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Smaller Building Blocks Form Larger Assemblies: Aggregation Behavior of Biaryl-Based Dendritic Facial Amphiphiles

Ashootosh V. Ambade, Sivakumar V. Aathimanikandan, Derek van der Poll, and S. Thayumanavan*

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

thai@chem.umass.edu

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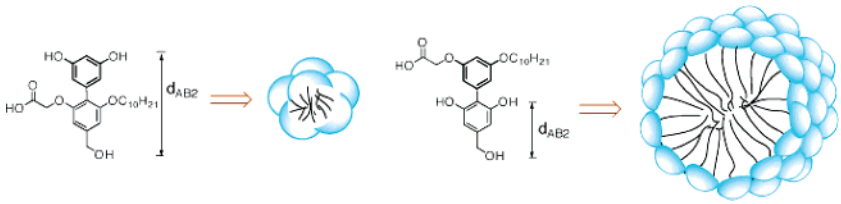

Synthesis and micellar behavior of biaryl-based benzyl ether dendritic molecules prepared from a new biaryl building block are described. The key objective of the study is to tune the size of individual dendritic molecules and investigate its effect on aggregation behavior of the resulting micelle-like assemblies. We show that the functional group placement in the building block influences flexibility of the dendritic backbone and interior volume available for packing the hydrophobic groups, which is reflected in different aggregation behavior and aggregate size of the two types of micellar assemblies.

Introduction

Most of the biomimetic structures are based on small molecules, because of the relative ease with which the spatial control of functional group display can be achieved.[1] However, considering the macromolecular nature of proteins and nucleic acids, it is interesting to be able to mimic these structures with controlled, high molecular weight scaffolds. Dendrimers provide a unique opportunity for such possibilities, because these molecules can be obtained with a high degree of control in molecular weight, i.e., polydispersity of one.[2] Also, most of the dendrimers attain a globular shape at high molecular weights[3] and therefore are interesting candidates for mimicking globular proteins.[4] In water-soluble proteins, most of the hydrophobic amino acid side chain functionalities are directed toward the interior while the hydrophilic ones are exposed to the solvent. Thus, often the protein cofactors are buried in the hydrophobic pockets of proteins, although the overall molecule is soluble in water. Similarly, water-soluble dendrimers with a hydrophobic interior containing electro- and photoactive functionalities have been reported previously.[5,6] These types of molecules also exhibit interesting unimolecular micellar characteristics. In all these designs, the backbone of these dendrimers is hydrophobic and the periphery is decorated with hydrophilic functionalities to optimize the surface contact with the solvent, water.

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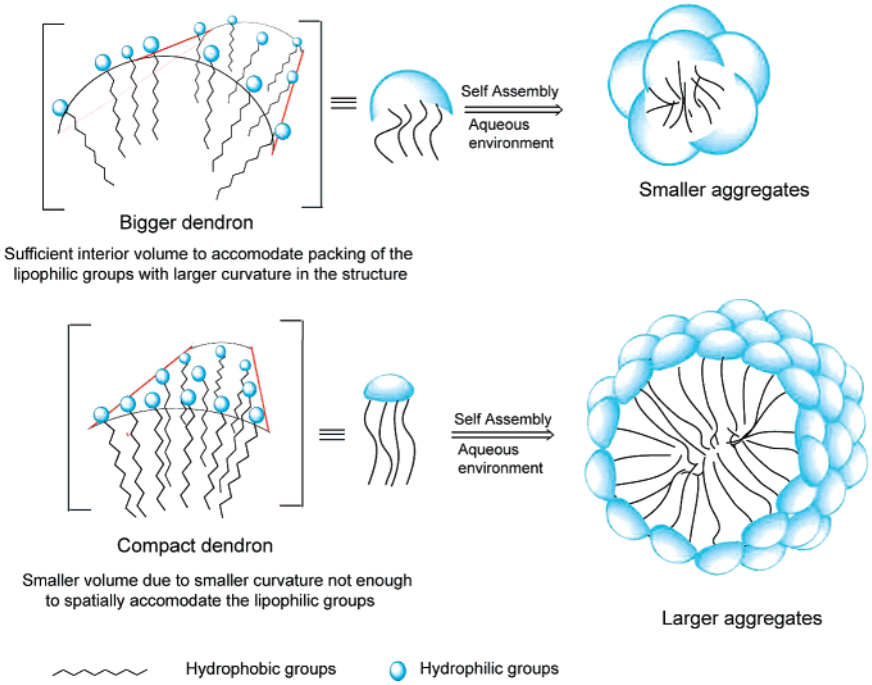

FIGURE 1. The hypothesis that the curvature of dendritic backbone influences the micelle-like assembly is illustrated. "Bigger" dendritic molecules with larger curvature may afford to form smaller aggregates (above) while "smaller" molecules with less curvature may form larger aggregates (below).

To more closely mimic the biomacromolecules, however, it is interesting to be able to direct modifiable side chain functionalities toward the micellar interiors of the dendrimers. For this purpose, we had disclosed a class of biaryl-based dendritic molecules, in which each repeat unit contains both hydrophilic and lipophilic functionalities.[7] The key feature here is the unique conformation that is presumably adopted by these dendritic molecules to form micelle-type assemblies. In classical water-soluble dendrimers, the functionalities within the internal layers of dendrimers are more buried with respect to the contact with the bulk solvent.[6] With our molecules, we had suggested that all hydrophilic functionalities are equally exposed to the polar solvent independent of the layer that it is present in. The simplest way to understand this possibility is to visualize these molecules as simple branched facial amphiphiles, where all the hydrophilic moieties are exposed to the bulk solvent and all the hydrophobic functionalities are buried in the interior of the assembly independent of their location (Figure 1). Note that this hypothesis is consistent with our previous data on the interaction of our dendritic molecules with proteins as well as with self-assembly of these molecules on surfaces.[8c,d]

If our structural hypotheses above were true, we envisaged that when dendritic molecules with similar molecular weights, but more compact size were synthesized, the size of the assembly would be larger. The reason for this assertion is schematically represented in Figure 1. Under our hypothesis, in a polar solvent, a certain number of lipophilic groups would be directed toward the interior of the micelle-type assembly. To minimize the surface contacts of these functionalities with the polar solvent, these molecules would adopt a conformation that would result in a certain curvature. If the molecule could attain a large curvature, then a relatively small number of molecules are needed for aggregation, where the self-assembled structure has a hydrophilic exterior and an encapsulated lipophilic interior. In the limiting case, a globular structure could be attained with a single molecule and one could achieve a unimolecular micelle. If one builds another dendritic molecule with the same number of lipophilic groups, but using a more compact building block unit, then this molecule will adopt a conformation with smaller curvature mainly because the molecule needs to accommodate the same number of amphiphilic

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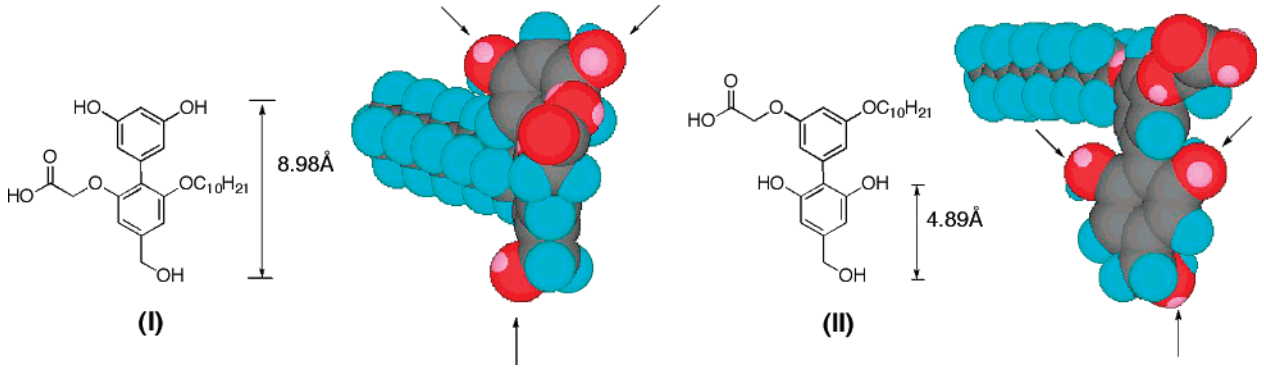
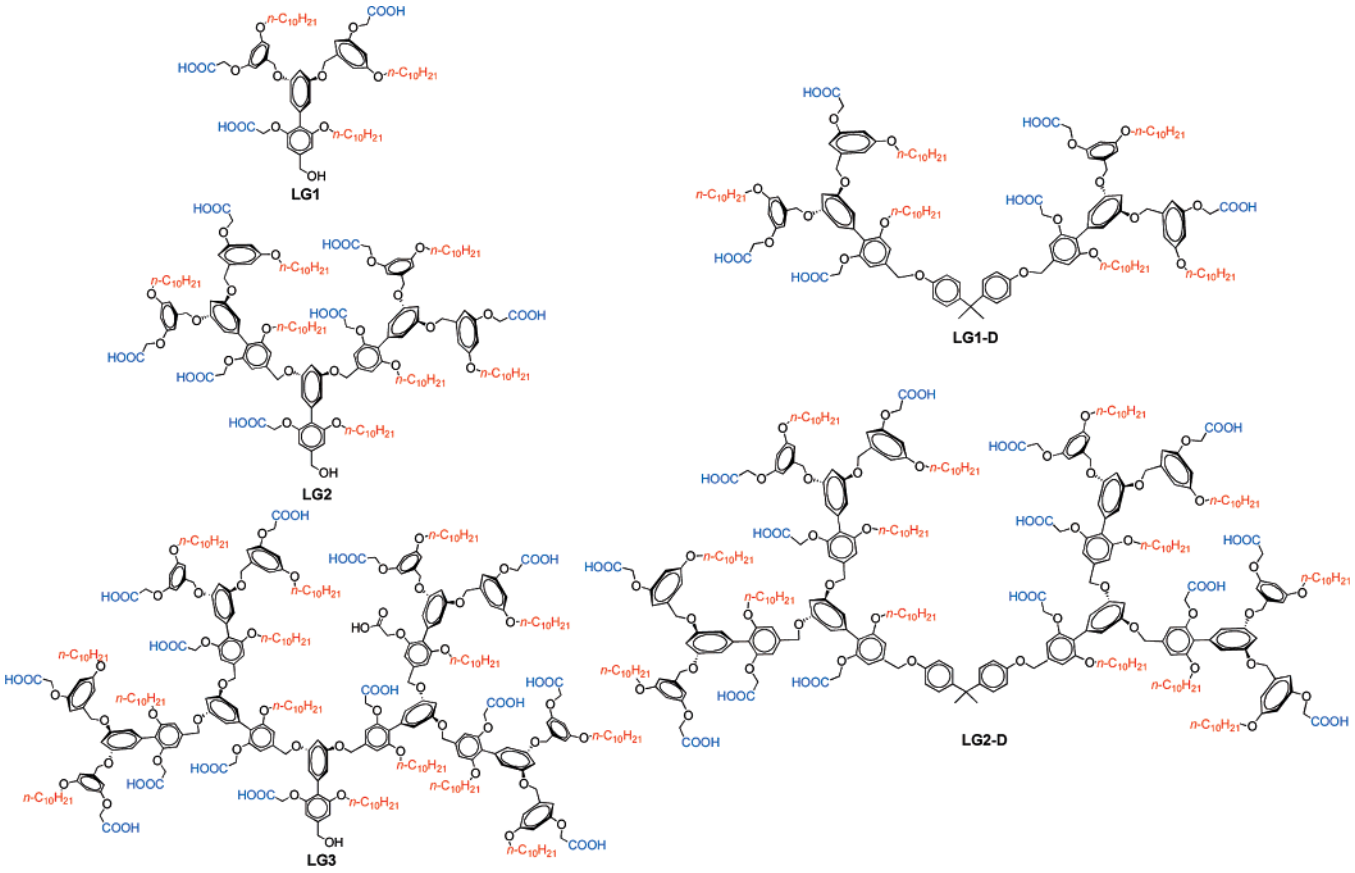


FIGURE 2. The phenolic groups are twice as far away from the hydroxymethyl group in building-block I reported earlier as those in II. These are indicated by arrows in the space-filling models.

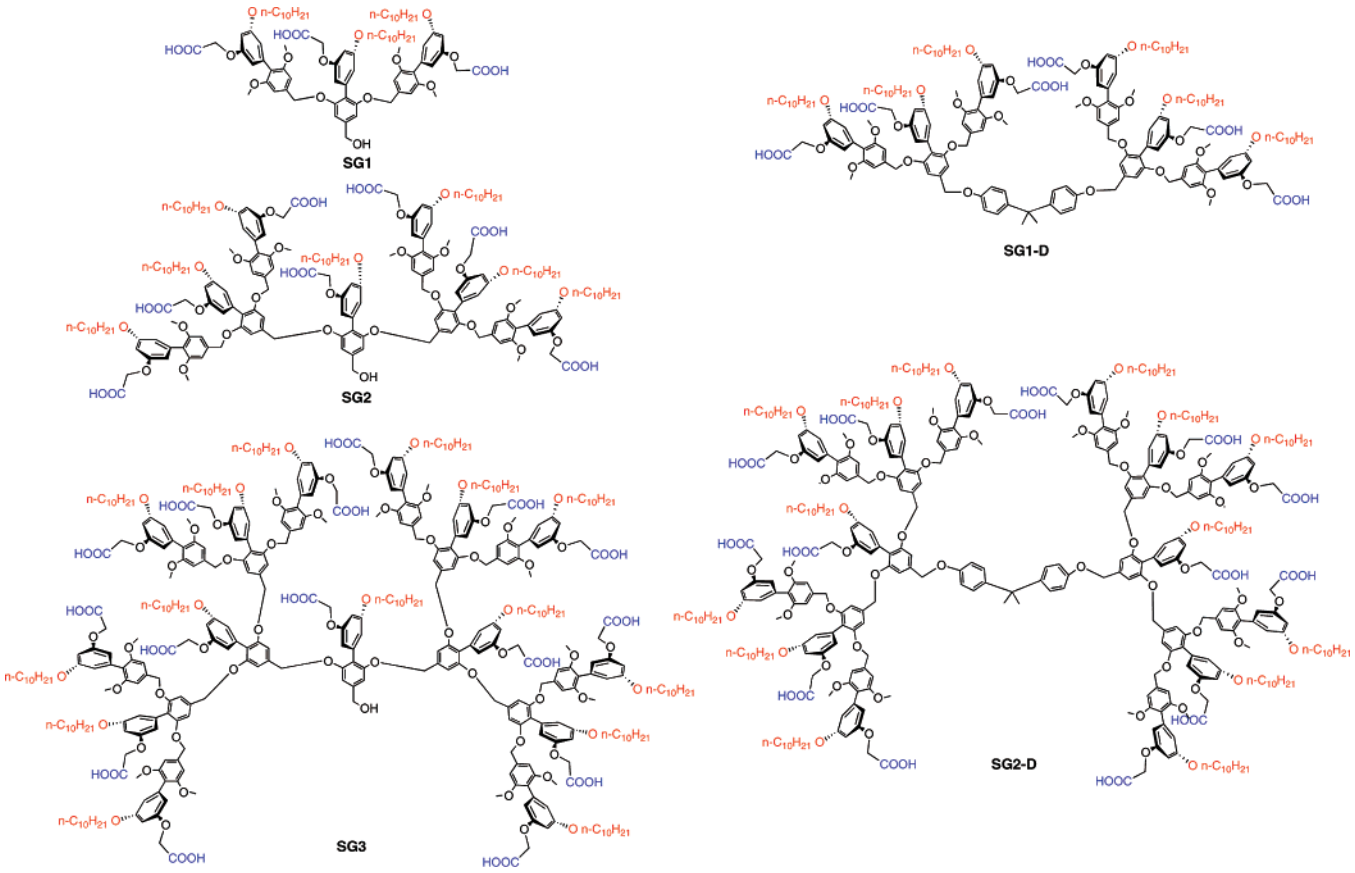
CHART 1



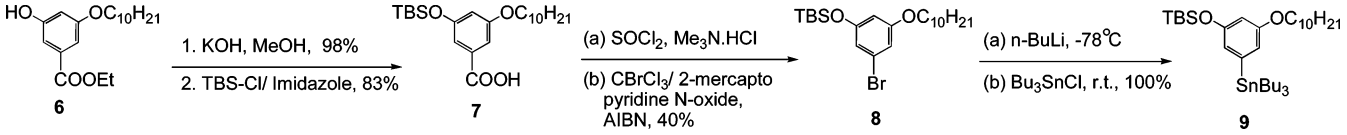
functionalities in a concave face that has a much smaller volume. With the smaller curvature, therefore, a larger number of molecules are needed for the formation of the micellar aggregate, as schematically illustrated in Figure 1. In other words, if our structural hypothesis is correct, then more compact dendritic molecules will form larger aggregates whereas the more open-structured ones will form smaller aggregates.

To test this hypothesis, we built a structurally compact analogue of our originally reported biaryl dendritic molecules.[8] Our previously reported biaryl building block is represented by **I** in Figure 2 and dendritic molecules synthesized from it are shown in Chart 1. Our structural hypothesis was that the aryl ring that defines the plane of the dendrimerizable functionalities should be orthogonal to the aryl ring that contains the amphiphilic functionalities. Thus, the amphiphilic functionalities are presented at either side of the plane containing the dendrimerizable AB_2 functionalities.[7] Monomer **II** also satisfies this structural requirement, just as well as **I**. The key difference is that the hydroxymethyl group and the two phenolic moieties are all in the same aryl ring of the biaryl system **II**. Since the dendritic growth occurs from the AB_2 functionalities, the distance between these defines the dimensions of the building block unit and therefore the overall size of the dendrons. This distance is 8.98 Å in structure **I** and 4.89 Å in **II**; these were estimated from an energy-minimized monomer by using the Cirus 2 simulation program (Figure 2). Thus, the molecules arising from **II** will be more compact than those arising from **I**. To compare the nature of the assemblies obtained from **I** and **II**, we synthesized dendrons **SG1**−**SG3** and didendrons **SG1D**−**SG2D** shown in Chart 2 and characterized the assemblies from both designs using host−guest studies and dynamic light scattering.

CHART 2



SCHEME 1. Synthesis of the Aryltin Compound for the Smaller Biaryl Building Block



Results and Discussion

Synthesis. The dendritic structures reported here are based on aryl−alkyl ether connectivity.[9] For the synthesis of such benzyl ether dendritic molecules, one needs a bromomethyl compound and a diphenolic compound. These molecules are shown by structures **17** and **18**, where the former compound is the peripheral unit, and the latter constitutes the repeating unit. Both these molecules are biaryl compounds with hydrophobic and masked hydrophilic functionalities. We use the decyl chain as the hydrophobic moiety and the *tert*-butyl acetate group as the masked hydrophilic moiety (*tert*-butyl ester will be hydrolyzed to the hydrophilic carboxylic acid moiety in the last step of the syntheses). Biaryl molecules are routinely synthesized by Suzuki and Stille coupling among other methods.[10] In our laboratories, we have standardized the Stille coupling method for these molecules. To utilize this strategy for synthesis of biaryl compounds, we need an aryltin compound and an aryl bromide, which are coupled in a palladium-catalyzed reaction. In design **II**, the AB_2 functionalities are in the lower ring, which will contain the bromo moiety (**11** or **12**) for the Stille coupling. The hydrophilic and hydrophobic functionalities are in the upper aryl ring, which will contain the tributyltin functionality (compound **9**). Note that the precursor **9** has the hydrophobic decyl moiety, but does not contain the masked hydrophilic ester functionality. This is because we recognized that the optimal yields were obtained in the Stille coupling reactions only when the substituent para to the bromo moiety in the bottom ring is an electron-withdrawing unit, such as with esters **11** and **12**. After the biaryl coupling reaction, selective reduction of the ester in the bottom ring will be difficult if the top ring were to have the ester moiety as well. Therefore, we carried out the synthesis with a protecting group in place of the hydrophilic functionality in the top ring, as in structure **9**.

We envisaged the synthesis of **9** from the corresponding aryl bromide **8** using bromine−lithium exchange protocol as shown in Scheme 1. Synthesis of the starting material **6** was achieved from commercially available 3,5-dihydroxybenzoic acid in 43% yield. The ester moiety of **6** was then hydrolyzed and the phenolic moiety was protected as a *tert*-butyldimethylsilyl (TBS) ether in 82% overall yield to obtain the carboxylic acid **7**. The aryl carboxylic acid moiety of **7** was then converted to the corresponding aryl bromide **8** by using a radical-based method

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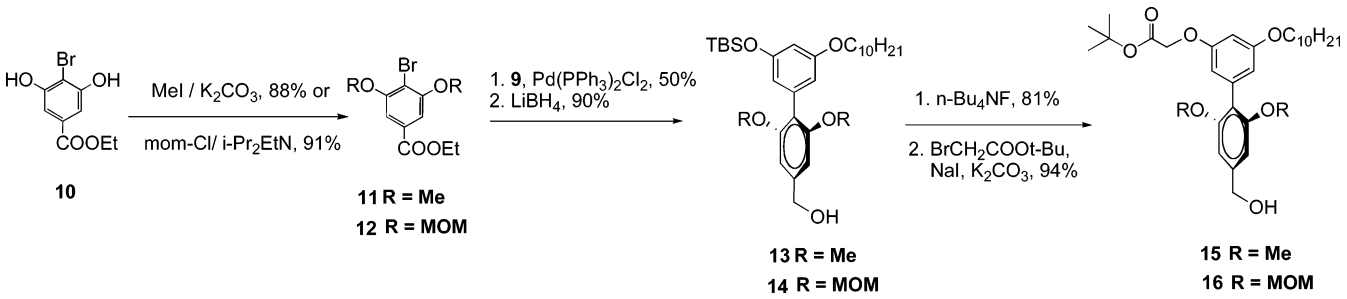
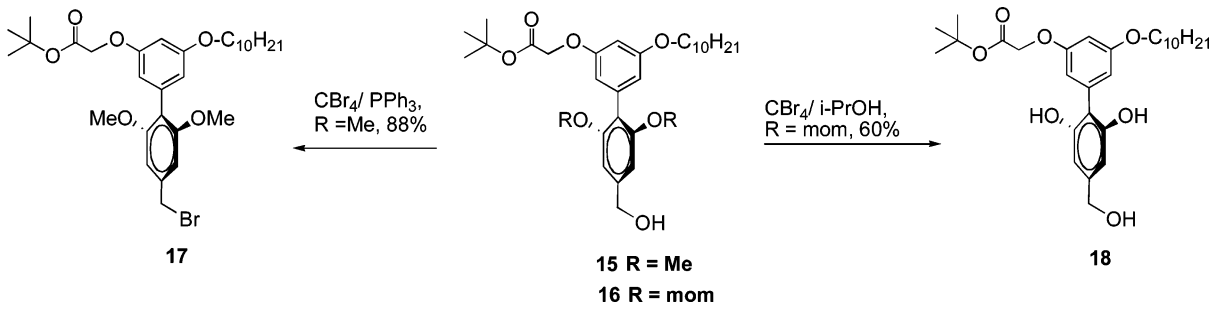
SCHEME 2. Synthesis of Biaryl Building Block Precursor via Stille Coupling



SCHEME 3. Synthesis of Biaryl Building Block and the Peripheral Unit



in 40% yield.[7,11] The aryl bromide was then converted to aryl stannane **9** and was taken to the coupling step without further purification.

The lower ring precursors **11** and **12** were synthesized by reacting ethyl 4-bromo-3,5-dihydroxybenzoate with methyl iodide and methoxymethyl chloride (mom-Cl), respectively, as shown in Scheme 2. Stille coupling of **11** or **12** with the aryltin compound **9** catalyzed by dichlorobis(triphenylphosphine)-palladium(II) then afforded the biaryl compounds in about 50−55% yield after chromatographic purification. The subsequent steps that lead to either peripheral or repeating unit are the same except for the last step and the yields of each of these steps were good to excellent. First the ethyl ester was reduced to alcohol with $LiBH_4$ to obtain compounds **13** and **14**. The TBS group was then cleaved with tetrabutylammonium fluoride followed by installation of the *tert*-butyl acetate group under Williamson etherification conditions to afford **15** and **16**, respectively.

At this stage, compound **15** was converted to the corresponding bromomethyl derivative **17** with use of triphenylphosphine and carbontetrabromide; this molecule is the peripheral monomer in the dendritic assembly. The mom-ethers in **16** were then subjected to a mild deprotection protocol to afford the repeating unit monomer **18**, as shown in Scheme 3. It is to be noted here that carefully optimized conditions were needed to cleave the mom-groups in presence of the *tert*-butyl ester, since both the functional groups are acid sensitive. After experimenting with different reaction conditions involving mild acids, a satisfactory condition was found that generates HBr in situ enough to cleave the mom-groups, but not the *tert*-butyl ester.[12] Thus, the cleavage of mom-groups could be achieved in 60% yield by refluxing compound **16** in isopropanol in the presence of 0.2 to 0.3 equiv of CBr_4, under dilute conditions.

The dendrons were then assembled by iterative synthetic procedures reported earlier (Scheme 4).[9] The bromomethyl derivative **17** was reacted with the building block monomer **18** under Williamson etherification conditions to afford G1-monodendron (**19**) in 67% yield. Bromination and alkylation reactions were repeated to obtain G2 and G3 monodendrons, **21** and **23**. The yields of alkylation decreased for higher generations with the yield of G3 being only 12%. We surmise that steric crowding does not favor the reaction at the focal point in the case of higher generations. G1-didendron (**24**) and G2-didendron (**25**) were obtained by bromomethylation of monodendrons followed by etherification with bisphenol A as shown in Scheme 5. Lack of formation of G3-didendron and low yields for other generations may be taken as an indication of the compact nature of these dendritic molecules when compared to ones from design **I**, where even the G3-didendron could be synthesized in moderate yield.

All monodendrons and didendrons were characterized by ^{1}H NMR, ^{13}C NMR, and MALDI-ToF spectrometry; GPC analysis was carried out as an additional check of purity. The *tert*-butyl ester groups were then hydrolyzed under refluxing aqueous KOH/MeOH/THF conditions to obtain carboxylated derivatives as the targeted amphiphilic monodendrons **SG1**−**SG3** and didendrons **SG1-D** and **SG2-D**. The absence of *tert*-butyl groups was ascertained by ^{1}H NMR and the structures were further confirmed by MALDI-ToF analysis.[13] For simplicity in further discussion the hydrolyzed monodendrons are referred to as G1, G2, and G3 while hydrolyzed didendrons are referred to as G1-D and G2-D with a prefix S or L for smaller or larger dendritic molecules as the case may be (see Charts 1 and 2).

Aggregation Behavior. As mentioned in the introduction, we had hypothesized that the smaller dendritic molecules (**SG1**−**SG3**, **SG1-D**, and **SG2-D**) would form larger aggregates and the larger ones (**LG1**−**LG3**, **LG1-D**, and **LG2-D**) would form smaller aggregates in aqueous solutions. A direct method to test this hypothesis is to carry out solution size measurements with dynamic light scattering (DLS) experiments. For this purpose, 10^{-4} M aqueous solutions of the dendritic molecules were

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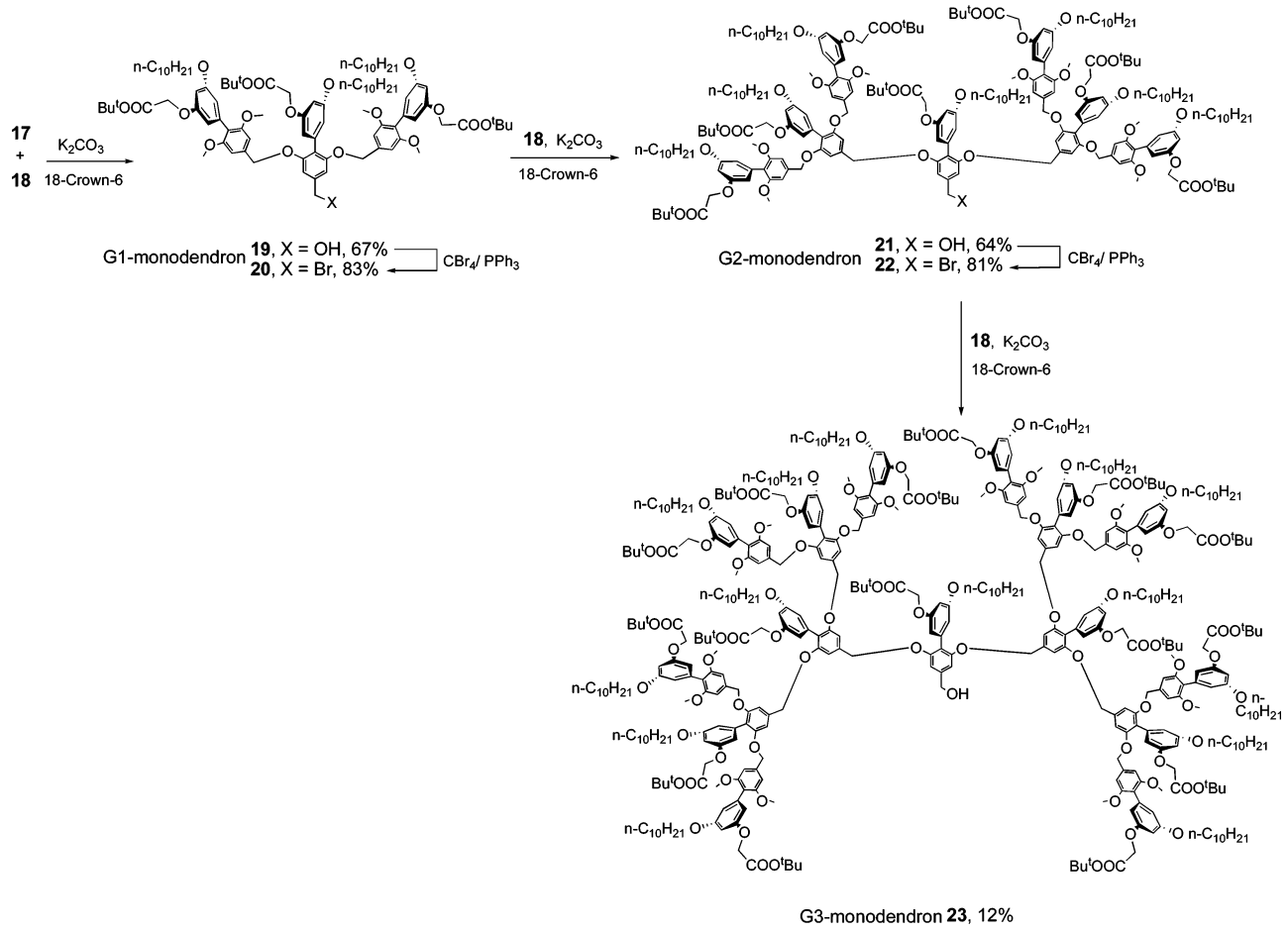
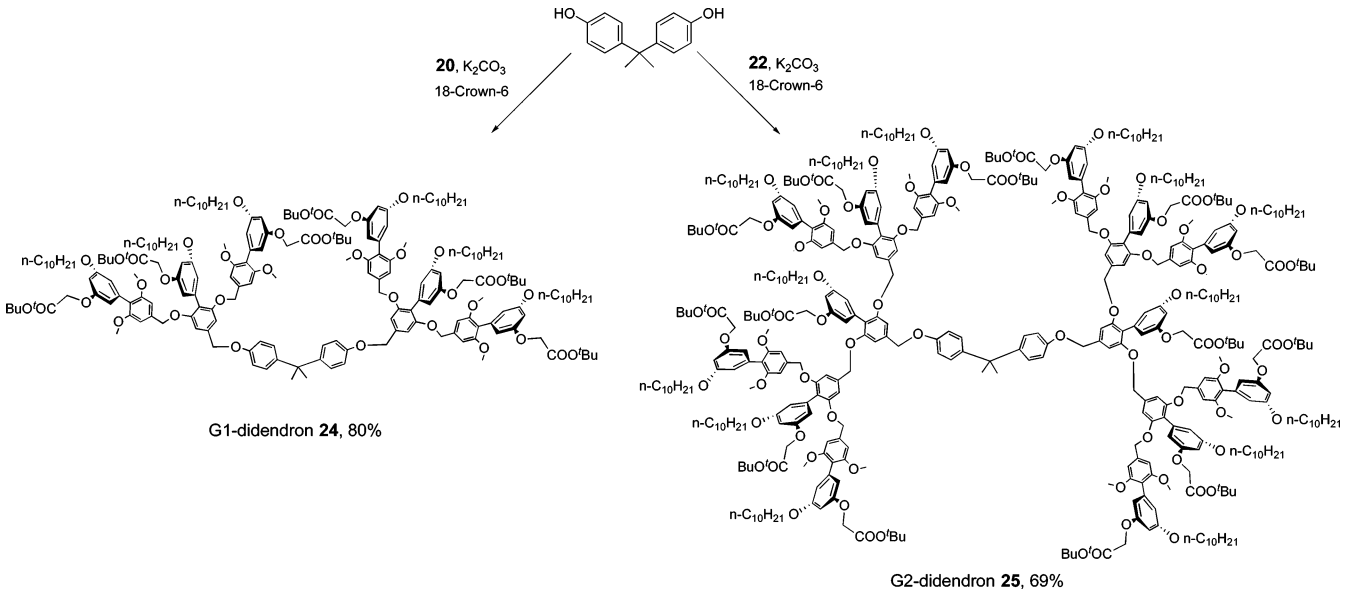
(13) See the Supporting Information for details.

SCHEME 4. Assembly of Dendrons from the Precursors 17 and 18



SCHEME 5. Synthesis of Didendrons from the Monodendron Precursors and Bisphenol A



prepared with 1−1.5 equiv of KOH per carboxylic acid unit. The hydrodynamic radii (R_h) values were obtained by DLS and the results are shown in Table 1. It is immediately obvious from Table 1 that the S molecules consistently form larger aggregates compared to the corresponding L ones. These results provide the supporting evidence for our structure vs aggregate size hypothesis. In fact, with the exception of **LG1**, all L molecules form much smaller aggregates than all of the S molecules.

It is also interesting to note that there is a dendritic effect in the aggregation in the case of L molecules, whereas this trend is much more irregular in the case of S. Upon going from **LG1** to **LG2** and **LG3**, the aggregate size clearly decreases. This is

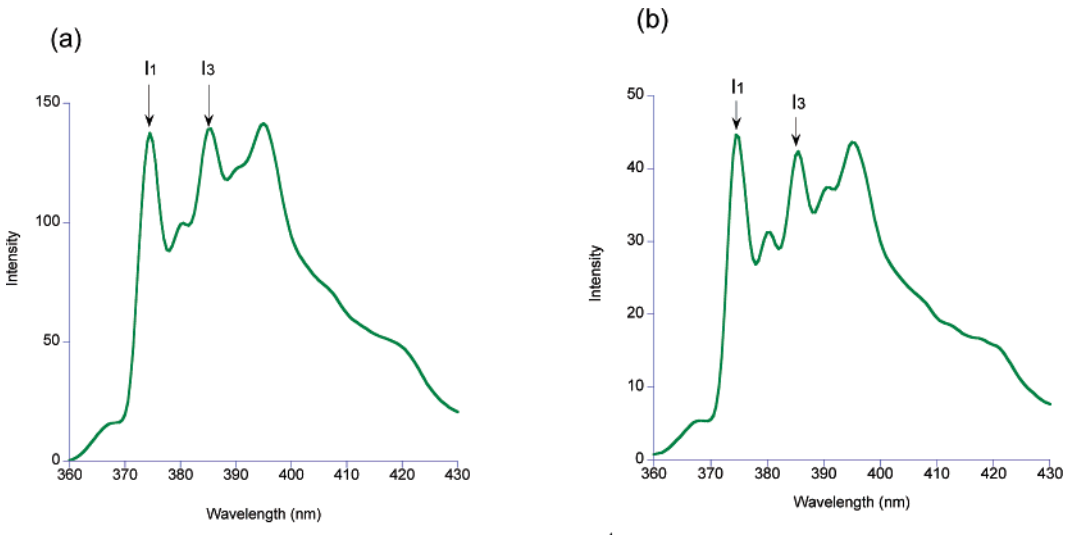


FIGURE 3. Emission spectra of pyrene encapsulated in 10^{-4} M aqueous solutions of (a) SG3 and (b) LG3.

TABLE 1. DLS Data for the S and L Dendritic Aggregates in Aqueous Solutions[a]

	R_h (nm)	
G*n*	S dendritic molecules	L dendritic molecules
G1	28	35
G2	15	5.0
G3	24	5.5
G1-D	20	4.0
G2-D	11	4.0

[a] The hydrodynamic radii reported here are obtained from the volume-average of the sizes obtained in the DLS measurements

perhaps understandable because in the case of higher generations, there is a forced curvature between the neighboring amphiphilic units within a dendron, because of the inherent architecture of the dendron itself. This could be providing the pathway for forming smaller aggregates. It is possible that the smaller dendrons also benefit from this forced curvature upon comparing **SG1** and **SG2**. However, there is a second issue involving the sterics of accommodating several decyl units within a smaller volume, as discussed earlier. This is a competing pathway for providing the curvature. It is possible that **SG3** is simply too crowded to afford a larger curvature than **SG2**, compared to the case with **LG2** and **LG3**. The comparison of didendrons can be explained in a similar fashion. These results can be taken to be consistent with the overall structural hypothesis proposed here. However, we obviously do not have unambiguous evidence for these suppositions. Therefore, these should be taken as explanations that are consistent with the data, but are provisional.

We also were interested in finding out whether these aggregates are indeed micellar. If these assemblies were micellar, these should be capable of sequestering hydrophobic guest molecules within their interiors. In fact, we were able to show that all these mono- and didendrons are capable of sequestering hydrophobic guest molecules such as pyrene and that the critical micelle concentrations of these molecules are about 10^{-6} M.[13] However, it should be noted that the capability of sequestering hydrophobic guest molecules alone is not sufficient to show that a molecule is capable of forming micellar assemblies, because even vesicular assemblies sequester hydrophobic guest molecules within their membranes. This distinction is especially important here, since our molecules form unusually large-sized aggregates for micelles and may lead one to think that these are vesicles. First of all, note that there are examples in the literature of micellar assemblies formed by small molecule surfactants and block copolymers that are bigger in size than expected.[14] Nonetheless, to test whether micelles are indeed the aggregates in our case, pyrene was used as a spectroscopic probe.[15]

Emission spectra of pyrene encapsulated in 10^{-4} M aqueous solutions of **SG3** and **LG3** are shown in Figure 3. The ratio of intensities of first and third peaks in the emission spectra of pyrene, i.e., the I_1/I_3 value, is an indicator of the polarity of its microenvironment.[16] In micellar aggregates, this ratio is between 1.0 and 1.2; this value is typically higher when pyrene is sequestered in vesicles. For all generations of S and L dendritic assemblies, the I_1/I_3 value was found to be between 1.0 and 1.1. Note also that this ratio is comparable to that found for pyrene encapsulated in micelles of a small molecule surfactant, viz. sodium dodecyl sulfate.[17] These results indicate that aggregates formed by these molecules are indeed micelle-like.

Summary

We have demonstrated that simple modification in the building block results in significant changes in the aggregation behavior of the biaryl-based dendritic facial amphiphiles. This is because the size of the building block dictates the size of each dendritic molecule, which is then translated into the conformation that it can adopt in aqueous medium to minimize the solvent contact with the hydrophobic groups. We have

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shown that small, compact dendritic molecules tend to form larger aggregates compared to the corresponding larger analogues. Dynamic light scattering experiments were used to ascertain this. Encapsulation of hydrophobic guest molecules in water and probing the hydrophobicity of the interior by using this guest molecule as the spectroscopic probe provide further evidence that micellar aggregates are indeed formed. These studies could form the basis for systematic structural guidelines for obtaining controlled dendritic aggregates, which could find applications in areas such as drug delivery.[18]

Experimental Section

This section describes the synthesis and characterization for key steps and details for all other compounds are provided in the Supporting Information.

General Procedure for Conversion of Benzylic Alcohol into the Corresponding Bromide. To a stirred solution of the appropriate benzyl alcohol and PPh_3 (2−3 equiv) in minimal dry THF was added carbon tetrabromide (2−3 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature and was monitored by TLC. The reaction mixture was treated with water and extracted two times with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography.

General Procedure for Hydrolysis of *tert*-Butyl Ester Dendritic Molecules. To a solution of the monodendron or didendron in THF was added a 10% aq KOH solution containing 8−10 equiv of KOH per ester group followed by a small amount of methanol to obtain a clear solution. This mixture was refluxed for 24 h and then organic solvents were evaporated. To the residue obtained, water was added and refluxed further for 12 h. The mixture was then diluted with water, neutralized with concentrated HCl, and filtered. The white residue obtained after filtration was washed repeatedly with water until filtrate was neutral. For higher generation monodendrons and didendrons, after the first 24 h, the residue was not completely soluble in either water or THF−water mixture. The suspension was then refluxed for a total of 36 h and neutralized. Completion of the reaction was confirmed from the absence of *tert*-butyl protons in ^{1}H NMR spectra.

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Supporting Information Available: Synthetic procedures and characterization data (^{1}H, ^{13}C NMR, MS) of all new compounds and ^{1}H NMR spectra of key biaryl compounds and dendritic molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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