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Synthesis and Self-Organization Characteristics of Amide Dendrons with Focal Ferrocenyl Moiety

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Introduction

Supramolecular materials are constructed from a variety of building blocks *i.e.* small molecules or macromolecules.[1-4] In particular, self-organization of dendritic building blocks towards supramolecular architectures has been demonstrated in a thermotropic fashion,[5] in aqueous phase,[6,12] in organic media,[7-11] and at solid-liquid interface.[11] This approach has been of great interest in that it would provide a new route to functional supramolecular materials with precise shape and functionality. In our previous studies, we reported on the amide dendrons that can self-organize not only in organic media but also in aqueous phase.[9,10,13] For example, dendron **1** forms thermoreversible supramolecular gels through self-organization of amide dendrons in organic media, and then lamella or columnar hexagonal arrays in dry state depending on the structures of the dendron building blocks. The key elements for self-organization are hydrogen bonding of the dendritic branches and van der Waals interactions of the alkyl peripheries for the stabilization of assembled structures. In addition, the amphiphilic nature due to the hydrophilic amide branches and the hydrophobic alkyl chains at the periphery provides an opportunity for the amide dendrons to self-organize in aqueous phase as well. For example, depending on the size of the hydrophilic MeO-PEG incorporated at focal moiety, the amide dendrons exhibited multiple morphologies such as vesicle, rod, and spherical micelle in water.[12] The amide dendrons with a focal moiety of methyl ester also self-organize in water.[9] The amide dendrons have capability of organizing various types of organic focal moieties into ordered states in aqueous phase.

Therefore, we reasoned that the amide dendrons should be able to organize not only organic but also organometallic focal units into ordred state. Here, we report on the self-organization behavior of the amide dendrons with organometallic focal unit, ferrocenyl moiety in this work, in organic and aqueous media. This type of self-assembly of dendrons would provide a unique methodology for the construction of supramolecular materials which have functional elements in a well-defined fashion.

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Experimental

Materials. Lauric acid, 1,1′-carbonyldiimidazole, ferrocenemethanol, ferrocenecarboxylic acid, ethylene diamine, 1,3-diisopropylcarbodiimide (DIPC, 99%), 4-(dimethylamino) pyridine (DMAP, 99%) from Aldrich were all used as received. *N*-(3-Aminopropyl)-propanediamine (98%) and triethylamine (TEA) from Aldrich were purified by vaccum distillation under calcium hydride. Succinic anhydride from Aldrich was recrystallized from *n*-hexane/acetone (2:8, v/v). Chloroform was distilled over calcium hydride before use.

Instruments. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA400 at 400 and 100 MHz respectively and were referenced to TMS. FTIR spectra were obtained using Perkin-Elmer System 2000 FTIR spectrophotometer. Elemental analysis data were obtained using CE Intstrument EA 1110. MALDI-TOF mass spectra were obtained using a Voyager Biospectrometry time of flight mass spectrometer (PerSeptive Biosystems) operated at 25 kV accelerating voltage in reflector mode with positive ionization. Dithranol (solvent: $CHCl_3$) was used as the matrix.

Dynamic Light Scattering. Dynamic light scattering measurements were performed using a Brookhaven BI-200SM goniometer and BI-9000AT autocorrelator. All the measurements were carried out at 25 °C. The sample solutions were filtered through 0.45 μm filters from Millipore. The scattered light of a vertically polarized He-Ne laser (632.8 nm) was measured at an angle of 90° and was collected on an autocorrelator. The hydrodynamic diameters (d) of micelles were calculated by using the Stokes-Einstein equation $d=k_BT/3\pi\eta D$, where k_B is the Boltzmann constant, T is the absolute temperature, η is the solvent viscosity, and D is the diffusion coefficient. The polydispersity factor of micelles, represented as μ_2/Γ^2, where μ_2 is the second cumulant of the decay function and Γ is the average characteristic line width, was calculated from the cumulant method.[15] CONTIN algorithms were used in the Laplace inversion of the autocorrelation function to obtain micelle size distribution.[16]

Transmission Electron Microscopy. Transmission electron microscopy (TEM) image was obtained by using a Philips CM 200, operated at an acceleration voltage of 80 kV. For the observation of size and distribution of vesicle particles, a drop of sample solution (concentration=60 mg/L) was placed onto a carbon-coated copper grid. About 2 min after deposi-

tion, the grid was trapped with filter paper, followed by air-drying. For the observation of the gel morphology, the gel was gently contacted on the surface of the carbon-coated copper grid. The sample on the grid was air-dried, and shadowed with Au/Pd of 10~14 Å thickness at 20° tilt angle.

Atomic Force Microscopy. Samples for the atomic force microscopy (AFM) study were prepared by transferring a drop of sample solution onto a silicon wafer and followed by air-drying. AFM images were recorded under ambient condition using a Park Scientific Instrument autoprobe CP with cantilever of ultra lever 06D, operated with non-contact mode.

X-Ray Diffraction. X-ray diffraction was carried out at the 4C1 X-ray beamline of Pohang Accelerator Laboratory. The scattered data was collected using a two-dimensional CCD detector and the X-ray wavelength was 1.608 Å.

Synthesis.

Synthesis of 1: Dendron **1** was synthesized according to a reference procedure.[9]

Synthesis of 2: Dendron **2** was prepared by coupling dendron **1** and ethylenediamine following the procedure reported previously.[13]

Synthesis of 3: A chloroform solution (50 mL) of ferrocenecarboxylic acid (0.178 g, 0.77 mmol) was added to a solution of compound **2** (0.91 g, 0.64 mmol), DIPC (197.7 μL, 1.27 mmol) and DMAP (0.021 g, 0.17 mmol) in chloroform (50 mL). After the solution was stirred for 4 h at 45 °C, the solvent was evaporated under reduced pressure. The product mixture was recrystallized from ethyl acetate and the residue was purified by silica gel (yield 0.45 g, 43.1%).

^{1}H NMR (400 MHz, $CDCl_3$) 0.84(t, J=6.8 Hz, 12H, CH_3-CH_2-), 1.17-1.21(s, 64H, -CH_2-), 1.58-1.80(br, 20H, -CH_2-CH_2-CO-, -NH-CH_2-CH_2-CH_2-N-), 2.12-2.16(m, 8H, -CH_2-CO-), 2.51-2.60(br, 12H, -CO-CH_2-CH_2-CO-), 3.10-3.53(br, 28H, -CO-NH-CH_2-, -CH_2-N-CO-, -CO-NH-CH_2-CH_2-NH-CO-), 4.00-4.22(s, 5H, FcC_5H_5), 4.21-4.80(m, 4H, FcCH); ^{13}C NMR (100 MHz, $CDCl_3$) 14.09, 22.65, 25.80, 25.85, 27.62, 27.71, 28.11, 28.50, 29.31, 29.40, 29.53, 29.60, 29.63, 31.23, 31.87, 36.62, 36.76, 39.70, 40.00, 42.68, 45.26, 68.26, 69.79, 70.53, 75.80, 171.45, 172.21, 172.35, 172.44, 172.86, 173.60, 173.91 MS (MALDI-TOF) calcd for $C_{91}H_{171}FeN_{11}O_{11}$ 1641.1. Found 1664.2 ($M+Na^+$). Anal. Calcd for $C_{91}H_{161}FeN_{11}O_{11}$: C, 66.60; H, 9.89; N, 9.39. Found: C, 66.54; H, 10.20; N, 9.10.

Synthesis of 4: A chloroform solution (50 mL) of **1** (1.0 g, 0.72 mmol) was added to a solution of ferrocenemethanol (0.18 g, 0.83 mmol), DIPC (226 l ,1.44 mmol) and DMAP (0.022 g, 0.18 mmol) in chloroform (50 mL). After the solution was stirred for 4 h at 45 °C, the solvent was evaporated under reduced pressure and the product was recrystallized from THF (yield 1.04 g, 91 %).

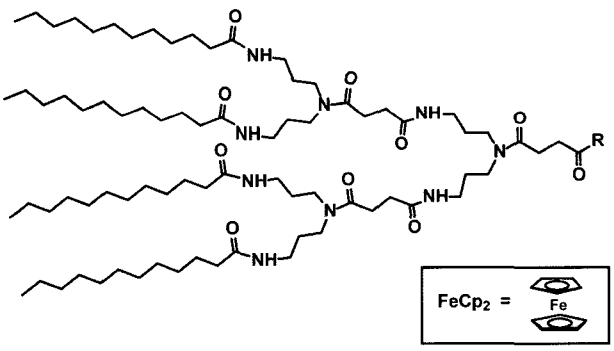
^{1}H NMR (400 MHz, $CDCl_3$) 0.85(t, J=6.9 Hz, 12H, CH_3-CH_2-), 1.20-1.25(s, 64H, -CH_2-), 1.59-1.70(br, 20H, -CH_2-CH_2-CO-, -NH-CH_2-CH_2-CH_2-N-), 2.11-2.15(m, 8H, -CH_2-CO-), 2.56-2.64(br, 12H, -CO-CH_2-CH_2-CO-), 3.12-3.35 (br, 24H, -CO-NH-CH_2-, -CH_2-N-CO-), 4.08-4.22(m, 5H, FcC_5H_5), 4.15-4.23(m, 4H, FcCH), 4.85-4.90(s, 2H, -COO-CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) 14.03, 22.59, 25.76, 25,79, 27.17, 27.61, 27.93, 28.44, 29.26, 29.36, 29.47, 29.54, 29.58, 30.99, 31.82, 36.38, 36.53, 36.72, 42.75, 45.20, 62.72, 69.30, 69.91, 81.87, 171.50, 172.21, 172.40, 172.76, 173.03, 173.56, 173.91 Anal. Calcd for $C_{84}H_{157}N_9O_{11}$: C, 67.44; H, 9.98; N, 7.95. Found: C, 67.28; H, 10.20; N, 8.25.

Results and Discussion

The amide dendrons with focal ferrocene moiety were prepared via a convergent method. The ferrocenyl unit was coupled with dendron **1** which was synthesized following the procedure reported previously.[9] Dendron **1** was treated with 1,1'-carbonyldiimidazole in chloroform, and subsequently reacted with an excess amount of ethylenediamine to obtain dendron **2** which contains focal amine functionality (Scheme I). Ferrocenecarboxylic acid was then allowed to react with dendron **2** in the presence of 1,3-diisopropylcarbodiimide (DIPC) and 4-(dimethylamino)pyridine (DMAP) to yield dendron **3** in which ferrocene unit was coupled to the focal carboxyl moiety of dendron **1** via short spacer with amide linkage. Dendron **4** was obtained by coupling of ferrocenemethanol with dendron **1** in the presence of DIPC and DMAP. The structure of the dendrons was confirmed by using ^{1}H NMR, ^{13}C NMR, MALDI-TOF, and elemental analysis.

The self-organization behaviors of dendrons **3** and **4** were investigated both in organic media and in aqueous phase. Dendrons **4** formed gels in organic media such as toluene, toluene/decanol (8:2 v/v,), *n*-hexane/n-decanol (8:2 v/v),

Scheme I



R = OH : **1**
R = $NHCH_2CH_2NH_2$: **2**
R = $NHCH_2CH_2NHCOFeCp_2$: **3**
R = OCH_2FeCp_2 : **4**

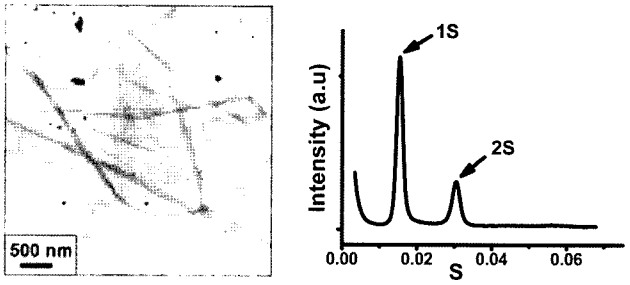


Figure 1. TEM image and XRD data of gels of dendron **4**. S($Å^{-1}$) = ($n\lambda$/ 2 sinθ).

and cyclohexane/*n*-decanol (8:2, v/v) with the concentration range of 1~3 wt%. The gel formation was thermoreversible. For example, in toluene (3 wt%), a homogeneous solution was observed above 90 °C. After cooling to room temperature, immobile gel was obtained after several hours. The structure of the dry gel was characterized by using transmission electron microscopy (TEM) and X-ray diffraction (XRD) techniques. The TEM image of the dry gel from 3 wt% solution showed thin fibrous morphologies (Figure 1). XRD measurement of the dendron **4** showed two sharp reflections corresponding to a lamellar structure with *d* spacing of 65.2 Å (Figure 1). Considering the dimension of the fully-stretched dendron **4** (40 Å), it is suggested that the lamellar spacing is associated with two dendron building blocks. Therefore, the non-polar alkyl peripheries from two dendron molecules are expected to stretch outward, while the polar amide branches with ferrocenyl unit would be placed in the central region of a lamellar layer. The gel formation of dendron **4** in organic media is possibly due to the formation of three dimensional network of the lamellar nanoribbons.[7-11] Dendron **3**, however, does not form gels in organic media but precipitates possibly because the extra amide bonds present in the spacer might accelerate the precipitation due to enhancement of hydrogen bonding between the dendrons through additional amide bonds.

The self-organized structure of dendron **3** and **4** in aqueous phase was characterized by using dynamic light scattering (DLS), SEM, TEM, AFM, and gel-filtration experiment. In aqueous phase, dendrons **3** and **4** form stable vesicles with average diameter of 182 and 229 nm respectively. The microscopic images from SEM, TEM, and AFM exhibited spherical or globular morphology (Figure 2). The gel filtration experiment coupled with DLS revealed the existence of water entrapped in the interior of the spherical supramolecular assembly. For gel-filtration experiment,[17-19] an aqueous solution of resorufin sodium salt (0.14 mM, 10 mL) was added to a THF solution of the dendron sample (0.5 mg). After removal of THF under reduced pressure, the solution (0.5 mL) was passed through a sephadex G-100 column (2.5 × 20 cm) to collect 40~50 fractions (2 mL each). All the fractions were subjected to dynamic light scattering and fluorescence measurements to obtain elution profiles and confirm the existence of water entrapped in the self-organized aggregates (Figure 3). The vesicular structure was further evidenced by investigating the release profile of the entrapped dye molecules before and after addition of Triton X-100. After addition of Triton X-100 which dissolves vesicular membranes, a prompt release of the water-soluble dye

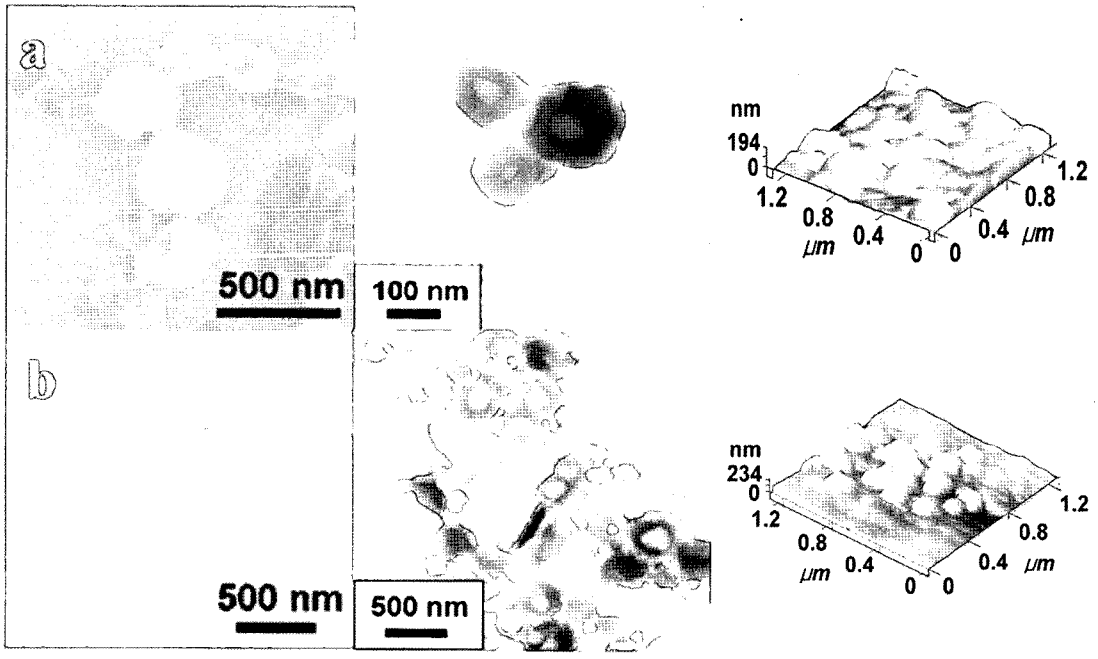


Figure 2. SEM, TEM, and AFM images of vesicles from dendron **3** (a) and dendron **4** (b).

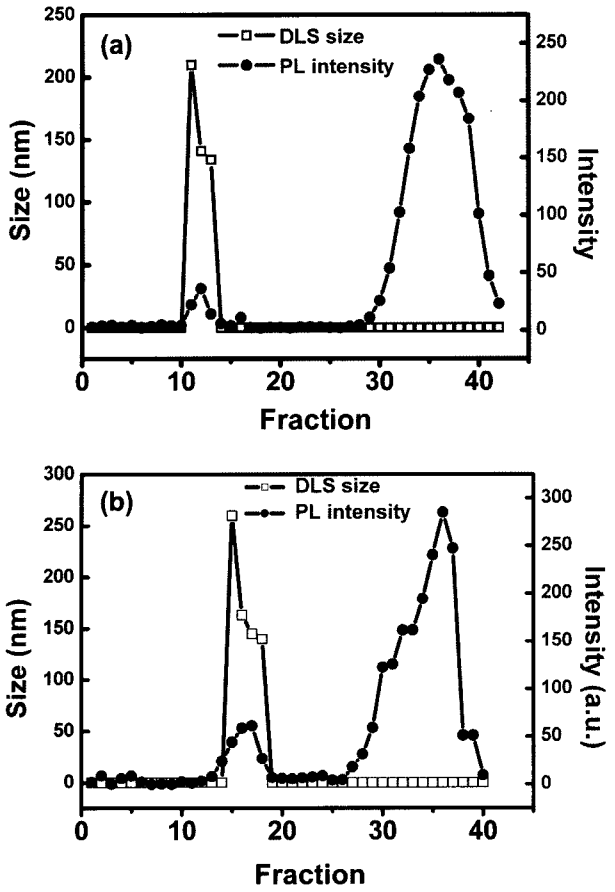


Figure 3. Elution profile in gel filtration of dendron **3** (a) and dendron **4** (b). Each fraction was subject to DLS and fluorescence measurement.

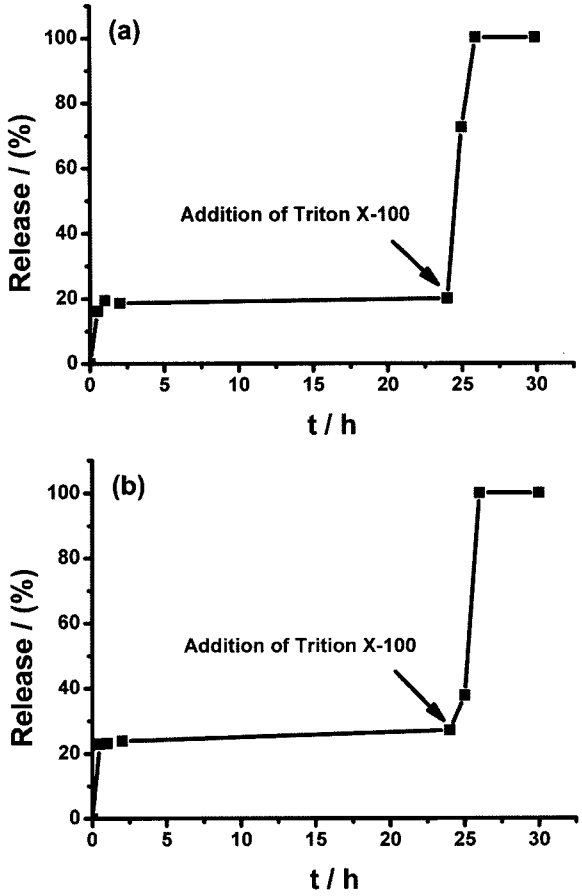


Figure 4. Release profile of the dye from the vesicles of dendron **3** (a) and dendron **4** (b).

molecules from the interior of the vesicle is observed (Figure 4).[14,17,18] The dye release profiles were calculated using following formula,

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

where I_0 is initial fluorescence intensity, I_t is fluorescence intensity at time t, and I_∞ is fluorescence intensity after addition of Triton-X 100.[17,18] The hydrophilic amide branches are expected to be exposed to the aqueous phase with the ferrocenyl moieties at the interfacial region between the vesicular membrane and water.

In summary, the amide dendrons with focal ferrocenyl moiety self-organize not only in organic media but also in aqueous phase. In toluene, dendron **4** forms thermoreversible gel which shows lamellar structure in dry state. The structural motif of self-organization in organic media would be hydrogen bonding of amide dendritic branches and van der Waals interactions of alkyl peripheries. In aqueous phase, dendrons **3** and **4** form stable vesicles due to the balance between hydrophilic amide branches and hydrophobic peripheries. The amide dendrons have unique characteristics of enforcing a variety of focal units into organized states. This approach would offer effective methodology to construct supramolecular materials with a variety of focal functional elements.

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