Molecular Recognition Using Dendrimer to Deliver Ti-sources into Reverse Micelle–Water Pool

Norifusa Satoh, Kenta Kamikura, and Kimihisa Yamamoto*
Department of Chemistry, Faculty of Science & Technology, Keio University, Yokohama 223-8522

(Received October 29, 2008; CL-081033; E-mail: yamamoto@chem.keio.ac.jp)

Molecular delivery using dendrimers has attracted much attention because dendrimers have a uniform molecular size and inner cavities containing small molecules. We describe the delivery of titanium ions into the reverse micelle–water pool using a dendrimer. The size of the Ti-assembling dendrimer was hierarchically recognized by the water pool size of the reverse micelles, resulting in the formation of smaller TiO_2 particles than samples obtained without the dendrimer.

Dendrimers have a perfectly regulated dendritic structure, resulting in a single molecular weight, a globular structure, and formation of inner cavities.[1] Because the inner cavities capture small molecules, dendrimers can be expected to be a nanosize container for drug delivery and gene delivery in the biochemical region.[2] We can recognize that the capture of small molecules is one method of molecular-size recognition; the dendrimers are the host.[3] The size of the dendrimers is also clearly defined. Therefore, the dendrimers would be hierarchically recognized as the guest. This paper describes our first experiment for the size recognition of phenylazomethine dendrimer (DPA G4, Figure 1)[4] to deliver assembled titanium compounds to the water pool of reverse micelles.

DPA G4 has 30 ligands as branching units to coordinate with metal chlorides and to assemble in a stepwise fashion.[5] We have already confirmed that DPA G4 stepwise assembles $Ti(acac)Cl_3$ (**1**, shown in Figure 2), and the Ti–dendrimer complexes are hydrolyzed in water to transform the rutile form of titanium oxide (TiO_2) nanoparticles (ca. 8 nm).[6] When the Ti–dendrimer complexes reach the water pool of the reverse micelles, hydrolysis occurs to produce TiO_2 particles.

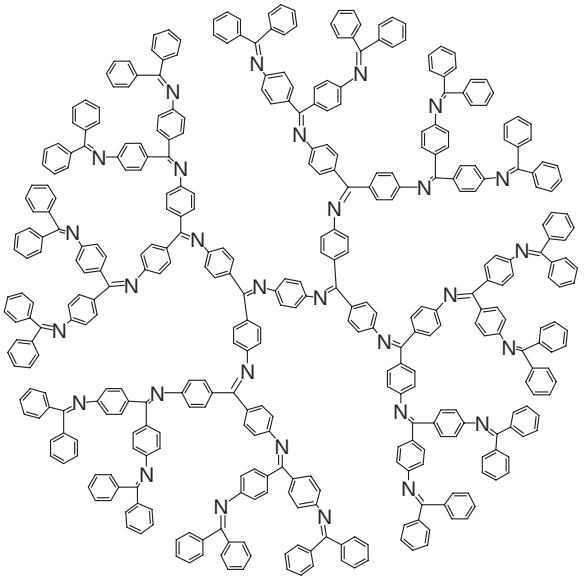

Figure 1. Fourth-generation phenylazomethine dendrimer.

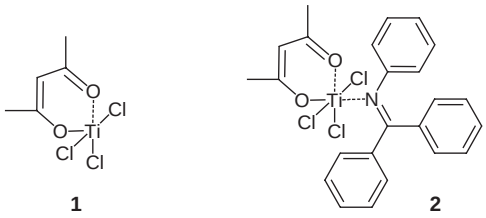

Figure 2. $Ti(acac)Cl_3$ (**1**), and Ti-model complex (**2**).

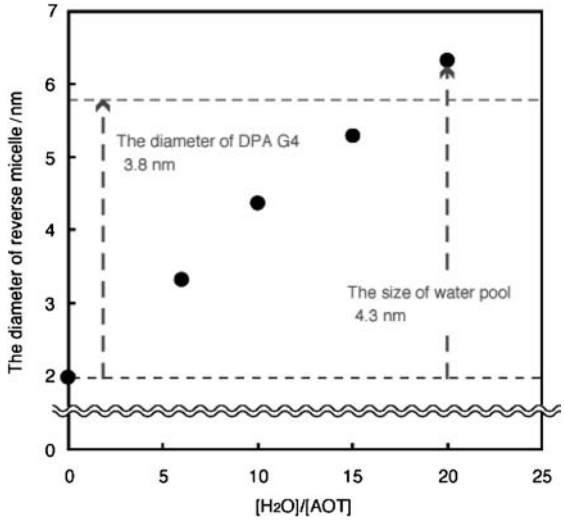

Figure 3. Diameter of reverse micelles at $[H_2O]/[AOT] = 0$–20.

The size of the water pool is adjustable by the control of the ratio of water and the surfactant, sodium bis(2-ethylhexyl) sulfonatosuccinate (AOT), $[H_2O]/[AOT]$.[7] We added various amounts of water (0–8 M) into an isooctane solution of AOT (5 mL, 100 mM) and characterized the size of the reverse micelles using a high-performance particle sizing (HPPS) system with a Malvern/Sysmex HPP5001 instrument by dynamic light scattering. The size of the reverse micelles increased from 2.0 to 6.3 nm in the region of 0–20 as $[H_2O]/[AOT]$. Thus, the size of the water pool, as entrance space for the dendrimer, is estimated to be 0–4.3 nm. We have found the dendrimer size to be 3.8 nm,[4] comparable with the water pool size at $[H_2O]/[AOT] = 20$ (Figure 3). On the other hand, we confirmed that the reverse micelles are destroyed by the addition of acid, such as HCl and HNO_3, and highly polar organic solvent, such as methanol and ethanol. Thus, we determined to add Ti-sources to the reverse micelles as an acetonitrile solution. The small amount of acetonitrile (<100 μL) does not affect the size of the reverse micelles.

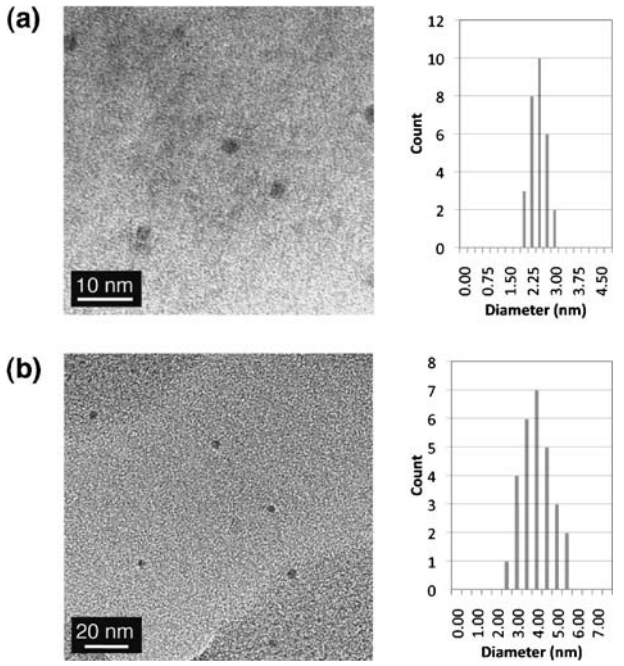

Figure 4. TEM images and histograms of TiO_2 particles obtained from Ti–dendrimer (a) and compound **1** (b).

The formed TiO_2 particles were also observed with the HPPS system after the following processes: Various amounts of water (0–8 M) were added into the isooctane solution of AOT (5 mL, 100 mM) to form the size-controlled water pool in the reverse micelles, and then the acetonitrile solution of the Ti-sources (100 μL, 1.5 mM as a Ti concentration), such as $[Ti(acac)Cl_3]_{14}$@DPA G4, $Ti(acac)Cl_3$ (**1**, shown in Figure 2), and Ti-model complex (**2**, shown in Figure 2), was added. The mixture solution was stirred 24 h at room temperature. Ethanol (1 mL) was added to the mixed solution and then collected to destroy the reverse micelles and to extract TiO_2 nanoparticles. The collected ethanol solution was filtrated through a membrane filter (0.2 μm) into a disposal cell (optical path length, 1 cm). In the blank experiment without any Ti-sources, no scattering signal was observed, indicating that the surfactant does not form the micelle structure and that the dendrimer does not exist in the collected ethanol. Even if present without transforming into TiO_2 particles, the Ti-sources quickly reacted with the added ethanol to produce titanium ethoxide. The HPPS system cannot detect such small molecules (<detectable limit; 0.6 nm).

Although the formation of particles was observed at $[H_2O]/[AOT] = 20$, no formation was observed in the region of $[H_2O]/[AOT] < 20$. The size of the water pool is larger than that of the Ti-assembling dendrimer at $[H_2O]/[AOT] = 20$. Thus, these results indicate that the size of the dendrimer recognizes that of the water pool in the reverse micelles. When the size of the water pool is larger than that of the dendrimer, the Ti-sources within the dendrimer are delivered to the water pool, resulting in the formation of TiO_2 particles.

The size of the particles obtained with the dendrimer was smaller than that of the water pool. In contrast, in a control experiment, the addition of **1** and **2** gave almost the same size particles as the water pool size. For example, the Ti–dendrimer, **1**, and **2** gave 2.1, 3.6, and 3.7 nm particles at $[H_2O]/[AOT] = 20$, respectively. The difference in the particle size was also confirmed in the TEM images (2.5 nm vs. 4.0 nm in the averages; Figure 4). The particle size obtained from **1** and **2** is consistent with the size of the water pool estimated from Figure 3. These obtained particles were stable during the measurements within a few hours at least. The 2.4 nm particle evaluated with TEM is also reported to be stable even in water at room templature.[8]

The difference in size also supports the idea that the dendrimer recognizes the water pool size. This means that the dendrimer recognizes the leftover space within the reverse micelles after the formation of the TiO_2 particles. As the particle grows within the water pool, the leftover space declines to hinder the entrance of the dendrimer. The leftover space would be useful to manufacture the controlled core/shell structure in the nanoparticles by addition of a small molecule as the source.

This work was partially supported by CREST from the Japan Science and Technology Agency, Grants-in-Aid for Scientific Research (Nos. 19205020 and 19022034) from MEXT.

References

1 a) D. A. Tomalia, *Prog. Polym. Sci.* **2005**, *30*, 294. b) S. M. Grayson, J. M. J. Fréchet, *Chem. Rev.* **2001**, *101*, 3819. c) A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665.

2 a) J. F. G. A. Jansen, E. M. M. de Brabander-van den Berg, E. W. Meijer, *Science* **1994**, *266*, 1226. b) N. Satoh, T. Watanabe, Y. Iketaki, T. Omatsu, M. Fujii, K. Yamamoto, *Polym. Adv. Technol.* **2004**, *15*, 159. c) R. Esfand, D. A. Tomalia, *Drug Discovery Today* **2001**, *6*, 427. d) C. Dufés, I. F. Uchegbu, A. G. Schätzlein, *Adv. Drug Delivery Rev.* **2005**, *57*, 2177.

3 a) F. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1681. b) S. Shinoda, *J. Inclusion Phenom. Macrocyclic Chem.* **2007**, *59*, 1. c) S. C. Zimmerman, M. S. Wendland, N. A. Rakow, I. Zharov, K. S. Suslick, *Nature* **2002**, *418*, 399.

4 a) M. Higuchi, S. Shiki, K. Ariga, K. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 4414. b) N. Satoh, J.-S. Cho, M. Higuchi, K. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 8104. c) N. Satoh, T. Nakashima, K. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 13030.

5 a) K. Yamamoto, M. Higuchi, S. Shiki, M. Tsuruta, H. Chiba, *Nature* **2002**, *415*, 509. b) R. Nakajima, M. Tsuruta, M. Higuchi, K. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 1630. c) K. Takanashi, A. Fujii, R. Nakajima, H. Chiba, M. Higuchi, Y. Einaga, K. Yamamoto, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1563.

6 N. Satoh, T. Nakashima, K. Kamikura, K. Yamamoto, *Nature Nanotechnol.* **2008**, *3*, 106.

7 a) M. L. Steigerwald, A. P. Alivisatos, J. M. Gibson, T. D. Harris, R. Kortan, A. J. Muller, A. M. Thayer, T. M. Duncan, D. C. Douglass, L. E. Brus, *J. Am. Chem. Soc.* **1988**, *110*, 3046. b) C. Burda, X. Chen, R. Narayanan, M. A. El-Sayed, *Chem. Rev.* **2005**, *105*, 1025.

8 C. Kormann, D. W. Bahnemann, M. R. Hoffmann, *J. Phys. Chem.* **1988**, *92*, 5196.

Published on the web (Advance View) December 20, 2008; doi:10.1246/cl.2009.88