AC_{60}-AC_{60}, and a series of bolaform macromolecules, AC_{60}-PEG-AC_{60}, were designed and synthesized (Scheme 1). The synthesis route is given in the Supporting Information (Scheme S1). NMR spectra of these

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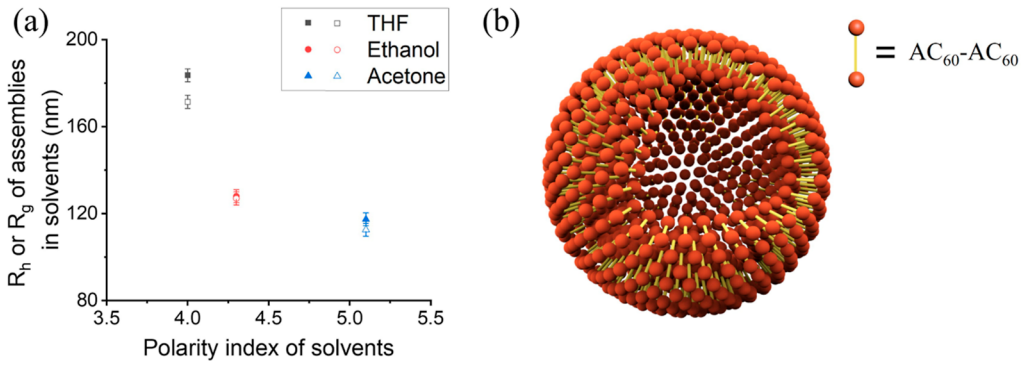

Figure 3. (a) Hydrodynamic radius (R_h, solid symbols) and radius of gyration (R_g, empty symbols) of the assemblies in different organic solvents as a function of the polarity index of the solvents. (b) Schematic representation of the blackberry structure model for the assembly of dumbbell-shaped AC_{60}-AC_{60} molecules.

molecules are shown in Figures S1−S3. Different from the previous dumbbell-shaped molecules we studied,[26] the new dumbbells here possess protons as counterions, thus excluding any possible contribution from TBA^+ for forming a hydrophobic domain.

2.2. Self-Assembly of AC_{60}-AC_{60} in Polar Organic Solvents. The dumbbell-shaped amphiphile AC_{60}-AC_{60} molecule is soluble in various polar organic solvents, including THF, acetone, ethanol, methanol, DMF, and DMSO. Time-resolved static light scattering (SLS) was used to monitor the self-assembly of AC_{60}-AC_{60} in solution. The scattered intensities of 0.5 mg/mL AC_{60}-AC_{60} in methanol, DMF, and DMSO were all very low (lower than the scattered intensity of the reference, benzene, which is 35 kcps), indicating the absence of any large, assembled supramolecular structures in these solutions due to the high solubility of AC_{60}-AC_{60} (Figure S4). In contrast, the scattered intensity of 0.5 mg/mL AC_{60}-AC_{60} in THF, ethanol, and acetone continuously increased with time and eventually reached equilibrium at high-intensity levels, indicating the formation of large structures (Figure 2a−c). Among them, the intensity from the ethanol solution is relatively low, presumably due to the good solubility of the dumbbells in ethanol, where abundant hydrogen bonds could form. The CONTIN analysis from the dynamic light scattering (DLS) study of AC_{60}-AC_{60} in these three polar organic solvents is shown in Figure 2d. Using the THF solution as an example, the self-assembled structures of the AC_{60}-AC_{60} in this solvent have the average hydrodynamic radius, $R_{h,0}$, of 184 nm. Meanwhile, the average radius of gyration (R_g) obtained from the SLS measurement based on AC_{60}-AC_{60} in a THF solution is ∼171 nm. The ratio of R_g/R_h ∼ 1.0 for spherical objects stands for a typical hollow sphere model. Similar hollow spherical supramolecular structures are also observed in the other solvents with $R_{h,0}$ = 128 nm and R_g = 127 nm in ethanol and $R_{h,0}$ = 117 nm and R_g = 113 nm in acetone. The TEM measurement further confirms the hollow spherical feature (Figure 2e).

The critical question is do AC_{60}-AC_{60} molecules form conventional vesicles or blackberry-type structures? Given the special molecular structure of the dumbbells, the number of polar head groups in the inner layer and outer layer of the assembly surface must be equivalent, making these dumbbell-based assemblies respond differently from surfactant vesicles, which have fewer polar head groups in the inner layer than that in the outer layer. For multiple charged surfactants with one polar head, more charges lead to smaller vesicles.[12] In contrast, dumbbell-shaped amphiphiles carrying more effective charges will assemble into more giant vesicles because of the stronger repulsion between the charged head groups in the inner layer. However, if the dumbbells follow the assembly mechanism of blackberry structures, smaller assemblies will form due to weaker counterion-mediated attraction when there are more charges on the head groups.[34,36] This difference can help us identify which type of assemblies the dumbbell molecules have formed. Here, the assemblies obviously have a smaller size in more polar solvents, as shown in Figure 3a, providing the first evidence for the typical feature of blackberry-type structures; i.e., smaller assemblies will be formed when macroions carry more charges. With all the charges distributed around the AC_{60} head groups, a side-by-side packing model in the blackberry structure is expected (Figure 3b).

2.3. pH-Dependent Self-Assembly of AC_{60}-AC_{60} Dumbbells in Aqueous Solution. The AC_{60}-AC_{60} molecules are almost insoluble in deionized water. Their carboxylic acid groups on the periphery of the dumbbell head groups endow them with weak acidity, leading to an adjustable degree of deprotonation and charge density with pH (Table S1). When dissolved in the aqueous solution with different pH adjusted by NaOH, the AC_{60}-AC_{60} molecules can be partially dissolved at pH = 11.3 or lower. The solubility improved to over 0.5 mg/mL at pH = 12.1 or above. The degree of deprotonation on each AC_{60} can be calculated by measuring the pH decrease in solution after dissolving the dumbbell samples.

At pH 12.1 and 13.2, the carboxylic acid groups can be completely deprotonated, and each dumbbell molecule carries 20 negative charges, making AC_{60}-AC_{60} molecules discrete polyanions in the solution, as confirmed by the very low scattered intensity from SLS measurements. At solvent pH 6.4−11.3 (pH of deionized water is ∼5.8), carboxylic acid groups partially deprotonated, with the corresponding charges carried by each dumbbell molecule ranging from ∼4 to 17 (Table S1). In these cases, the AC_{60}-AC_{60} solutions demonstrated very high scattered intensity, suggesting the formation of larger assemblies. As given in Table S2, the relationship of R_g/R_h ∼ 1 for these assemblies at different pH values is valid for all pH conditions, indicating their hollow and spherical characteristics. Notably, when the AC_{60}-AC_{60} molecules carry more charges (at higher pH), smaller assemblies are formed (Figure 4), consistent with the trend for blackberry structures, i.e., heavier charged macroions assemble into smaller blackberry structures,[33] but against the

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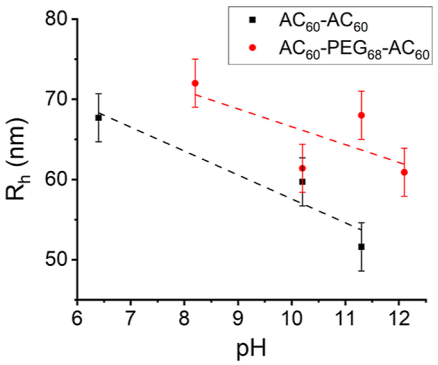

Figure 4. Hydrodynamic radii of assemblies from AC_{60}-AC_{60} molecules and AC_{60}-PEG_{68}-AC_{60} molecules in aqueous solutions at different pH values.

expected trend for amphiphilic vesicles, as discussed earlier. Our earlier work showed that small monovalent cations, such as Na^+, at low concentrations (<20 mM) do not affect the self-assembly process and the assembly size.[37] In this work, the Na^+ concentrations at pH ∼ 12 and ∼11 are 10 and 1 mM, respectively. Therefore, the introduction of extra Na^+ ions does not affect the self-assembly of the dumbbell and bola molecules that we discussed here.

All-atom molecular dynamics simulations further confirm the experimental results. The details of simulations and system preparation are provided in the Supporting Information. The present study explores the extent of deprotonation, as characterized by the cumulative charge of an AC_{60}-AC_{60} molecule. To get quantitative information on the conformation of the AC_{60}-AC_{60} molecule in water, the intramolecular distances between the center of mass of the C_{60} groups within one AC_{60}-AC_{60} were computed. Figure 5 illustrates the number

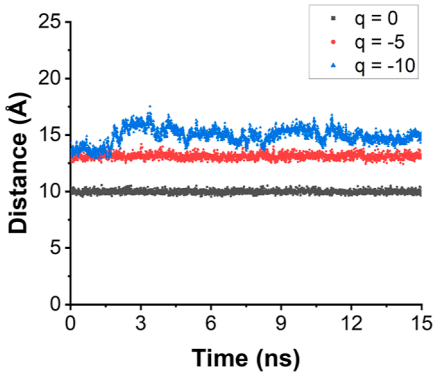

Figure 5. Intramolecular distance between the center of mass of two C_{60} with a single AC_{60}-AC_{60} dumbbell molecule in water. q: charge carried by one AC_{60}-AC_{60} dumbbell molecule.

average intramolecular distances between the centers of mass of two C_{60} over the course of the simulation when a single dumbbell-shaped molecule is solvated in water with varying degrees of deprotonation. The neutral case exhibits the smallest intramolecular distance, while the −10 charged case displays the greatest intramolecular distance. In other words, a higher degree of deprotonation leads to an extension of the dumbbell-shaped molecule. We have also investigated the average intermolecular distance between the center of mass of C_{60} groups belonging to different dumbbell molecules in a system containing 10 AC_{60}-AC_{60} molecules. While generating a smooth intermolecular distance distribution was not possible because of the small number (ten) of AC_{60}-AC_{60} we simulated, the neutral case constantly showed a smaller intermolecular distance as low as 11 Å due to the hydrophobic interaction. In general, an increase in the degree of deprotonation leads to a corresponding increase in the intermolecular distance between the C_{60} groups due to electrostatic repulsion.

Snapshots in Figure S5 demonstrate the state of 10 AC_{60}-AC_{60} molecules in water from molecular dynamic simulations. When the dumbbell molecules are neutral (Figure S5a), they aggregate (less soluble) in water, the same as what we observed from the experiment. For q = −10 (Figure S5c), the molecules lead to the incorporation of a considerable fraction of dumbbell molecules into a monolayer self-assembled structure, while some dumbbells exist as discrete anionic molecules since the incorporation of those molecules could happen at a much longer time. The q = −5 case shows the characteristics between the neutral and q = −10 cases (Figure S5b), with a small fraction of dumbbells forming a monolayer, while others are insoluble aggregates. When running the simulation, we observed that the self-assembly kinetics becomes slower in higher charge cases as the self-assembled conformations need a longer time to form with increasing charge numbers. The current results demonstrated that the degree of deprotonation, i.e., the charge, has primary roles in the kinetics and self-assembly of dumbbell-shaped molecules. To shed light on the self-assembly of dumbbell molecules configuration in atomistic details, a snapshot of −10 charged molecules solvated in water as a cluster unit is shown in Figure 6. In the snapshot, each color corresponds to a distinct molecule where C_{60}, the tether link, and polar functional groups are shown in van der Waals, CPK, and line styles, respectively. Figure 6 shows that dumbbell molecules can take different orientations, side-by-side and head-to-head. While the tether link does not fill up the space between the dumbbells, the polar functional groups, shown in thin lines, interdigitate with that from proximal molecules, which can further stabilize the self-assembly and hinder the molecules from extra packing. These results show that the assemblies from AC_{60}-AC_{60} dumbbells do not possess any hydrophobic domain, thus further confirming that the nature of these assemblies is the blackberry-type structures driven by counterion-mediated attraction rather than vesicles driven by the hydrophobic interactions.

2.4. Self-Assembly of Dumbbells without Hydrophobic Domains. To further demonstrate that the dumbbell-shaped amphiphiles with bulky polar head groups assemble into blackberry-type structures, a series of bolaform macromolecules, AC_{60}-PEG_{68}-AC_{60}, AC_{60}-PEG_{227}-AC_{60}, and AC_{60}-PEG_{455}-AC_{60}, were synthesized and studied in aqueous solution. The subscripts of PEG refer to the number of ethylene oxide repeating units in the linkers. They have no hydrophobic domains; therefore, the hydrophobic interaction (then the amphiphilic vesicular structures) can be ruled out from their solution. If they can still assemble, then we can safely exclude the amphiphilic vesicle model and confirm that counterion-mediated attraction dominates the assembly of dumbbell-shaped amphiphiles.

The solubility and degree of deprotonation of AC_{60}-PEG_{68}-AC_{60} at a concentration of 0.5 mg/mL are given in Table S5. The macromolecule exists as individual macroions when dissolving in NaOH solutions with pH = 12.1 and 13.2. Notably, they self-assemble into stable supramolecular structures within a pH range of 8.2 to 12.1, with negative

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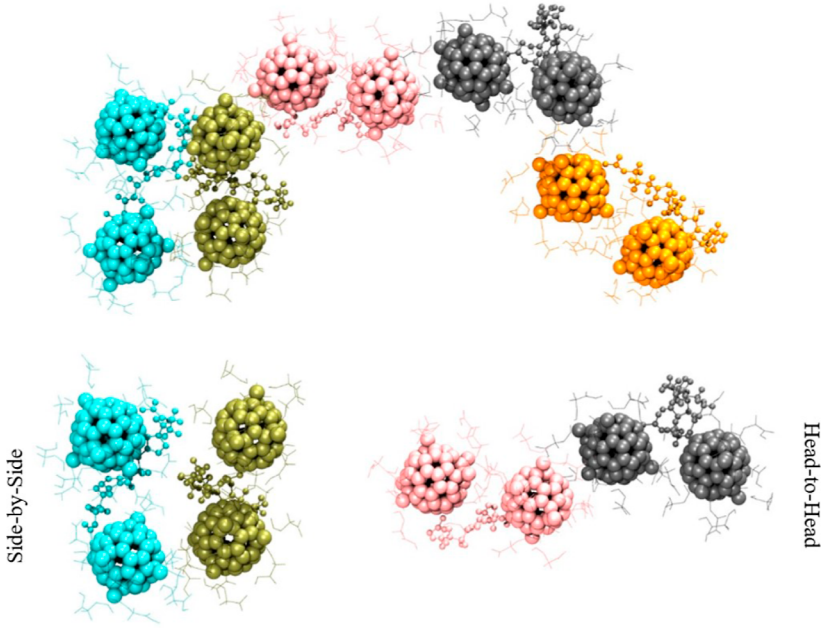

Figure 6. Snapshot of −10 charged dumbbell multimolecules solvated in water. Each color represents a distinct molecule. In the figure, the residues of C_{60}, the tether link, and functional groups are shown in van der Waals, CPK, and line style, respectively. Two conformations, side-by-side and head-to-head, are shown in the snapshot.

charge carried by each bola molecule ranging from ∼2 to 20, respectively. The final assemblies were characterized by SLS and DLS techniques. The comparable R_h and R_g values, as shown in Table S6, suggest the formation of hollow spherical assemblies. The sizes of assemblies from AC_{60}-PEG_{68}-AC_{60} exhibit a pH dependence similar to that of AC_{60}-AC_{60} assemblies, i.e., smaller sizes at higher pH. Therefore, as discussed earlier, these assemblies display the typical features of blackberry structures instead of vesicular structures.

Comparing the pH dependence of the assembly size between the dumbbell and bola molecules shows the effect of PEG chain length (Figure 4). AC_{60}-PEG_{68}-AC_{60} always forms larger assemblies than AC_{60}-AC_{60} at a given pH. This can be attributed to the shielding effect of the PEG chains, as well as their hydrophilic, extended conformation in solution, which contributes to the increment of the overall assembly size. The relatively large error bars in the average R_h values are from the DLS measurements, especially after considering the size distribution of the samples from the CONTIN analysis. Meanwhile, the linear fitting lines relating to AC_{60}-AC_{60} and AC_{60}-PEG_{68}-AC_{60} have slopes of −3.0 and −2.2, respectively. Given the limited data points, the slopes qualitatively confirm that the two types of macromolecules follow similar self-assembly mechanisms.

The solubility of AC_{60}-PEG_{227}-AC_{60} and AC_{60}-PEG_{455}-AC_{60} in water is further improved by increasing the length of hydrophilic PEG chains. Thus, they can fully dissolve in neutral deionized water; however, they show no assembly in aqueous solutions at any pH. In both cases, long PEG chains are so dominant that they can completely shield any effective attraction between the AC_{60} head groups.

All of the results in this paper lead to the conclusion that the dumbbell and bola types of amphiphiles might form blackberry-type structures rather than conventional vesicular structures when the polar head groups carry a moderate amount of charges. Given the special molecular architecture of these macromolecules, these two possible assembled structures happen to be very similar at first look—both are formed by side-by-side packing of these molecules into a hollow, spherical supramolecular structure; as a result, the nature of the assembly was not properly discussed in the literature, including ourselves. With the identification of the driving force of the self-assembly, we see promising flexibility and potential applications of such assembled structures: they do not have a condensed hydrophobic domain, which prohibits the exchange of materials inside and outside the hollow assemblies; instead, they possess a unique, porous surface, and the porosity and pore size might be adjustable with external conditions or proper design of the molecules.

3. SUMMARY

In summary, we demonstrated that a new dumbbell-shaped amphiphile carrying tuneable charges self-assembles into single-layered hollow, spherical, blackberry-type structures with porous surfaces. Unlike traditional surfactants that can easily adjust their packing on the vesicle surface, the numbers of charged "head groups" from dumbbells on the inner and outer layers of the assembly surface remain identical, making the assemblies from amphiphilic dumbbells respond differently from conventional surfactant vesicles. When carrying more charges in solution, these molecular dumbbells and bolaform macromolecules self-assemble into smaller aggregated structures, exhibiting the typical feature of blackberry-type structures; i.e., the weaker counterion-mediated attraction between more heavily charged molecules leads to smaller assemblies. This is attributed to the architecture of the AC_{60}-AC_{60} and the AC_{60}-PEG_{68}-AC_{60}, neither of which has enough hydrophobic segments to drive the formation of the condensed hydrophobic zone for vesicles. Overall, we conclude that multicharged amphiphilic molecular dumbbells self-assemble into blackberry-type structures with a porous surface rather

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than conventional vesicles with an enclosed hydrophobic domain inside the surface layer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.3c02288.

Materials and instrumentations, synthesis procedures, simulation methods, and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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