

Dendrimers with Both Polar and Apolar Nanocontainer Characteristics

Dharma Rao Vutukuri, Subhadeep Basu, and S. Thayumanavan*

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

Received August 20, 2004; E-mail: thai@chem.umass.edu

Dendrimers could be touted as an excellent scaffold for structurally mimicking globular proteins for three reasons: (i) dendrimers are globular in shape at high molecular weights;¹ (ii) the convergent synthetic strategy allows the synthesis of these macromolecules with excellent control in molecular weight;² (iii) synthetic methods are now available to introduce functionally diverse sequences in dendrimers.³ Moreover, proteins are macromolecular frameworks and most of the current biomimetic approaches are based on small molecules.⁴ To further realize the potential of dendrimers as a biomimetic entity, it is necessary that functional groups are selectively directed toward the concave interior of a globular dendrimer. Toward this goal, we have recently proposed a molecular design that uses solvophobic driving force.⁵ We suggested that placing hydrophobic and hydrophilic substituents at an orthogonal plane containing the AB₂ functionalities in the monomer unit would afford a dendrimer with either of these amphiphilic substituents displayed at its concave interior. A molecule that satisfies the design criteria is represented by the biaryl monomer **9**. If the resulting dendrimer is in a polar solvent, the hydrophilic substituents will be presented at the convex surface of the dendrimer and the solvent-incompatible hydrophobic substituents will be placed at the concave interior and vice versa. The molecular design suggests that such a dendrimer would behave like a micelle in polar solvents and like an inverted micelle in apolar solvents, as schematically represented in Figure 1. In this contribution, we report on the synthesis, characterization, and properties of such dendrimers (**1–6** in Chart 1).

We found that the use of carboxylic acid as the hydrophilic moiety and a decyl chain as the hydrophobic moiety renders the dendrimers soluble in both polar and apolar solvents. The target monomer unit **9** was assembled by Stille coupling as the key step, as shown in Scheme 1. Note that the design does not require that the peripheral units are also based on the biaryl. Therefore, the amphiphilic functionalities are incorporated on to a 3,5-dihydroxybenzyl alcohol unit in the periphery. Dendrimers were obtained using the reported procedures,⁶ where alkylation and the conversion of hydroxymethyl to bromomethyl moieties are iteratively used. Details of the synthesis of dendrimers **1–6** from the monomer unit **9** are outlined in the Supporting Information. All dendrimers were characterized by ¹H NMR, ¹³C NMR, and MALDI-ToF mass spectrometry. The dendrimers were also analyzed using size exclusion chromatography as an additional check for purity.

As mentioned above, if our structural hypothesis is correct, then these dendrimers should form hydrophobic nanocontainers in polar solvents and hydrophilic nanocontainers in apolar solvents.⁷ We carried out dye encapsulation studies to investigate this possibility.

Treatment of the carboxylic acid dendrimers **1–6** with 1–2 equiv of potassium hydroxide afforded the corresponding polycarboxylates, which are soluble in water. To probe the microenvironment of the dendrimers in aqueous solution, solvatochromic and water-insoluble Reichardt's dye (pyridinium-*N*-phenoxide betaine) was added. The color of the resultant solutions indicated that these

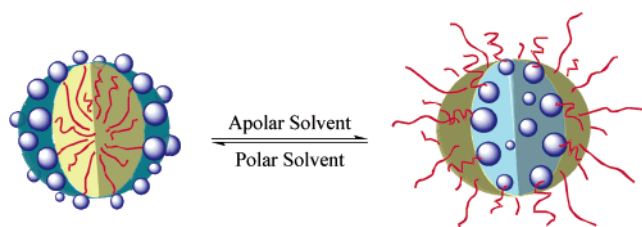
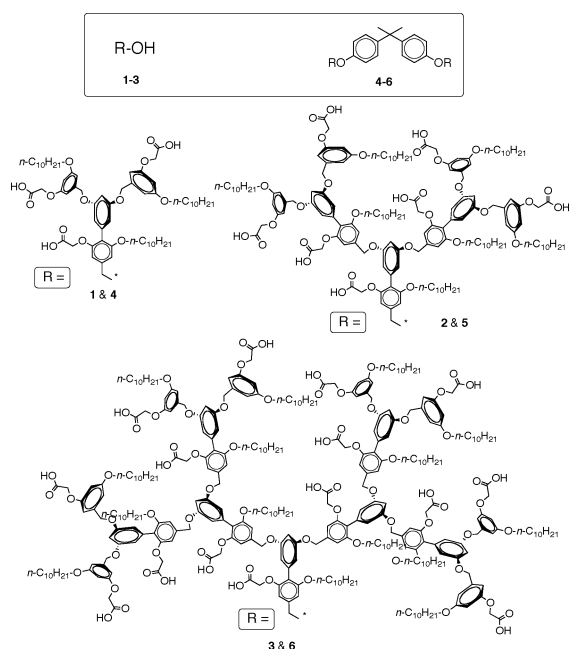
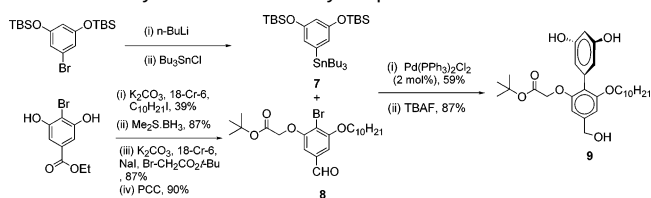


Figure 1. Cartoon of the polar and apolar nanocontainers.

Chart 1. Structures of Amphiphilic Dendrons and Dendrimers



Scheme 1. Synthesis of the Biaryl Repeat Unit



dendrimers are capable of sequestering hydrophobic guest molecules within its interior. The linear absorption spectrum of these solutions exhibited a broad peak with a λ_{max} at about 502 nm, which corresponds to an ET(30) value of 56.9 (comparable to the polarity of glycerol).⁸ When pyrene was incorporated as the guest, the polarity of the dendritic interior of **6** was comparable to that of ethanol. This was based on I_1/I_3 value in the emission spectrum of pyrene. This polarity compares favorably with the micellar interiors provided by small molecule surfactants such as NaLS (sodium lauryl sulfate).⁹

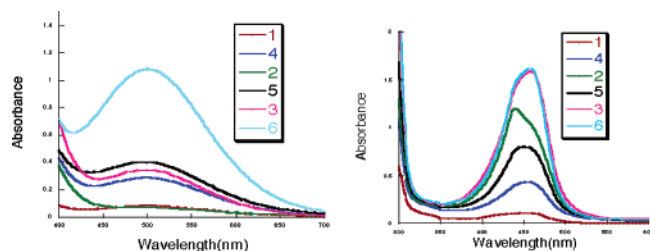


Figure 2. Absorption spectra of (Left) Reichardt's dye in H₂O. (Right) Proflavine·HCl in toluene in the presence of dendrimers 1–6 (10^{-4} M).

Using the extinction coefficient of Reichardt's dye in glycerol, the number of these guest molecules incorporated in the dendrimers was estimated. There is clear generation dependence in the capability of these dendrimers to sequester guests (Figure 2, left). The third-generation dendrimer **6** was able to encapsulate about 8.5 molecules of Reichardt's dye. The second-generation dendrimer **5** and the third-generation monodendrimer **3** were able to acquire about 3.2 and 2.8 dye molecules, respectively. Note that even the first-generation monodendrimer **1** was able to sequester 0.6 dye molecules in its interior, which is likely to be the result of an aggregation.

To investigate the inverted micelle-like behavior of these macromolecules, we incorporated a hydrophilic dye within the dendritic interiors in an apolar solvent. The dendrimers **1**–**6** were all soluble in most of the common organic solvents. We solubilized the dendrimers in toluene and added the hydrophilic dye, proflavine.¹⁰ Proflavine is not soluble in toluene by itself in the absence of the dendrimers. In the presence of any of the dendrimers **1**–**6**, proflavine was solubilized in toluene (Figure 2, right). We attribute this to the combination of the fact that the dendritic interior is polar and the possibility of specific acid–base interaction between the carboxylic acid units of the dendrimer and the amine units of the guest molecule. Interestingly, the number of molecules incorporated in the hydrophilic dendritic interiors is much smaller than those observed with the Reichardt's dye in a hydrophobic container. For example, the third-generation dendrimer **6** sequestered an average of only 1.5 molecules. It is possible that the size of the nanocontainer is dictated by the size and nature of the functionality that is directed toward the interior. In toluene, the smaller and self-complementary carboxylic acid units seem to form small containers that acquire fewer guest molecules. While these macromolecules are clearly capable of providing containers with polar or apolar interiors, we have not unambiguously identified the spatial disposition of the amphiphilic functionalities within each layer of the dendrimer. This is a subject of current investigation in our laboratories.

It is also interesting to investigate whether these container properties arise from unimolecular dendrimers or due to aggregation.¹¹ We utilized dynamic light scattering (DLS) to identify the size of the dendrimer particles in 10^{-4} and 10^{-5} M solutions, the concentrations at which the dye studies above were carried out. At 10^{-5} M concentration toluene solution of the third-generation dendrimer **6** exhibited particles with an average size of about 2.8 nm, whereas a 10^{-4} M solution afforded particles with an average size of about 44 nm. Note that this dendrimer exhibits the ability to sequester dye molecules at 10^{-5} M concentration also. Therefore, the DLS results suggest that dendrimer **6** affords a unimolecular hydrophilic container in toluene. Dendrimers **3** and **5** exhibited

particle sizes of 4.2 and 2.3 nm, respectively, at 10^{-5} M concentration in toluene. This result suggests that, while the didendrimer **5** could act as a unimolecular container, the monodendrimer **3** seems to afford an aggregated particle. Considering that these dendrimers have similar molecular weights, the reason for the difference in aggregation state is not clear at this time.

In aqueous solutions, we found that even the third-generation dendrimer **6** formed an aggregate with average particle size of 25 nm (10^{-4} M) or 22 nm (10^{-5} M). Similarly, dendrimers **3** and **5** afforded aggregates of about 42 and 28 nm, respectively. Note that the particle sizes in micelle-type structures are larger for all dendrimers compared to the inverse micelle-type assemblies obtained in toluene. This result could be due to the difficulty in packing the bigger decyl chains in the interior in this case, compared to the smaller carboxylic acid functionalities in the toluene solution. Also, it is likely that the smaller dendrimers formed aggregates to exhibit the container properties. However, we experienced difficulties in obtaining unambiguous DLS measurements with these dendrimers.

In summary, we have shown that the amphiphilic dendrimers reported here are capable of forming either hydrophobic or hydrophilic nanocontainers, depending on the solvent environment. Whether these containers are unimolecular or an aggregate seems to depend on the size of the functionality in the interior as well as the size of the dendrimer itself. Ultimately, we are interested in arriving at structures where diverse functionalities could be converged in the hydrophobic interiors of the dendrimer in water. Such multifunctional macromolecules are the first step toward structurally complex biomimetic assemblies.

Acknowledgment. Support from the NIGMS of the National Institutes of Health is gratefully acknowledged.

Supporting Information Available: Synthetic and other experimental details. This material is available free of charge at <http://pubs.acs.org>.

References

- (1) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*; Wiley-VCH: New York, 2001. (b) *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; John Wiley & Sons: New York, 2002. (c) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, 99, 1665. (d) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, 97, 1681. (e) Diederich, F.; Felber, B. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, 99, 4778.
- (2) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, 101, 3819.
- (3) (a) Sivanandan, K.; Sandanaraj, B. S.; Thayumanavan, S. *J. Org. Chem.* **2004**, 69, 2937. (b) Zeng, W.; Nowlan, D. T., III; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. *J. Am. Chem. Soc.* **2001**, 123, 8914. (c) Sivanandan, K.; Vutukuri, D.; Thayumanavan, S. *Org. Lett.* **2002**, 4, 3751. (d) Vutukuri, D.; Sivanandan, K.; Thayumanavan, S. *Chem. Commun.* **2003**, 796.
- (4) (a) Cram, D. J. *Nature* **1992**, 356, 29. (b) Breslow, R. *Acc. Chem. Res.* **1995**, 28, 146. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, 32, 278. (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, 31, 173.
- (5) Bharathi, P.; Zhao, H.; Thayumanavan, S. *Org. Lett.* **2001**, 3, 1961.
- (6) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, 112, 7638.
- (7) For a polymer with similar properties, see: Basu, S.; Vutukuri, D.; Shyamroy, S.; Sandanaraj, B. S.; Thayumanavan, S. *J. Am. Chem. Soc.* **2004**, 126, 9890.
- (8) Reichardt, C. *Chem. Rev.* **1994**, 94, 2319.
- (9) Kalyanasundaram, K.; Thomas, J. K. *J. Am. Chem. Soc.* **1977**, 99, 2039.
- (10) Smith, D. K. *Chem. Commun.* **1999**, 1685.
- (11) For the concept of unimolecular micelles with dendrimers, see: Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders, M. J.; Grossman, S. H. *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 1178. For a dendrimer that contains both hydrophilic and hydrophobic substituents in the periphery, see: Pan, Y.; Ford, W. T. *Macromolecules* **2000**, 33, 3731.

JA0449628