Self-Assembly

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Photoinduced Release of Guest Molecules by Supramolecular Transformation of Self-Assembled Aggregates Derived from Dendrons**

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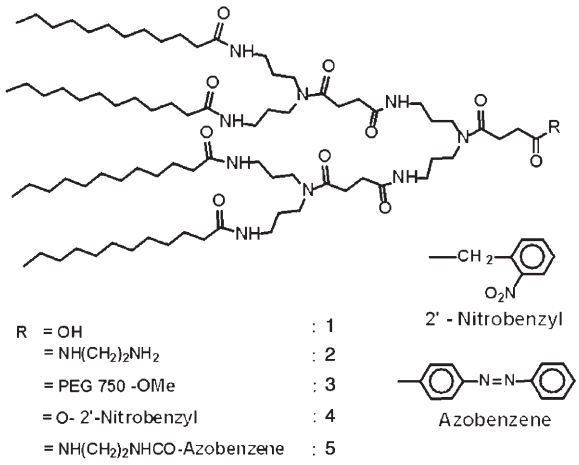
Self-assembly provides a unique way to create supramolecular functional materials.[1,2] Since a variety of supramolecules have been reported to date, the control of architectures and functions triggered by external stimuli has always been a challenging subject.[3–7]

Dendrimers and dendrons have been of great interest in a variety of scientific fields because of their unique assembly characteristics and functional performances.[8–22] Recently, we investigated the self-assembly characteristics of amide dendrons and revealed that the dendrons can self-assemble into hierachical nanostructures under various conditions.[23–30] The supramolecular structure of the amide dendrons can be controlled by tuning the focal functionality of the dendrons.[29,30] For example, photoisomerizable or photocleavable units introduced at the focal moiety could be utilized to control the photoresponsive functions of dendron-based supramolecular materials. In this regard, we envisioned that the incorporation of stimuli-responsive functional groups in the amide dendrons would be an effective approach toward the construction of well-defined stimuli-responsive nanomaterials (Scheme 1).[7] The formation of the dendritic architecture is one of the important factors for the self-organization of the amide dendrons.[23] Thus, the self-assembly of amphiphilic dendrons would provide opportunities not only for structural versatility but also for functional modulation of the stimuli-responsive materials.

Herein we describe the rational design of dendritic building blocks with a photocleavable unit that can self-assemble into a vesicular structure and can undergo a structural transformation on application of a external photostimulus (Figure 1 a,b). Furthermore, the introduction of a photoisomerizable chemical modulator at the focal moiety of the dendron would provide a tool to control the photoactivated release of guest molecules from the supramolecular aggregates of the dendrons (Figure 1 c,d). Thus, we have investigated the photoresponsive release behaviors not only of hydrophilic guest molecules from the inner water compartment but also of hydrophobic guest molecules from the membrane of the vesicles derived from the dendritic building blocks.



Scheme 1. The structure of the amide dendrons.

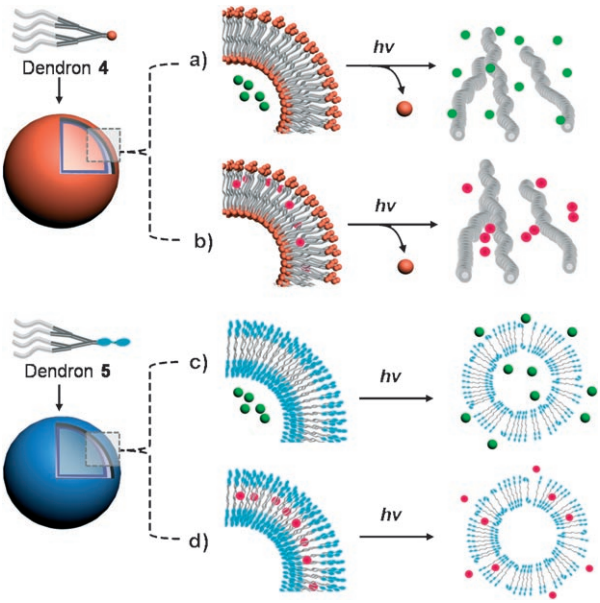


Figure 1. Schematic illustrations for the release characteristics of the vesicles of: a, b) dendron **4** and c, d) dendron **5** upon irradiation with UV light. Green sphere: calcein, Red: Nile Red.

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The photocleavable 2-nitrobenzyl ester moiety and photoisomerizable azobenzene unit were introduced at the focal point of the amide dendron to construct supramolecular structures with a photoswitchable function as shown in Scheme 1. Dendrons **1**, **2**, and **3** with the focal poly(ethylene glycol) unit ($M_n = 750$, PEG750) were prepared by following the literature procedure.[23,29,30] As summarized in Scheme 1, dendron **4** with a focal photocleavable unit was prepared by coupling dendron **1** with 2-nitrobenzyl alcohol. Dendron **5**, which contains a photoisomerizable focal moiety, was synthesized by coupling dendron **2** with azobenzene-4-carbonyl chloride. Structural characterization of the products were carried out by using ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy as well as MALDI-TOF MS (see Figure S1 in the Supporting Information).

The suparmolecular assembly and transformation of dendron **4** with a photocleavable functionality were investigated in the aqueous phase. In a basic aqueous phase, dendron **4** formed a vesicular structure (10 mM NaOH) with a hydrodynamic radius of 113 nm (PDI = 0.184), as determined by dynamic light scattering (DLS) analysis. A gel filtration experiment coupled with DLS measurements confirmed the existence of water entrapped in the interior of the spherical supramolecular assembly.

For gel filtration, an aqueous solution of a water-soluble dye—resorufin sodium salt—was added to a solution of dendron **4** in THF.[30,31] After removal of the THF under reduced pressure, the solution was passed through a Sephadex G-100 column (2.5 × 20 cm) and 36 fractions collected (2.5 mL each). All the fractions were subjected to dynamic light scattering and fluorescence measurements to obtain elution profiles. As shown in Figure 2a, the DLS and fluorescence experiments showed that the self-aggregates (average diameter 180–350 nm) containing the water-soluble dye were eluted in fractions 11–14. The vesicular structure of dendron **4** was further evidenced by investigating the release profile of the entrapped water-soluble dye molecules before and after addition of Triton X-100 (Figure 2b). In the case of the vesicle of dendron **4** loaded with resorufin sodium salt, the 12th fraction underwent self-quenching of the fluorescence, which arose as a consequence of its high local concentration inside the vesicle. After addition of Triton X-100, self-quenching no-longer occurred because of the egress of the water-soluble dye from the vesicle—the surfactant caused disruption of the vesicular membrane. The release profile was obtained by using Equation (1).

$$\text{Release percentage } (\%) = (I_t - I_0)/(I_\infty - I_0)\,100 \qquad (1)$$

I_0 is the initial fluorescence intensity, I_t is the fluorescence intensity at time t, and I_∞ is the fluorescence intensity after addition of Triton X-100. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) analysis showed the presence of spherical nanostructures with diameters of 100–200 nm in aqueous solution (10 mM NaOH; Figure 2b and Figure S2a in the Supporting Information).

Exposure of the solution to UV light ($\lambda = 350$ nm) resulted in photocleavage of 2-nitrobenzyl unit, which resulted in the absorption band of dendron **4** at 265 nm decreasing and the absorption band at 310 nm increasing (Figure 3a). The DLS autocorrelation functions were measured to investigate the assembly behavior in aqueous solution (10 mM NaOH) after irradiation ($\lambda = 350$ nm) of the vesicle solution of dendron **4** with UV light. CONTIN analysis of the autocorrelation functions showed a broad distribution of particles with an average hydrodynamic radius (R_h) of approximately 215 nm (Figure 3b). The slope of the angular dependence of the apparent diffusion coefficient (D_{app}) was found to be 0.033 (Figure 3c), which is consistent

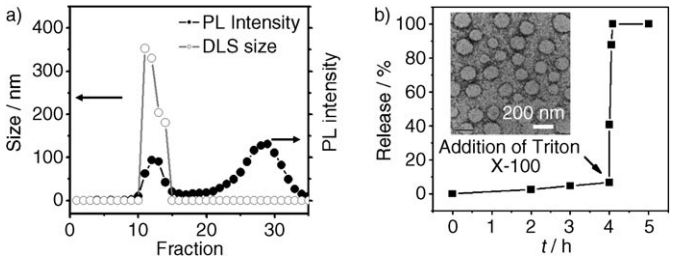

Figure 2. a) Elution profile of the gel filtration of vesicles of dendron **4** in aqueous solution (10 mM NaOH). Each fraction was subjected to DLS and fluorescence measurement. b) Release profile of resorufin sodium salt from vesicles of dendron **4**. The inset shows the TEM image of vesicles of dendron **4** in aqueous solution (10 mM NaOH).

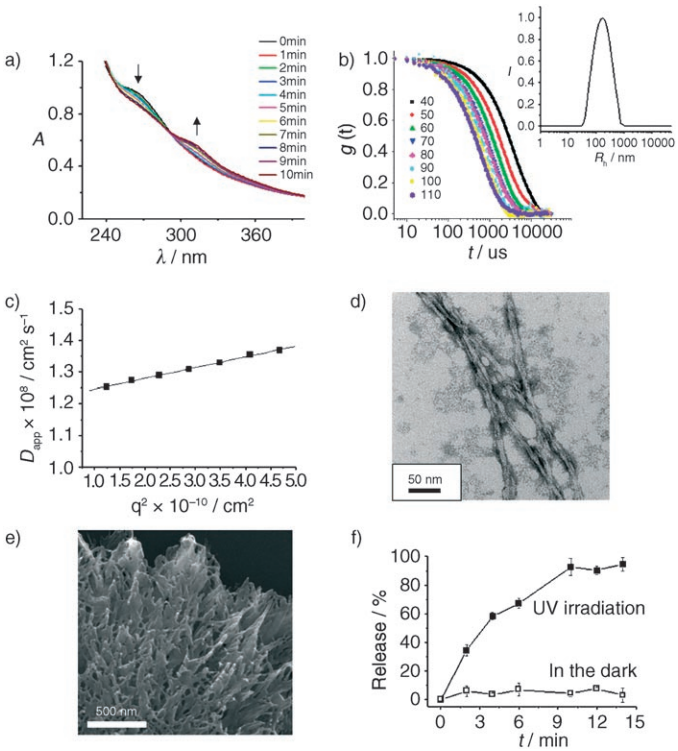

Figure 3. a) Change in the absorption spectra of vesicles of dendron **4** in aqueous solution (10 mM NaOH) in response to UV light. b) Autocorrelation functions and size-distribution histogram of a cylindrical micelle of dendron **4** (4 mg L^{-1} in H_2O) at different scattering angles. c) Angular dependence of the apparent diffusion coefficient for cylindrical micelles of **4**. d) TEM and e) SEM images of the fibrous nanostructures obtained from vesicles of **4** in aqueous phase after irradiation with UV light for 10 min (negative staining with 2 wt% uranyl acetate). f) Release profiles of calcein from vesicles of **4** in aqueous solution (10 mM NaOH).

with the value predicted for cylindrical aggregates (0.03).[32] Interestingly, a fibrous nanostructure with a width of about 10 nm was observed by TEM after irradiation of the vesicular solution of dendron **4** with UV light ($\lambda = 350$ nm; Figure 3d). The SEM experiment also revealed the fibrous suprastructure of dendron **4** after irradiation ($\lambda = 350$ nm, Figure 3e). After the photolysis, dendron **4** would be converted into dendron **1**, which can self-assemble into rodlike nanostructures in aqueous solution (10 mM NaOH), as reported previously (see Figure S2b in the Supporting Information).[29] These results indicate that the vesicles of dendron **4** undergo supramolecular reorganization to form a fibrous nanostructure after photolysis of the 2-nitrobenzyl focal moiety from the building block (dendron **4**) in aqueous solution (10 mM NaOH). Furthermore, these results suggest that the vesicles of dendron **4** can be used as photoresponsive nanocarriers. Therefore, we investigated the photoresponsive release characteristics of the vesicle. The release of calcein molecules entrapped within the vesicle of dendron **4** was suppressed in the dark (Figure 3f). However, when vesicles of dendron **4** were exposed to UV light (350 nm), the entrapped dye molecules were released from the interior of the vesicles. Most of the dye molecules were released from the vesicle after irradiation with UV light for 10 min (Figure 3f), which suggests that the photolysis of the 2-nitrobenzyl ester from dendron **4** triggers the transformation of the vesicle into the fibrous structure with concurrent release of the encapsulated molecules (Figure 1a).

For another approach to control the photoinduced release characteristics of the supramolecular aggregates of the dendron, we prepared dendron **5** with a focal azobenzene moiety which formed self-assembled structure in the aqueous phase. CONTIN analysis of the autocorrelation function showed a monomodal distribution with a translational diffusive mode (see Figure S3a,b in the Supporting Information). The average hydrodynamic radius of the aggregates formed from dendron **5** as measured by DLS was 119 nm (PDI = 0.097). The slope of the angular dependence of the apparent diffusion coefficient (D_{app}) was zero, and the size of the aggregates was constant for the investigated range of angles, which confirmed the spherical shape of the aggregates (see Figure S3c in the Supporting Information).[33] The TEM image of the self-aggregate derived from dendron **5** in an aqueous phase showed a vesicular structure (Figure 4a). The spherical shape of the aggregates was also confirmed by SEM analysis (Figure 4b). The gel filtration experiment with the resorufin sodium salt confirmed the existence of water entrapped in the interior of the spherical supramolecular assembly of dendron **5** (see Figure S4a in the Supporting Information). The 27th fraction isolated by the gel filtration experiment was observed by confocal laser scanning microscopy (CLSM), which confirmed that the water-soluble dye molecules were entrapped in the interior of the vesicle, as shown in Figure 4c. The vesicular structure was further evidenced by investigating the release profile of the entrapped water-soluble dye molecules before and after addition of Triton X-100 (see Figure S4b in the Supporting Information).

The photoresponsive release characteristics of the vesicle derived from dendron **5** were investigated. The UV/Vis spectra of the vesicles showed the changes in the absorbtion profile upon irradiation with UV ($\lambda = 350$ nm) and visible irradiation ($\lambda > 400$ nm; see Figure S5 in the Supporting Information). Upon irradiation with UV light, the UV/Vis spectra of the vesicle of dendron **5** showed an increase in the intensity of the absorption band at 425 nm and a decrease in the absorption band at 325 nm, which indicated that *trans*-to-*cis* isomerization of the focal azobenzene unit had occurred (see Figure S5 in the Supporting Information). In contrast, the absorption at 325 nm of vesicles of dendron **5** increased in intensity upon exposure of the solution to visible light. This process can be repeated with alternating irradiation with UV and visible light as shown in Figure 4e. It was confirmed through DLS and TEM experiments that the vesicular structure was not noticeably deformed by irradiation with UV light ($\lambda = 350$ nm) for 60 minutes (Figure 4d). The DLS analysis showed that the average R_h value of the vesicle was 116 nm (PDI = 0.171), which is similar to that of the vesicle before irradiation with UV light (see Figure S3b in the Supporting Information). The TEM experiment also confirmed the spherical shape of the vesicle after irradiation with UV light. However, the permeability of the vesicle was dependent on the photoisomerization of the focal azo moiety. The permeability coefficient (P) of vesicles of dendron **5** to calcein was determined as 1.0×10^{-9} cm s^{-1} at 25 °C in the dark.[34] Upon exposure to UV light ($\lambda = 350$ nm), the *cis*-azobenzene moiety in the vesicle membrane gave rise to remarkably enhanced permeability ($P = 8.6 \times 10^{-8}$ cm s^{-1}) as a result of a repulsive interaction[35] between the geometrically distorted amphiphiles, which would lead to an enhanced release of encapsulated molecules from the vesicle (Figure 4f). On the other hand, the permeability of vesicles of dendron **5** to calcein decreased after exposure to visible light

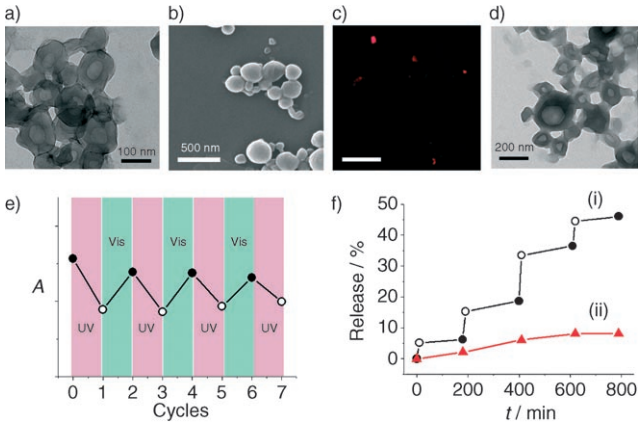

Figure 4. a) TEM and b) SEM images of the vesicle of dendron **5**. c) CLSM image of vesicles of dendron **5** with entrapped resorufin sodium salt (scale bar = 5 μm). d) TEM image of vesicles of dendron **5** after irradiation with UV light ($\lambda = 350$ nm) for 1 h. e) Change in the absorbance at 325 nm of vesicles of dendron **5** on alternately irradiating with UV and visible light. f) (i) Photocontrolled release profile of calcein from the vesicle of dendron **5** after periodic irradiation with UV and visible light. Black circles and open circles indicate irradiation with UV ($\lambda = 350$ nm) and visible light ($\lambda > 400$ nm) for 3 min, respectively. (ii) Release profile of calcein from the vesicle of dendron **5** in the dark.

($P = 1.0 \times 10^{-9}$ cm s^{-1}). The rate of calcein release increased after irradiation with UV light ($\lambda = 350$ nm) and was suppressed by exposure to visible light ($\lambda > 400$ nm), which also indicates that the photoinduced release of clacein was triggered by photoisomerization of the focal azobenzene moiety. Hence, this moiety could behave as a "valve" with an "on-off" function under specific stimulus in a photoresponsive release system (Figure 1c).

We also investigated the capability of the vesicles of **4** and **5** to release hydrophobic molecules from their hydrophobic compartment in response to UV light ($\lambda = 350$ nm) by using Nile Red, a hydrophobic fluorescent guest (Figure 1b,d). The release of Nile Red molecules from the membrane of the vesicle into the aqueous phase was monitored by fluorescence spectroscopy since the fluorescence intensity of Nile Red is lower in aqueous solution than in the hydrophobic environment of the vesicle membrane.[36,37] In the case of vesicles of **4** (Figure 5a) the fluorescence of Nile Red decreased upon irradiation with UV light, thus indicating that the release of

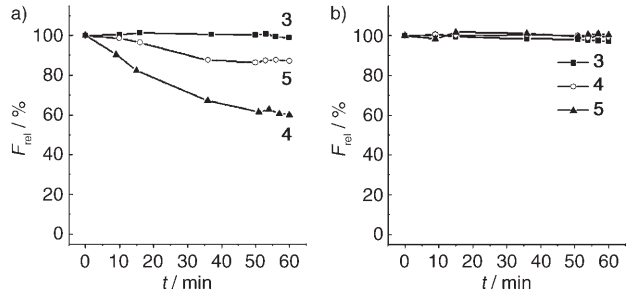

Figure 5. Change in the fluorescence of Nile Red in vesicles of dendrons **3**, **4**, and **5** upon a) irradiation with UV light ($\lambda = 350$ nm) and b) in the dark.

the guest molecules was triggered by the supramolecular transformation from the vesicle to the fibrous structure. For vesicles of **5**, Nile Red was released more slowly than from vesicles of **4** on irradiation with UV light because the vesicles of **5** maintained their vesicular structure. However, in the dark, the fluorescence of Nile Red remained constant for the vesicles of **4** and **5** (Figure 5b). In the case of vesicles of dendron **3** with the focal PEG750 unit, in contrast to the dendrons with photoresponsive functionality, the fluorescence of Nile Red did not decrease either under ambient conditions or after irradiation with UV light.

In conclusion, we have demonstrated that the self-assembly of the amide dendrons with a photoresponsive focal functionality provides an efficient route to stimuli-responsive supramolecular materials. Dendrons **4** and **5** formed vesicular structures in the aqueous phase. The vesicle of dendron **4** with photocleavable 2-nitrobenzyl ester unit was transformed into a fibrous nanostructure with concurrent release of entrapped molecules upon exposure to UV light in a basic aqueous solution. Vesicles of dendron **5** with a focal azobenzene moiety exhibited photocontrolled behavior in the release of guest molecules from the interior or the membrane of the vesicle. The use of dendritic building blocks in these supramolecular approaches would provide a unique methodology to construct stimuli-responsive smart materials.

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