

Synthesis and Assembly of Amphiphilic Tadpole-Shaped Block Copolymers Based on Poly(amido amine) Dendrimer

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ABSTRACT: A concept of “three-dimensional space architectures” by dendrimer-based nano-organized systems having “inter- and intradendrimer cavities” linked with each other through an peripheral array of tailor-made surface substituents with controlled permeability was presented from the standpoint of utilization of amphiphilic dendrimers. As a systematic study on macromolecular design of amphiphilic dendrimers, two tadpole-shaped block copolymers, AB-type linear polymer/dendrimer block copolymers, were synthesized by two different synthetic methodologies. A novel amphiphilic *surface-N-hexylamide-type poly(amido amine) (PAMAM) dendrimer (generation 2.5) / polysarcosine (poly(*N*-methylglycine)) block copolymer 4* was synthesized by living ring-opening polymerization of sarcosine *N*-carboxyanhydride initiated with a *core*-monofunctional PAMAM dendrimer. An aqueous solution of poly(2-methyl-2-oxazoline)-*block*-poly(amido amine) dendrimer (**9**) (generation 3.5, 4.5, and 5.5), prepared by divergent dendrimer construction from ω -end-functionalized polyoxazoline, showed critical micelle concentrations (CMCs). The CMC values decrease as the generation of the dendrimer increases, which means that the large globular dendrimer with a strong hydrophilic polyoxazoline linear tail tends to gather on the air/water interface more efficiently than the copolymer having the small oblate dendritic block. Small angle neutron scattering (SANS) investigations of a D₂O solution of the dendrimer-containing block copolymer **9** ($G = 5.5$) suggested formation of a spherically assembled mesoscopic structure of 54 nm diameter with an aggregation number of ca. 2.4×10^3 , while the diameter of the dendritic block was estimated to be 3.2 nm.

KEY WORDS Dendrimer / Block Copolymer / Living Polymerization / Ring-Opening Polymerization / Amphiphilicity / Mesoscopic Materials / Small Angle Neutron Scattering /

As an elemental building block of supramolecular architecture,¹ globular dendrimers are interesting and important,²⁻⁶ since dendrimer-based amphiphiles have definite molecular size and shape. Distinct from conventional linear polymers, common dendrimers²⁻⁶ themselves have a great feature of an inner cavity⁷ and an ideally spherical molecular surface in a nanometer order.

Based on bio-inspired molecular architecture combined with natural biomolecules and spherical polymers, we have already reported globular carbohydrate macromolecule “Sugar Balls” having geometrically controlled sugar residues on the sphere.⁸⁻¹² In the previous paper,⁸ we have stated that versatile supramolecular assemblies and covalent architecture of sugar-carrying biofunctional molecules should be achieved by the facile synthesis of globular sugar balls. Further sophisticated molecular design has been shown using a surface-block dendritic structure with natural oligosaccharide-like sugar residues on the periphery of the hemisphere.⁹ In the present article, concepts of (a) hybridized dendrimer-based nano-organized systems and (b) a higher-order structural hierarchy of the organized molecular systems of dendrimers are proposed after this introductory remark.

Concept

As a concept of “functional space architecture,” dendrimer-based nano-organized systems have a significant feature to generate “inter- and intradendrimer pockets” connected each other through peripheral substituents arranged around the globular molecule with regulated permeability. By using amphiphilic block dendrimers, e.g.,

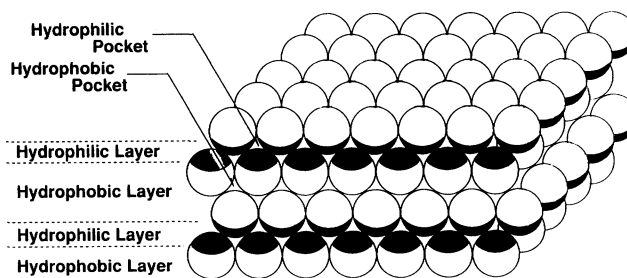


Figure 1. Illustration of a packed layer assembly of surface-block dendrimers or segment-block dendrimers with inter- and intradendrimer cavities. Alternative hydrophilic and hydrophobic interdendrimer pockets are linked with each other by angstrom- to nano-size channels. The surface of the assembly consists of continuous peripheries. High-generation dendrimers with dense peripheries would provide the globular model, while deformed low-generation dendrimer will also offer assemblies with interdendrimer cavities and flat surface.

surface-block dendrimers,⁹ as an elemental structure, hybridized packed layer assemblies will be formed by accompanying hydrophilic and hydrophobic interdendrimer cavities with repeated sequence in a nanometer scale as schematically illustrated in Figure 1. Recognition and selection of guest molecules might be tuned in wide ranges of size, shape, and chemical structure. Mobility and an amount of guest molecules will be controlled between the hydrophilic and hydrophobic pockets by designing peripheral structure of dendrimers. Creation of function induced by an assembly of molecules is regarded as “functional organization.” The superstructure of the amphiphilic spherical molecule with a variety of cavities will offer a new class of mesoscopic functional materials, which can be, for instance, applied as new reaction media and catalytic systems. Organic and inorganic higher-order

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hybridized systems with a nano-scale sequence can be designed.¹³ Additionally, degradation of the organic component would produce an ordered structure of the inorganic multicomponent with spatial distribution control. Furthermore, the dendrimer-based nano-organized systems provide a new type of surface of materials with continuous hemisphere packed flatly on a nano-level. The surface design using dendrimers should open a new aspect in materials science, since it can be utilized for various applications, e.g., coating technology and electronic, optical, and biochemical applications.^{14,15}

Assemblies on the basis of dendrimers potentially lie at a higher hierarchy of structural order and regularity as mesoscopic functional materials, in comparison with a conventional higher-order supramolecular assemblies, since a dendrimer itself is regarded as a unimolecular micelle² (Figure 2). Actually, one globular dendrimer molecule has outstanding features such as an inner cavity, an isolated center core, and arranged functionality on the periphery, which have been hitherto given by supramolecular organization of a low-molecular-weight amphiphile. Even simple assemblies of homodendrimers generate three-dimensionally alternative structures of inter- and intradendrimer space easily. In contrast, to pile up this organization, second association of the first supramolecular self-assembled structure is required, conventionally. Versatile materials design would be feasible by the dendrimer cluster.

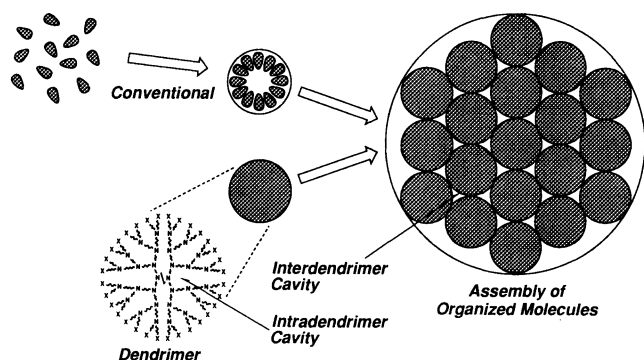


Figure 2. Conceptual building pathways toward higher-order superstructures by amphiphilic dendrimers and by stepwise self-assembling supramolecular systems.

Amphiphilic block structures of dendrimers are of importance toward mesoscopic macromolecular design in order to control size, shape, topology, and character of the assembled structure. To this end, surface-block dendrimers and linear polymer/dendrimer block copolymers supply typical amphiphilic structures.^{3,4} Therefore, development of precise, three-dimensional macromolecular architecture on the basis of stepwise dendrimer construction and living polymerization is necessary to accumulate information concerning the relationship between the self-associate mesostructure and the covalently bonded elementary structure. This article describes a fundamental synthetic study of the latter tadpole-shaped amphiphile.^{16,17} Although dendrimer chemistry is growing rapidly, a few synthetic examples of linear polymer/dendrimer block copolymers have been reported until now.^{16,18-21} As functional dendrimer-containing block copolymers, studies

on tadpole-shaped polymers would increase, considering their relatively simple synthetic routes.

EXPERIMENTAL

Materials

Commercially available methyl acrylate, ethylenediamine, *n*-hexylamine, methyl trifluoromethanesulfonate, and 2-methyl-2-oxazoline (Aldrich Chemical Co.) were purified by repeated distillations under a nitrogen atmosphere. Sarcosine *N*-carboxyanhydride (NCA), i.e., *N*-methylglycine NCA, was prepared according to the literature,²² and purified by repeated recrystallization from 1,4-dioxane to hexane under nitrogen.

Ring-Opening Polymerization of Sarcosine NCA with core-Amine-type Poly(amido amine) (PAMAM) Dendrimer (Generation 2.5) Having Terminal Hexyl Groups (3)

In a test tube equipped with a three-way stopcock and a magnetic stirring bar, 38.3 mg (0.333 mmol) of sarcosine NCA was dissolved in 3.78 ml of dry chloroform under a nitrogen atmosphere. To the solution, 111 mg (26.8 μ mol) of **3** was added by using a gastight syringe. The solution was stirred at 27 °C for 60 hours. The product was purified by repeated reprecipitations from methanol to diethyl ether. White powdery product was obtained in 88.7% yield (119 mg).

4: IR (KBr) 3080 ($\nu_{\text{N-H}}$), 2958, 2928, 2856 ($\nu_{\text{C-H}}$), 1650 ($\nu_{\text{C=O}}$, amide), 1554 ($\delta_{\text{N-H}}$, amide), 1097, 1031, 800 cm^{-1} . ¹H NMR (CDCl_3 , TMS, 27 °C, 400 MHz) δ = 7.96 (broad, NH), 7.66 (broad, NH), 7.36 (broad, NH), 4.40-3.86 (m, CH_2 of polysarcosine), 3.26 (broad, $\text{NHCH}_2\text{CH}_2\text{N}$), 3.17 (m, $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 3.13-2.84 (m, CH_2 of polysarcosine), 2.76 (broad, $\text{NCH}_2\text{CH}_2\text{CONH}$), 2.57 (broad, $\text{NHCH}_2\text{CH}_2\text{N}$), 2.36 (broad, $\text{NCH}_2\text{CH}_2\text{CONH}$), 1.49 (m, $\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.28 (m, $(\text{CH}_2)_3\text{CH}_3$), 0.88 (m, $(\text{CH}_2)_5\text{CH}_3$). ¹³C NMR (CDCl_3 , 27 °C, 100 MHz) δ = 172.6 (CONH), 168.4 (CO of polysarcosine), 52.5 ($\text{NHCH}_2\text{CH}_2\text{N}$), 50.4 ($\text{NCH}_2\text{CH}_2\text{CONH}$), 49.4 (CH_2 of polysarcosine), 39.6 ($\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 37.6 ($\text{NHCH}_2\text{CH}_2\text{N}$), 35.8 (CH_3 of polysarcosine), 34.3 ($\text{NCH}_2\text{CH}_2\text{CONH}$), 31.6 ($\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 29.6, ($\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 26.8, ($\text{CH}_2\text{CH}_2\text{CH}_3$), 22.6, (CH_2CH_3), 14.1 ($(\text{CH}_2)_5\text{CH}_3$).

ω -N,N,N'-Tris(methoxycarbonyl)ethyl)ethylenediamine-Terminated Poly(2-methyl-2-oxazoline) (7) ¹⁶

IR (KBr) 2950 ($\nu_{\text{C-H}}$), 1740 ($\nu_{\text{C=O}}$, ester), 1640 cm^{-1} ($\nu_{\text{C=O}}$, amide). ¹H NMR (CDCl_3 , TMS, 27 °C, 400 MHz) δ = 3.69 (s, CH_3O), 3.46 (broad, CH_2 of polyoxazoline and $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3)_2$), 3.05 (m, CH_3N), 2.85 (m, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3)_2$), 2.66 (t, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.48 (t, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.15, 2.12, 2.09 (m, CH_3 of polyoxazoline). ¹³C NMR (CDCl_3 , TMS, 27 °C, 67.8 MHz) δ = 173.2 (CO_2CH_3), 170.4 (CH_3CO), 51.8 (CH_3O), 50.6 ($\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 48.5-43.5 ($\text{NCH}_2\text{CH}_2\text{N}$), 34.8 ($\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 21.2 (CH_3 of polyoxazoline).

*Poly(2-methyl-2-oxazoline)-block-poly(amido amine) dendrimer ((generation 0) (8 (G = 0))*¹⁶

IR (KBr) 3450 ($\nu_{\text{N-H}}$), 2950 ($\nu_{\text{C-H}}$), 1640 cm^{-1} ($\nu_{\text{C=O}}$, amide). ^1H NMR (CDCl_3 , TMS, 27 °C, 400 MHz) δ = 3.45 (broad, CH_2 of polyoxazoline and $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2)_2$), 3.27 (m, $\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 3.06, 2.96 (m, CH_3N), 2.85 (m, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2)_2$), 2.80 (m, $\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 2.63 (m, $\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 2.36 (m, $\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 2.16, 2.13, 2.09 (m, CH_3 of polyoxazoline). ^{13}C NMR (CDCl_3 , TMS, 27 °C, 100 MHz) δ = 174.1 ($\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 171.9 (CH_3CO), 50.4 ($\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 48.9 ($\text{NCH}_2\text{CH}_2\text{N}$), 40.5 ($\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 38.9 (CH_2NH_2), 35.9 ($\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 21.9 (CH_3 of polyoxazoline).

*Poly(2-methyl-2-oxazoline)-block-poly(amido amine) dendrimer (generation 5.0) (8 (G = 5.0))*¹⁶

IR (KBr) 3450 ($\nu_{\text{N-H}}$), 2950 ($\nu_{\text{C-H}}$), 1640 ($\nu_{\text{C=O}}$, amide), 1560 cm^{-1} ($\delta_{\text{N-H}}$, amide). ^{13}C NMR (D_2O , sodium 2,2-dimethyl-2-silapentane-5-sulfonate, 27 °C, 100 MHz) δ = 177.9 (CONH), 177.3, 177.0 (CH_3CO), 53.9 ($\text{NHCH}_2\text{CH}_2\text{N}$ of PAMAM), 51.6 ($\text{CH}_2\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 49.8-45.6 ($\text{NCH}_2\text{CH}_2\text{N}$), 42.8 ($\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 42.3 (CH_2NH_2), 39.4 ($\text{NHCH}_2\text{CH}_2\text{N}$ of PAMAM), 35.4 ($\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{NH}_2$), 22.8 (CH_3 of polyoxazoline).

Measurement

^1H and ^{13}C NMR spectra were recorded by a Bruker ARX-400 spectrometer operating at 400 MHz (^1H) and 100 MHz (^{13}C), or by a JEOL JNM-EX-270 operating at 270 MHz (^1H) and 67.8 MHz (^{13}C). IR spectra were taken with a JASCO FT/IR-610 spectrophotometer. Size exclusion chromatography (SEC) was performed by a Tosoh HLC-8020 high performance liquid chromatography (HPLC) system (column, Tosoh TSK-Gel G3000H_{XL} and G2000H_{XL}; eluent, chloroform; flow rate, 1.0 ml/min; temp., 38 °C), by a JASCO Model BIP-1 HPLC system (column, Shodex KF803 and KF804; eluent, dimethyl sulfoxide; flow rate, 0.4 ml/min; temp., 27 °C), or by a JASCO PU-980 system (column, Pharmacia Biotech Superdex 75HR 10/30 or 200HR 10/30; eluent, methanol/50 mmol/l K_2HPO_4 aq. (3:7 (v/v))); flow rate, 0.5 ml/min; temp., 27 °C). Turbidity of complex was analyzed by a Molecular Devices SPECTRAMax 250 microplate reader photospectrometer.

Surface tension γ values were obtained by the drop weight method.²³ Molecular areas of amphiphiles adsorbed at the air/water interface were calculated according to the literatures.^{23,24}

Small angle neutron scattering (SANS) measurement was performed on a cold neutron small-angle scattering instrument SANS-U at JRR-3M of the Japan Atomic Energy Research Institute, Tokai (the beam wavelength of the spectrometer, 7 Å; the scattering vector Q range, 0.004-0.08 Å⁻¹; temp., 25 °C; the sample thickness, 4 mm).

RESULTS AND DISCUSSION

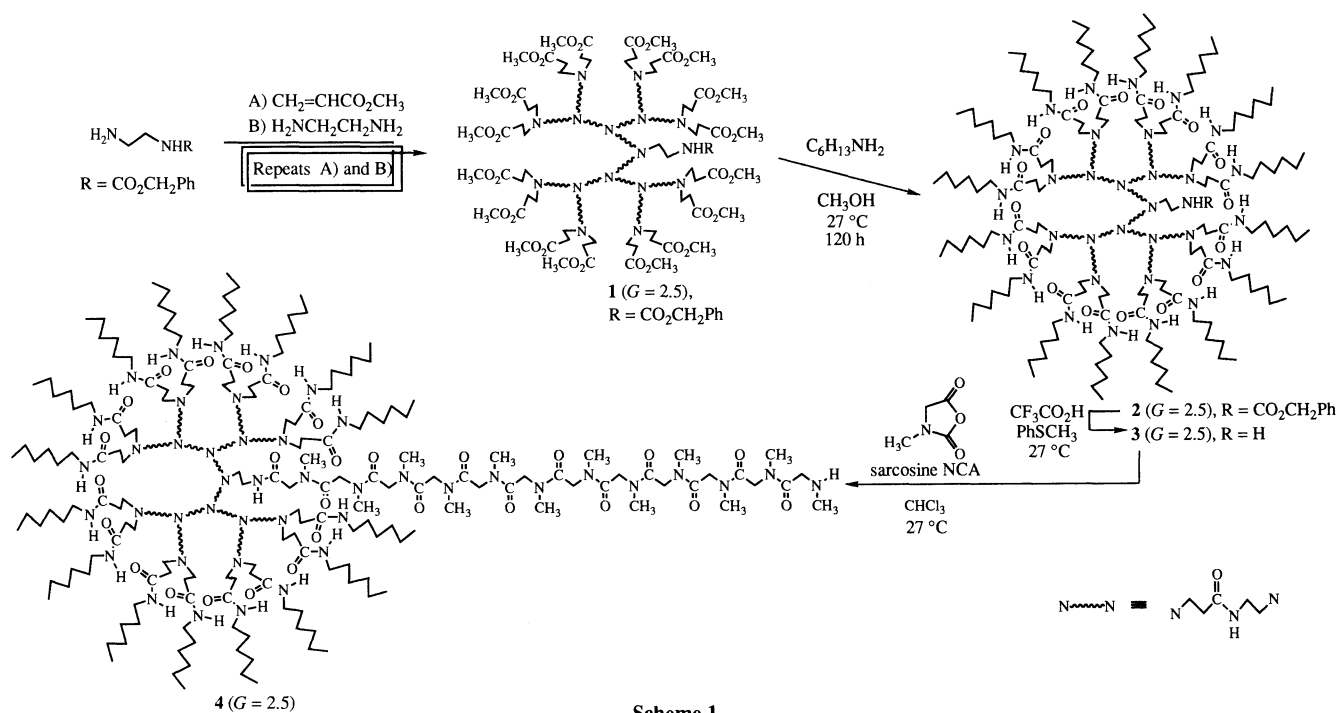
Living Polymerization Initiated with a Monofunctional Dendrimer

Synthetic approaches to tadpole-shaped dendrimers, linear polymer/dendrimer block copolymers, are classified into three patterns, i.e., (a) living polymerization initiated with a monofunctional dendrimer, (b) divergent-growth dendrimer construction from an end of a living polymer, and (c) coupling between a living polymer and a monofunctional dendrimer. The third method is supposed to involve inevitable contamination of homopolymers due to reduced coupling efficiency by steric hindrance of a focal point of a dendron. For this reason, the first and the second synthetic routes are studied in the present article.

A novel tadpole-shaped block copolymer, *surface-N*-hexylamide-type poly(amido amine) (PAMAM) dendrimer (generation 2.5) / polysarcosine block copolymer **4** ($G = 2.5$) was synthesized by means of living polymerization initiated with a *core*-monofunctional dendrimer. Polysarcosine is a polymer of *N*-methylglycine, naturally occurring amino acid. In order to prepare a well-defined amphiphilic block copolymer easily in homogeneous organic reaction media, we chose a synthetic way of *hydrophilic* linear chain extension with a *hydrophobic* dendritic initiator, instead of *hydrophobic* chain growth initiated with a *hydrophilic* dendrimer. Quantitative initiation of living polymerization with the *core*-functionalized dendrimer is the key to precise macromolecular architecture of the block copolymer of a dendritic globule connected with a linear tail.

As a dendritic block, *core-Z*-protected PAMAM dendrimer **1** ($G = 2.5$) was prepared according to the previously reported procedure.⁹ In the present case, terminal hexyl-persubstituted dendrimer **2** ($G = 2.5$) was synthesized by the reaction of *n*-hexylamine with *surface*-methyl ester-type half-generational *core-Z*-protected PAMAM dendrimer **1** ($G = 2.5$) in methanol at 27 °C under a nitrogen atmosphere, according to Scheme 1. Deprotection of the *Z*-group of the center core was readily performed by using trifluoroacetic acid in the presence of thioanisole at 27 °C via a push-pull mechanism, to generate a free amino-group at the initiator core of **3** ($G = 2.5$).²⁵

A linear tail attached to the dendritic globule was synthesized by living polymerization of sarcosine *N*-carboxyanhydride (NCA), i.e., *N*-methylglycine NCA, initiated by the *core*-amino-functional poly(amido amine) dendrimer **3** ($G = 2.5$). Due to the *N*-alkyl-substituted monomer, ring-opening polymerization of sarcosine NCA is suitable for hydrophilic peptide-related chain formation with a controlled chain length by clean propagation mechanisms without side reactions. Polymerization of sarcosine NCA was carried out with **3** ($G = 2.5$) in chloroform at 27 °C for 60 h. The resulting polymer **4** ($G = 2.5$) was purified by reprecipitation from methanol into diethyl ether. The chemical structure of the tadpole-shaped block copolymer was confirmed by NMR and IR analyses. Signals ascribed to methyl and methylene groups of newly formed polysarcosine chain were observed at 35.8 and 49.4 ppm, respectively, in the ^{13}C NMR spectrum of **4**. Neither unreacted α - and β -methylene carbons of the *core*-amino



group of the initiator **3** were detected in the spectrum. A molecular weight distribution of **4** was estimated by size exclusion chromatography (SEC). The M_w/M_n value was 1.05, which is reasonably narrow on the account of a Poisson distribution of the linearly propagated chain. The degree of polymerization (DP = 12) of the polysarcosine segment of **4** ($G = 2.5$), as determined by the ^1H NMR spectrum, was in good agreement with the feed molar ratios of sarcosine NCA to **3** ($G = 2.5$) ($[\text{sarcosine NCA}]_0/[\mathbf{3}]_0 = 12.4$). These results suggest that controlled polymerization initiated from an inner core of dendrimer is possible. Monomers and reagents will diffuse freely inside dendrimers in an appropriate solvent.²⁶ As expected, no side reaction between the *N*-substituted NCA monomer and tertiary amino groups of dendritic branching points of **3** ($G = 2.5$) occurs inside the dendrimer.

Solubility of **4** ($G = 2.5$) was examined to discuss amphiphilic character of the dendrimer-containing tadpole-shaped polymer qualitatively. The block copolymer **4** ($G = 2.5$) was soluble in water, methanol, ethanol, *N,N*-dimethylformamide, dimethyl sulfoxide, and chloroform at a concentration of 1.0 mg/ml, while the polymer was insoluble in diethyl ether and hexane. Although PAMAM dendritic skeleton is hydrophilic, hexyl group-persubstituted dendritic block **2** ($G = 2.5$) was insoluble in water. Thus, hydrophilicity of the block copolymer **4** ($G = 2.5$) increased by introduction of water-soluble polysarcosine chain.

In the SEC profile of **4** ($G = 2.5$) using a mixed eluent of methanol and 50 mmol/l K_2HPO_4 aq. (3:7 (v/v)), aggregate formation was interestingly observed in addition to a peak of the unimolecular amphiphile. The M_n value of the aggregate was estimated to be $> 1 \times 10^5$ by the SEC. Even though the hexyl group is a short hydrophobic group, it is suggested that a bundle of the short alkyl groups on a dendrimer functions as an efficient hydrophobic part.

A surface tension measurement of an aqueous solution of **4** ($G = 2.5$) was carried out in order to investigate the assembled structure on the air/water interface. Critical micelle concentration (CMC) was observed at a

concentration of 0.09 wt%. The γ value at the CMC (γ_{CMC}) was 28 mN/m, which suggests terminal alkyl groups of the dendritic block are arranged on the surface. The mean area, i.e., the *A* value, of a terminal group at the air/water interface was $23 \text{ \AA}^2/\text{terminal unit}$. It is presumed that the block copolymer is on the surface as illustrated in Figure 3, since end groups of low-generational dendrimers should be able to align in one direction.

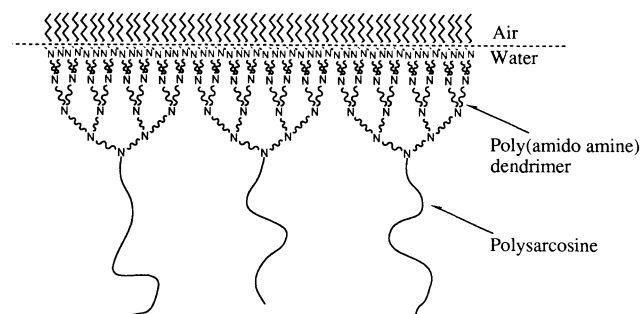
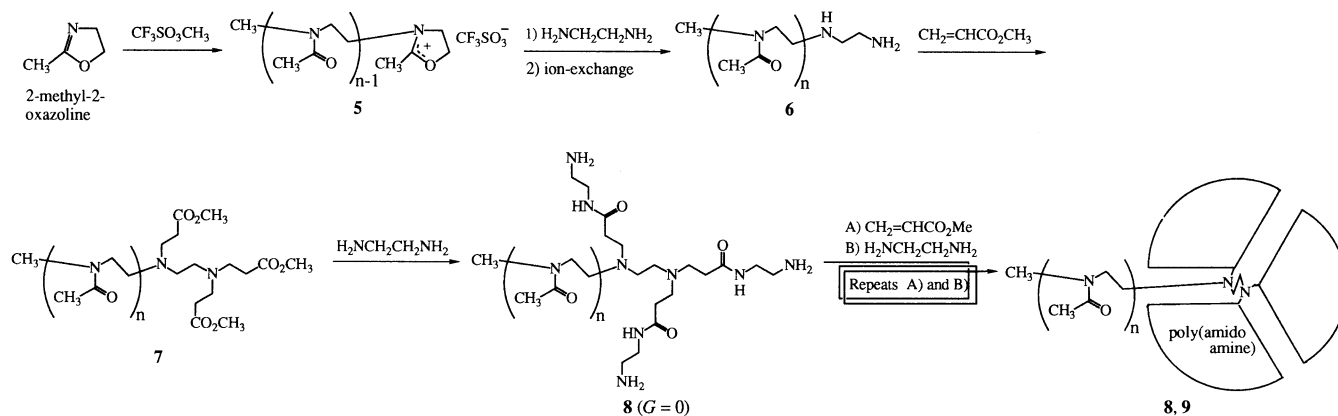


Figure 3. A schematic illustration of an assembly of dendrimer-containing block copolymer **4** ($G = 2.5$) on an air/water interface.

Divergent Dendrimer Construction from an End of a Living Polymer

AB-type block copolymers between a dendrimer and a linear polymer can be synthesized by divergent-growth dendrimer building with an end of living polymer as a macroinitiator core. The advantage of the present method is quantitative block-dendrimer construction, free from contamination of homopolymers. Actually, poly(2-methyl-2-oxazoline)-*block*-poly(amido amine) (PAMAM) dendrimer (**8**, **9**) was successfully prepared by PAMAM dendritic branch formation from ω -ethylenediamine-terminated poly(2-methyl-2-oxazoline) according to Scheme 2.¹⁶

The results are shown in Table I. The short length of the polyoxazoline chain was set up for the purpose of ready



Scheme 2.

characterization and of matching hydrophilicity of the tail with that of the low hydrophobic dendritic head. Degree of polymerization was determined by ^1H NMR, and was well-controlled by the feed molar ratios of the monomer to the initiator.²⁷⁻³²

Termination of an active oxazolinium species of **5** was carried out with an excess amount of ethylenediamine at 27 °C (Table II).¹⁶ Trifunctional ω -ethylenediamine-terminated poly(2-methyl-2-oxazoline) **6** was readily obtained by treating the quaternary salt with ion-exchange resin, Amberlist-21. The terminal amino groups of **6** were shown by titration using 0.060N hydrochloric acid to be free amine structure.

The PAMAM dendrimer block was constructed by the divergent method with trifunctional ω -ethylenediamine-terminated poly(2-methyl-2-oxazoline) **6**. Michael addition of amino groups of **6** to methyl acrylate was carried out in methanol at 40 °C.² Since an important point on the early stage of the present dendrimer preparation is to clarify regulated branch formation with the macroinitiator core, products derived from shorter polyoxazoline (DP = 11)

were employed for confirmation of the branched structure. Especially, terminal *N,N,N'*-tris(methoxycarbonylethyl)-ethylenediamine structure of **7** was carefully characterized by ^1H and ^{13}C NMR, and IR measurement. As indicated in Table III, quantitiveness of the ω -end functionality was confirmed by ^1H NMR spectroscopy using signal intensity ratios of α -methylene protons (2.48 ppm) of ester groups to methylene protons (3.46 ppm) of poly(2-methyl-2-oxazoline). The branched ester ends were readily converted to primary amino groups by the reaction of **7** with a large excess of ethylenediamine at 27 °C.² End-branched polyoxazoline having three primary amino groups **8** ($G = 0$) was obtained in 96% yield. Poly(amido amine) dendrimer block copolymers (**8** ($G = 0 - 5.0$) and **9** ($G = 0.5 - 5.5$)) were given by repeating the Michael addition and the amide formation reactions.

Results of a solubility test of the block copolymers **8** and **9** were listed in Table IV. Although **8** having a dendritic globule of 5th-generation with terminal amino groups was soluble in polar solvents such as water, methanol, and dimethyl sulfoxide, it was insoluble in chloroform, acetone, and acetonitrile, which are solvents for block copolymer **9** containing half-generational dendrimer with methyl ester ends. The block copolymer **9** possess a wide range of solubility from polar solvents to non-polar solvents.

Shape and size of PAMAM dendrimer have been already reported by Tomalia et al.² According to the calculation method using a Corey-Pauling-Koltum (CPK) model, molecular shape and size of the tadpole-shaped block copolymer having 5th-generational dendrimer **8** were illustrated in Figure 4, although conformation of the poly(2-methyl-2-oxazoline) chain does not have regularity. In the figure, both models of three-dimensionally extended and contracted branches are depicted. A shape of the 5th-generational dendrimer block is a nearly symmetrical spheroid, while the dendrimers of 3rd- and 4th-generation have a shape of an oblate spheroid, according to the literature.²

Conventional amphiphiles have a hydrophobic group such as longer alkyl groups. Although the half-generational dendrimer possesses no typical hydrophobic alkyl group, the dendrimer has an ordered unimolecular structure with crowded, slightly hydrophobic terminal groups on the periphery of a dendritic nano-scale globule. The dendritic globule would be able to act as a hydrophobic part. As a

Table I. Ring-opening polymerization of 2-methyl-2-oxazoline^a

Monomer		Yield		$M_n^b \times 10^{-3}$	DP ^b	M_w / M_n^c
g (mmol)	[M] ₀ /[I] ₀	%	%			
4.8 (56)	11	94	1.0	11	1.1 ₄	
2.7 (32)	25	97	2.4	26	1.1 ₆	

^a Initiator, methyl trifluoromethanesulfonate; solv., acetonitrile; [M]₀, 3.0 mol/l; temp., 70 °C; time, 7 h. ^b Determined by ^1H NMR in CDCl_3 at 25 °C. ^c Estimated by SEC in CHCl_3 at 38 °C (polystyrene standard).

Table II. Preparation of ω -ethylenediamine-terminated poly(2-methyl-2-oxazoline) (**2**)^a

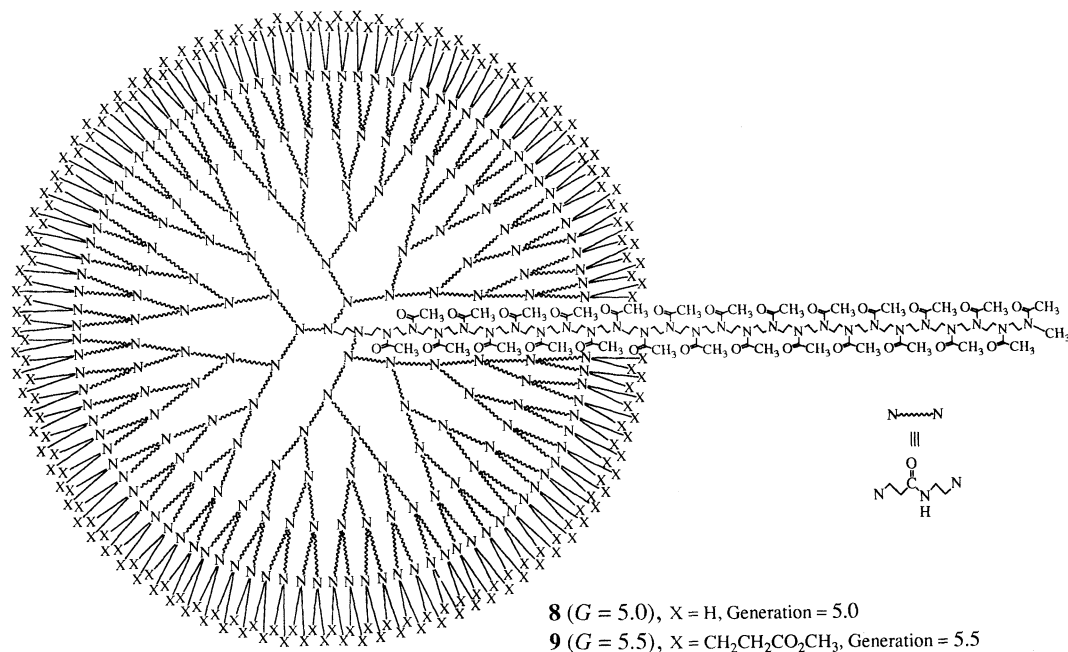
5	EDA ^b	Yield	$M_n^{c,d} \times 10^{-3}$	DP ^{c,d}	$M_w / M_n^{c,e}$
6.8 (5.9)	100 (1.5)	6.4 (95)	1.0	11	1.0 ₉
2.5 (1.0)	30 (0.45)	2.8 (92)	2.3	26	1.1 ₂

^a Temp., 27 °C; Time, 72 h. ^b Ethylenediamine. ^c Product after ion-exchange using Amberlist-21 in CHCl_3 at 27 °C. ^d Determined by ^1H NMR in CDCl_3 at 25 °C. ^e Estimated by SEC in CHCl_3 at 38 °C (polystyrene standard).

dendrimer itself is regarded as a unimolecular micelle, assembled structures of dendrimers are energetically favorable in comparison with conventional low-molecular-weight amphiphiles. In the present case, the tadpole-shaped macromolecule consists of the dendritic globule with a strong hydrophilic poly(2-methyl-2-oxazoline) tail.

Hydrophilicity of poly(2-methyl-2-oxazoline) is clearly stronger than that of poly(ethylene oxide).²⁹ Hence, the tadpole-shaped block copolymer would be a new type of amphiphilic copolymer.

Association of the tadpole-shaped macromolecule was investigated by surface tension measurement, which



Scheme 3.

Table III. Michael addition of **6** to methyl acrylate ^a

6		MA ^c	MeOH	Yield	M_n^d	M_w / M_n^d	Functionality ^e
g (mmol)	DP ^b	ml (mmol)	ml	g (%)	$\times 10^{-3}$		
1.7 (1.7)	11	0.50 (5.6)	1.3	1.9 (88)	1.1	1.0 ₈	2.9 ₇
1.8 (0.80)	26	0.24 (2.7)	3.0	1.7 (85)	2.2	1.1 ₁	2.9 ₅

^a Temp., 45 °C; time, 96 h. ^b By ¹H NMR in CDCl₃ at 25 °C. ^c Methyl acrylate. ^d Estimated by SEC in CHCl₃ at 38 °C (polystyrene standard). ^e [Methyl ester groups of **7**] / [polyoxazoline chain], determined by ¹H NMR in CDCl₃ at 25 °C.

Table IV. Solubility of poly(2-methyl-2-oxazoline)-*block*-poly(amido amine) dendrimer ^a

Solvent	8 (DP = 11)		9 (DP = 11)	8 (DP = 26)			9 (DP = 26)			Poly(2-methyl-2-oxazoline) (DP = 40)
	0.0 ^b	1.0 ^b	0.5 ^b	3.0 ^b	4.0 ^b	5.0 ^b	2.5 ^b	3.5 ^b	4.5 ^b	
Diethyl ether	—	—	—	—	—	—	—	—	—	—
Dioxane	—	—	+	+	—	—	+	+	+	—
Benzene	+	—	—	+	+	—	+	+	—	—
CHCl ₃	+	+	+	+	+	—	+	+	+	+
Pyridine	+	—	+	—	—	—	+	+	+	+
Acetone	—	—	+	—	—	—	+	+	+	+
MeOH	+	+	+	+	+	+	+	+	+	+
DMF	+	—	+	+	—	—	+	+	+	+
MeCN	—	—	+	—	—	—	+	+	+	+
DMSO	+	+	+	+	+	+	+	+	+	+
H ₂ O	+	+	+	+	+	+	+	+	+	+

^a +, Soluble; —, insoluble; temp., 25 °C; conc., 1.0 g/L. ^b Generation of dendrimer.

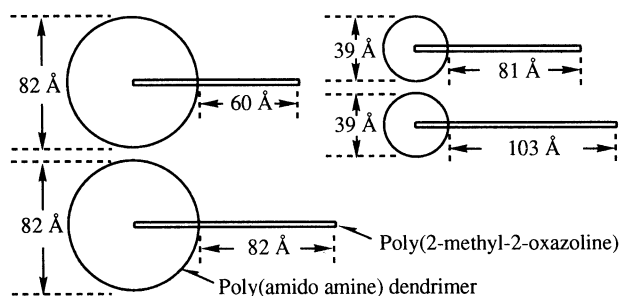


Figure 4. Molecular size of tadpole-shaped block copolymer **8** ($G = 5.0$) with three-dimensional contracted and extended models (see the text).²

was carried out for aqueous solutions of the block copolymer **9** ($G = 3.5, 4.5,$ and 5.5). The structure of **9** is shown in Scheme 3). The results are shown in Figure 5 and Table V. CMCs of all the dendrimer derivatives examined were observed, while the values are relatively high probably owing to hydrophilic character of the molecule based on water-soluble PAMAM skeleton. However, the CMC

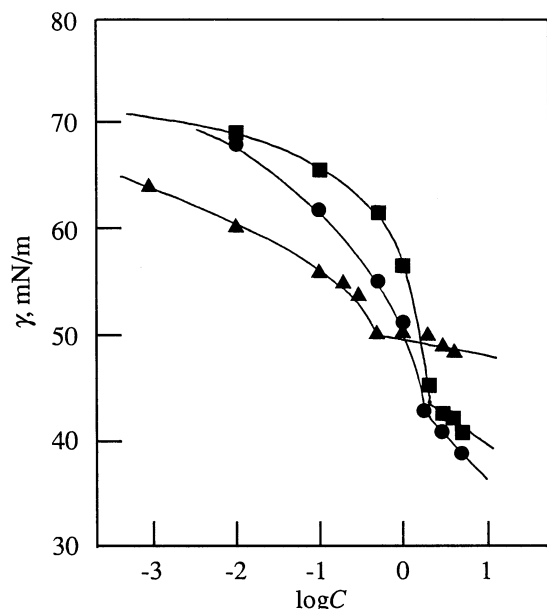


Figure 5. Surface tension (γ) of aqueous solutions of tadpole-shaped block copolymer **9** ($G = 3.5$ (■), 4.5 (●), and 5.5 (▲)) as a function of its concentration at $25\text{ }^{\circ}\text{C}$.

values decrease as the generation of the dendrimer increases. This means interestingly that the large globular dendrimer with a hydrophilic linear tail tends to gather on the air/water interface more efficiently than the copolymer having the small oblate dendrimer. Furthermore, γ_{CMC} value of **9** ($G = 5.5$) was higher than those of **9** ($G = 3.5$) and **9** ($G = 4.5$). An apparent averaged area (A) of a terminal group of the dendritic globule at the air/water interface increases by increasing the generation (Table V). The data of the A value and γ_{CMC} reasonably imply that the nanoscale globular dendrimer head is arranged on the air/water interface. Although a vertical force for the amphiphile on the interface would deform the globular shape, an array of an oblate or a near spherical particle of the dendrimer on the water surface should be formed.

Table V. Characterization of an aqueous solution of **9** ($G = 3.5, 4.5, 5.5$) by surface tension measurement^a

Polymer	$\gamma_{\text{CMC}}^{\text{b}}$	A^{c}
	mN/m	$\text{\AA}^2/\text{terminal unit}$
9 ($G = 3.5$)	43.7	24
9 ($G = 4.5$)	42.5	36
9 ($G = 5.5$)	50.3	55

^a Temp., $25\text{ }^{\circ}\text{C}$. ^b Surface tension at critical micelle concentration (CMC). ^c Molecular area per a terminal methyl group of dendrimer of **9**, calculated according to Refs. 23 and 24. The concentration of **9** was used to calculate the A value.

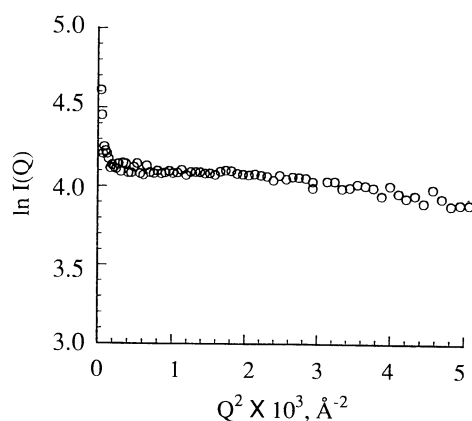


Figure 6. A Guinier plots of SANS for a D_2O solution of **9** ($G = 5.5$) at a concentration of $3.0\text{ wt}\%$.

Small angle neutron scattering (SANS) is a suitable technique to study nano- and meso-structures of molecular assemblies. So far, a supramolecular assembled structure of **9** in a bulk phase of an aqueous solution was estimated by means of SANS investigations. The SANS measurements were performed on a D_2O solution of **9** ($G = 5.5$) at $25\text{ }^{\circ}\text{C}$ at a concentration of $3.0\text{ wt}\%$, which is sufficiently higher than the CMC. The obtained scattering data well-fitted a Guinier equation of a spherical particle model (Figure 6).¹⁶ The plot of the logarithmic SANS intensity displayed a linear decrease with Q^2 in a Q value region below 0.009 \AA^{-1} . The diameter of the spherical particle was calculated to be 54 nm with a narrow size distribution.^{33,34} Moreover, the Guinier plots in a Q region from 0.009 to 0.07 \AA^{-1} gave a straight fitting line. The diameter of one dendritic globule was estimated to be 3.2 nm , although the size is smaller than that calculated by using a three-dimensional contracted molecular model. Then, an assembly number of **9** ($G = 5.5$) was obtained to be approximately 2.4×10^3 . The size and shape of the assembly are schematically illustrated in Figure 7. Although shape and order of the assembled structure are different from the closely packed assemblies conceptually presented after the introductory remarks, the supramolecular self-assembled mesoscopic particles of the tadpole-shaped macromolecule were actually obtained, with accompanying inter- and intradendrimer cavities. Thus, the mesoscopic sphere, which consists of dendritic globule regarded as a unimolecular micelle, belongs to a higher structural hierarchy of supramolecular organized systems.

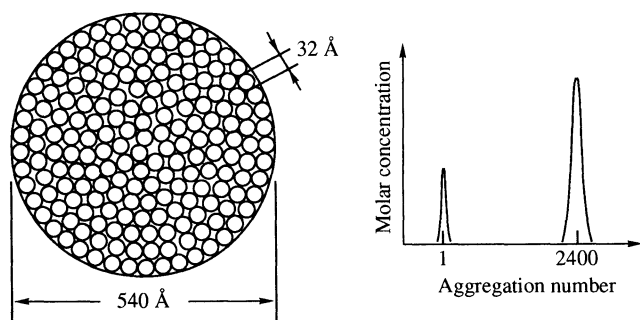


Figure 7. A schematic representation of the assembly of tadpole-shaped macromolecule **9** ($G = 5.5$) in a D_2O solution estimated by small angle neutron scattering (SANS) analysis (left). The evaluated average particle radius of assembled **9** ($G = 5.5$) was 27 nm. The diameter of one dendrimer globule was estimated to be 3.2 nm. The Guinier plot implies a narrow size distribution of the assembled structure. Distributions of numbers of the aggregate are also illustrated (right).

CONCLUSIONS

As an illustration of hybridized dendrimer-based nano-organized systems having "inter- and intradendrimer cavities", AB-type amphiphilic linear polymer/dendrimer block copolymers were synthesized in two different routes. Dendrimer construction followed by living polymerization and vice versa appear to be versatile and general. An amphiphilic character of poly(2-methyl-2-oxazoline)-block-poly(amido amine) dendrimer, prepared by the latter method, was examined by surface tension measurement. It is worthwhile to note that the large dendritic globule having a hydrophilic linear tail is favorably arranged at the air/water interface. An assembled structure of the block copolymer in an aqueous solution at a concentration higher than the critical micelle concentration was revealed as a spherical large particle of 54 nm diameter with a relatively narrow size distribution. Size and shape of a dendrimer itself are easily designed and controlled by organic synthesis, whereas further self-organization needs much information in relation to size and shape of the higher-order assembled structure. Precision control of a sequence including a block segment might be important in future three-dimensional architecture of mesoscopic organized systems of a dendritic amphiphile. Among biopolymers, globular macromolecules linked with a linear tail function as synchronically mobile organized systems such as myosin and actin. The tadpole-shaped macromolecules are important as an essential building block of bio-inspired molecular architectures. We hope that the synthetic guideline and the concept presented in this article contribute to creation of mesoscopic functional materials.

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