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Selected Papers

High-Yield Synthesis of Dendrimers through Alternate Multiaddition Reactions with Commercially Available Reagents

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An alternate multiaddition (AMA) process consisting of Michael addition and urethane formation is proposed to achieve the quantity synthesis of dendrimers without by-product formation and any weight loss by using commercially available compounds. α-Thioglycerol (**TG**) was added to pentaerythritol tetraacrylate (**PETA**) to give the corresponding octaol, but the subsequent reaction with 1,1-bis(acryloyloxymethyl)ethyl isocyanate (**BEI**) resulted in incomplete urethane formation because of the steric effect of the secondary OH groups. The replacement of **BEI** with 2-isocyanatoethyl acrylate (**AOI**) improved the efficiency of the addition of NCO to the secondary OH groups, but an excess amount of **AOI** was required. Subsequently, we employed the combination of **PETA**, 2-sulfanylethanol (**SE**), and **BEI**. The addition of **SE** to **PETA** produced readily the tetraol, which was reacted with **BEI** to afford dendritic octaacrylate (**Ac8b**). The repetition of the two addition reactions gave dendritic octaol and hexadecylacrylate (**Ac16b**), respectively, in large scales. The base-catalyzed Michael addition of 2-naphthalenethiol to acrylate residues of **Ac8a** and **Ac16b** gave naphthylthio-terminated dendrimers **N8b** and **N16b**, respectively, which were purified by column chromatography. GPC as well as UV-spectroscopic analysis of **N8b** and **N16b** revealed that **N8b** is reasonably monodispersed whereas the purity of **N16b** is slightly reduced.

Dendritic polymers are distinguished into a family of highly branched compounds expanding building blocks from a central core to an outer shell by reiterative constructions.[1] They are categorized into the following two types; dendrimers with a well-defined structure and a uniform molecular weight and hyperbranched polymers (HBPs) having rather high molecular weight distribution. In general, a large-scale synthesis of HBPs is relatively easy, as exemplified by hyperbranched polyester polyols[2] and by commercially available compounds referred to as Boltorn H*x*. The HBPs and their derivatives therefore have been of interest from practical view points to improve performances of polyurethanes,[3] epoxy resins,[4] UV-curable resins,[5] gas separation membranes[6] and to provide mesoporous silica,[7] crosslinkable vesicles,[8] and so forth. This is simply because of their large-scale productivity. Dendrimers, on the other hand, possess monodispersed molecular weights with uniform structures. Their unique chemical and physical properties originated from well-defined chemical structures have been extensively studied in versatile cases, leading to various sophisticated applications including drug delivery,[9] biomedical purposes,[10] catalysts,[11] sensors,[12] solar cells,[13] and so forth. The major advantages of dendrimers compared with those of HBPs consist of the ability to arrange objective functional groups selectively at their outermost positions or molecular surfaces,[14] which can lead to the enhancement of chemical reactions as a result of the local concentration of active residues and to exhibit unique physical properties such as low viscosity and high solubility in solvents because of the reduction of entanglement of polymer main chains. However, these benefits have been difficult to utilize especially in material and engineering sciences. This is because dendrimer syntheses developed so far are usually accompanied by tedious synthetic and/or purification processes for generation growth. Cost-effective and large-scale synthesis of dendrimers has been highly desired. One of the approaches for convenient dendrimer synthesis is the utilization of click chemistry composed of the 1,3-dipolar cycloaddition of azido group with acetylene bond without forming any by-product,[15] but it is necessary to convert a chlorinated precursor into the corresponding building block bearing azido group at every step. Whereas the one-pot syntheses of dendrimers have been described,[16–19] great endeavors have been focused on large-scale preparation. They include phosphorus-containing dendrimers[20] and glycerin-based dendrimers[21] starting from compounds with reasonable availability, whereas the condensation of chlorinated *s*-triazine with *N*-monoprotected piperidine[22] and the photoinduced radical addition of α-thioglycerol (**TG**) as a

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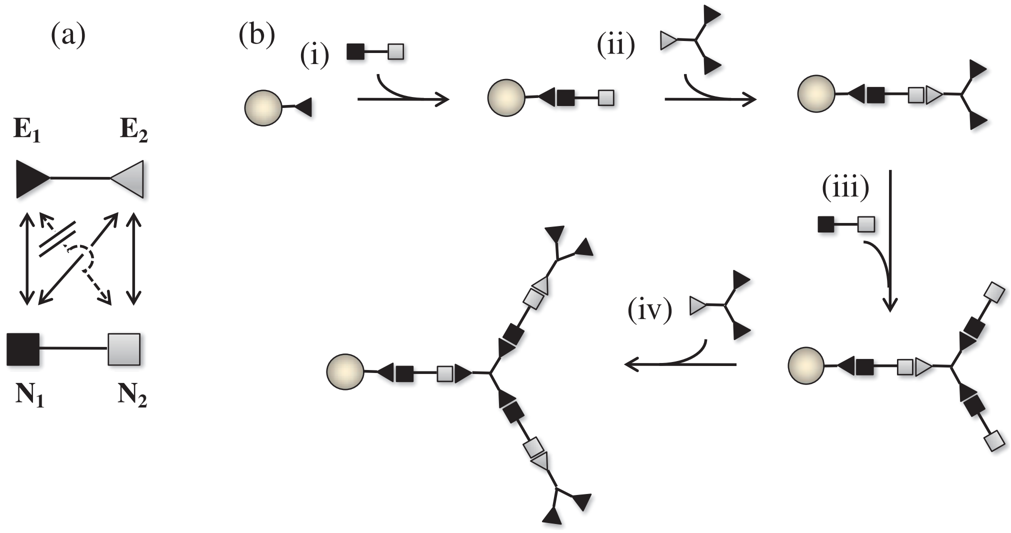


Figure 1. (a) The selection rule of electrophilic (E_1 and E_2) with nucleophilic (N_1 and N_2) substituents. (b) (i) E_1 (closed triangle) of a core molecule ($\mathrm{R{-}E_1}$) adds to N_1 (closed square) of $\mathrm{N_1{-}N_2}$ to convert the terminus of the product specifically into N_2 (gray square), (ii) which reacts with the trifunctional $\mathrm{E_2{-}(E_1)_2}$. (iii and iv) The both additions are repeated for the generation growth.

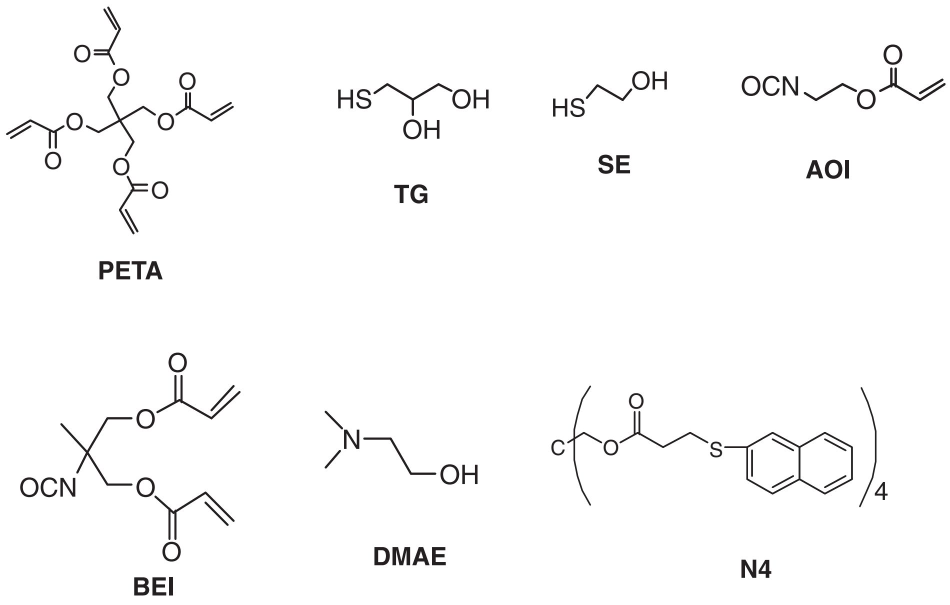
branched building block to an unsaturated carboxylic acid have played a key role in synthesizing readily available dendrimers.[23] However, these methods still require protection/deprotection and the consequent purification processes. Accordingly, the development of quantity synthesis of dendrimer has been a challenging subject since the path-breaking studies.[24]

Whereas substitution or condensation reactions have been predominantly employed so far for dendrimer syntheses, the combination of addition reactions are ideal to bind building blocks to assemble molecular frameworks of dendrimers because of no formation of any by-product and no weight loss of fed materials. Taking notice of the facts that Michael addition[25] and urethane formation[26] take place in a stoichiometric manner in high yields, we undertook to select suitable combinations of building blocks and finally employed the monomers, which are all commercially available.[27] A similar concept has been recently reported by Radosz et al. by selecting chemoselective Michael additions of amine/acrylate and thiol/methacrylates,[28] but this reaction requires excess amounts of building blocks to obtain defect-free dedrimers. We have reported preliminarily a novel approach to specialty dendrimers based on "alternate multiaddition (AMA) process" composed of the combination of two types of addition reactions starting from a tetraacrylate to join building blocks in stoichiometric manners without forming any by-product.[27] We describe herein the optimization of building blocks and reaction conditions for generation growth of dendrimers having polyfunctional hydroxy and acrylate residues at their termini, aimed at achieving the preparation of dendrimers in a cost-effective way. To the best of the authors' knowledge, this is the first example to prepare dendrimers starting directly from readily available compounds acting as core, spacer, and branched building blocks.

Results and Discussion

Strategy. Our strategy to provide dendrimers in large scale through the AMA process is based on the alternate bond formation through two kinds of addition reactions, whereas at least one of the monomers for the chain lengthening has to be a branched building block. In order to simplify prerequisites required for the alternate bond formation of dendrimer synthesis, let us consider a couple of difunctional monomers denoted as $\mathrm{E_1{-}E_2}$ and $\mathrm{N_1{-}N_2}$ to prepare linear oligomers comprised of alternate monomer units. E_1 and E_2 are electrophilic, while N_1 and N_2 nucleophilic. In order to accomplish chain lengthening, monomers should fulfill the following requirements. First, E_1 should be reactive with N_1, but not with N_2 at all, whereas E_2 is allowed to react with both N_1 and N_2 in such a way that any cross-talk between the two addition reactions is avoided, as shown in Figure 1a. Second, both of the additions involved attain high yields to omit purification processes, leading to the generation growth in a one-pot manner. When $\mathrm{R{-}E_1}$ as a monofunctional core molecule having an electrophilic residue reacts with an equimolar amount of $\mathrm{N_1{-}N_2}$, we obtain specifically $\mathrm{R{-}E_1{=}N_1{-}N_2}$, whereas the double bond stands for the new linkage. The molecule can be converted into $\mathrm{R{-}E_1{=}N_1{-}N_2{=}E_2{-}E_1}$ by adding an equimolar amount of the second difunctional electrophilic monomer, $\mathrm{E_1{-}E_2}$, and E_1 is regenerated at the termini to finish one cycle. If one of the monomers is branched and designated as $\mathrm{N_2{-}(N_1)_2}$, for instance, the repetition of the addition reactions for the generation growth of dendrimers or dendrons gives branched chains, as sketched in Figure 1b. In the case of the involvement of two branched monomers, $\mathrm{N_2{-}(N_1)_2}$ and $\mathrm{E_2{-}(E_1)_2}$, one cycle consisting of the alternate reactions results in the doubled branching. Starting from a multifunctional core molecule of $\mathrm{R{-}(E_1)}_x$ type ($x \geq 2$), the terminal E_1 moieties first react with $\mathrm{N_1{-}(N_2)_2}$ to give $\mathrm{R{-}[E_1{=}N_1{-}(N_2)_2]}_x$. If the addition occurs quantitatively, the reaction between the peripheral N_2 and $\mathrm{E_2{-}(E_1)_2}$ gives $\mathrm{R{-}\{E_1{=}N_1{-}[N_2{=}E_2{-}(E_1)_2]_2\}}_x$. Thus, E_1 are reconstructed at the terminal positions and can be used for the further generation growth by the repetition of the alternate addition reactions.

Among candidates of nucleophilic and electrophilic residues for the AMA process, we selected the combination of SH and OH groups as nucleophilic substituents (N_1 and N_2) and of

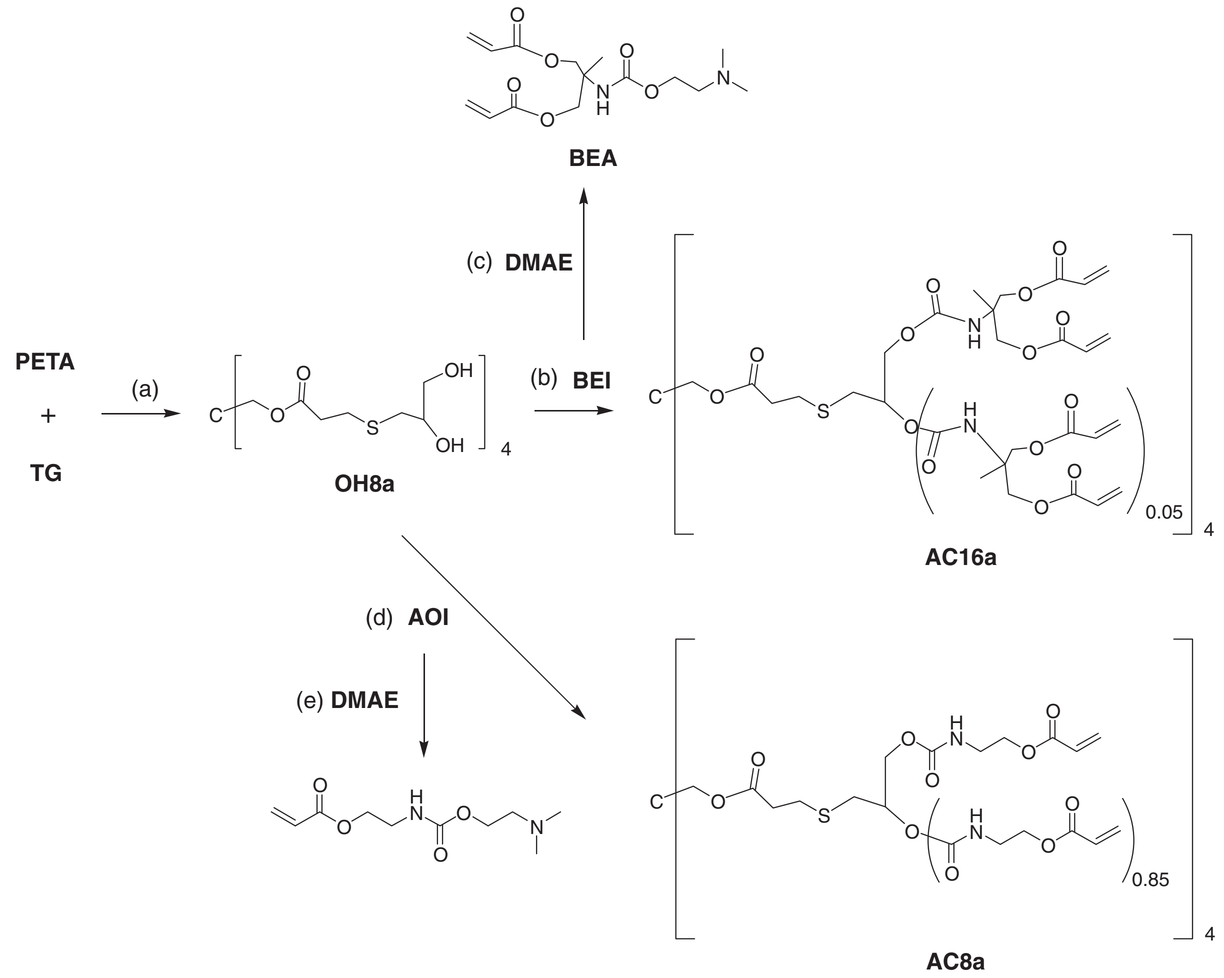


Scheme 1. The compounds used in this study.

acrylate and NCO groups as electrophiles (E_1 and E_2) to fulfill the aforementioned requirements for monomers. The compounds used in this study are shown in Scheme 1. Note that all of the key compounds including **SE** and **TG** as difunctional and trifunctional nucleophilic monomers, respectively, and **AOI** as a difunctional electrophile and **BEI** as a trifunctional electrophiles are commercially available. **PETA** was employed as a tetrafunctional electrophilic core compound, since it is readily available and reactive with thiols under basic conditions through the Michael addition.[29]

Dendrimers Derived from PETA and TG. The AMA process was performed first by employing **PETA** as a R–$(E_1)_4$ type core molecule and the combination of **TG** and **BEI** as N_2–$(N_1)_2$ and E_2–$(E_1)_2$, respectively, taking the fact into consideration that every addition step doubles the corresponding OH or acrylate groups, leading to the efficient branching of interior chains (Scheme 2).[27] The Michael addition of 4-molar equivalents of **TG** to **PETA** was carried out in THF in the presence of triethylamine (**TEA**) as a basic catalyst at an ambient temperature. The reaction was monitored with the aid of ^{1}H NMR spectra, and proton signals due to acrylate residues at around 5.9, 6.1, and 6.4 ppm disappeared finally, whereas new signals appeared at around 2.5–2.8 ppm assignable to $–SCH_2CH_2COO–$ and 3.5–3.8 ppm due to $–CH_2–OH$ and $–CH–OH$, as shown in Figures 2a and 2b, supporting the quantitative formation of the octaol (**OH8a**). The structure of **OH8a** was revealed unequivocally by MALDI-TOF/MS measurements, displaying a single parent peak at $m/z = 807$ corresponding to the sodium-additive form of **OH8a** (Figure 3a).

OH8a possesses four sets of primary and secondary OH groups derived from **TG** so that 8-molar equivalents of **BEI** was reacted with **OH8a** in THF under reflux in the presence of dibutyltin dilaurate (**DBTDL**) as a catalyst to accelerate the urethane formation[26] and a polymerization inhibitor. Among inhibitors tested, we finally employed cupferron because of its efficient inhibitory effect as well as the absence of OH group reactive with NCO of **BEI**. ^{1}H NMR spectra of products after heating a reaction mixture for various periods suggested, however, that the secondary OH is far less reactive with **BEI**. Accordingly, an excess amount of **BEI** was treated with **OH8a** under reflux. After confirming the thorough disappearance of $HO–CH_2$ proton signals appearing at 3.5–3.8 ppm (Figure 2c), the reaction mixture was treated with *N*,*N*-dimethylaminoethanol (**DMAE**) to convert remaining **BEI** into the corresponding carbamate substituted with tertiary amino group (Scheme 2; **BEA**), whereas the compound was not characterized. The treatment with **DMAE** served our purpose to remove remaining **BEI**, since the addition product **BEA** can be removed together with **DMAE** by washing with an acidic aqueous solution without deterioration of the polyacrylate (**Ac16a**), which possesses 16 acrylate units theoretically. However, it was found that the product after the treatment consists of complicated mixtures, as suggested by ^{1}H NMR and MALDI-TOF/MS measurement. Since the evaluation of conversion level of OH groups was difficult by these physical measurements, the Michael addition of **Fmoc-SH**[29] to acrylate groups were undertaken to estimate a molecular weight per each 9-fluorenylmethoxycarbonyl (Fmoc) unit spectroscopically by using molar absorption coefficient of **Fmoc-SH** as a model compound. We reported previously that branched polyacrylate oligomers are reacted with **Fmoc-SH** quantitatively in the presence of a tertiary amine to produce Fmoc-terminated oligomers to develop novel base-amplifying agents that molecular weights per Fmoc unit of oligomers are in accordance with those calculated from well-defined chemical structures of oligomers.[30] The addition of **Fmoc-SH** to crude **Ac8a** proceeded quantitatively, as confirmed by the complete disappearance of the acrylate proton signals in the ^{1}H NMR spectrum. The Fmoc-terminated product was subsequently purified by column chromatography to be subjected to UV spectral measurement. The molar equivalent weight was estimated to be 513, while the theoretical value is 468, indicating that that the number of Fmoc units is 8.4 on average. Since four primary OH groups of **OH8a** are quantitatively



Scheme 2. Synthetic route to give (path a) **OH8a**, (path b) **AC16a**, and (path d) **AC8a**. The reactions of **DMAE** (paths c and e) were used for the removal of excess of **BEI** and **AOI**, respectively (see text).

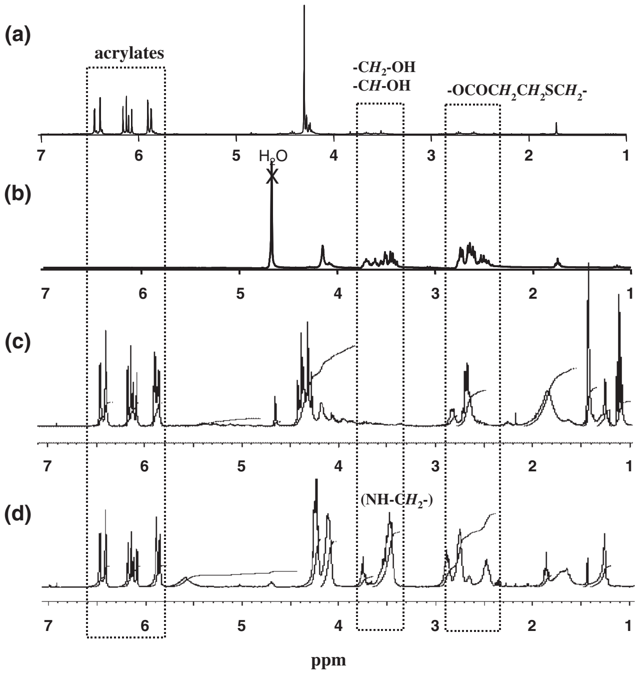


Figure 2. ^{1}H NMR spectra of (a) **PETA**, (b) **OH8a**, (c) crude **Ac16a**, and (d) crude **Ac8a**.

consumed to generate eight acrylate groups, as supported by ^{1}H NMR spectra, the estimated value suggests that the conversion of the four secondary OH groups is only 5% (Scheme 3). Such a poor reactivity of the secondary OH groups of **Ac16a** arises predominantly from the steric effect due to the tertiary isocyanate structure of **BEI**.

Consequently, **BEI** was replaced by **AOI** having a primary NCO group to determine the reactivity with eight OH groups of **OH8a**, as shown in Scheme 2 (path (d)), in order to reduce the steric hindrance. An excess amount of **AOI** was used in a way similar to **BEI**, followed by the treatment with **DMAE** to remove remaining **AOI**. As expected, **AOI** reacted with the secondary OH groups of **OH8a** to give **Ac8a** in a moderate yield. The structural determination of the product was first achieved by MALDI-TOF/MS measurement. The results are shown in Figure 3b. When the eight OH groups are all reacted with **AOI**, the molecular weight of **Ac8a** having eight acrylates is 1912. The peaks appearing at $m/z = 1935$ and 1952 are ascribable to $[M + Na]^+$ and $[M + K]^+$, whereas M denotes the molecular weight of fully acrylated **Ac8a**. On the other hand, the signals at $m/z = 1794$ and 1810 correspond to $[M + Na]^+$ and $[M + K]^+$ minus the molecular weight of **AOI** ($m/z = 141$), respectively. This means that **Ac8a** is contaminated with adducts with insufficient urethane formation.

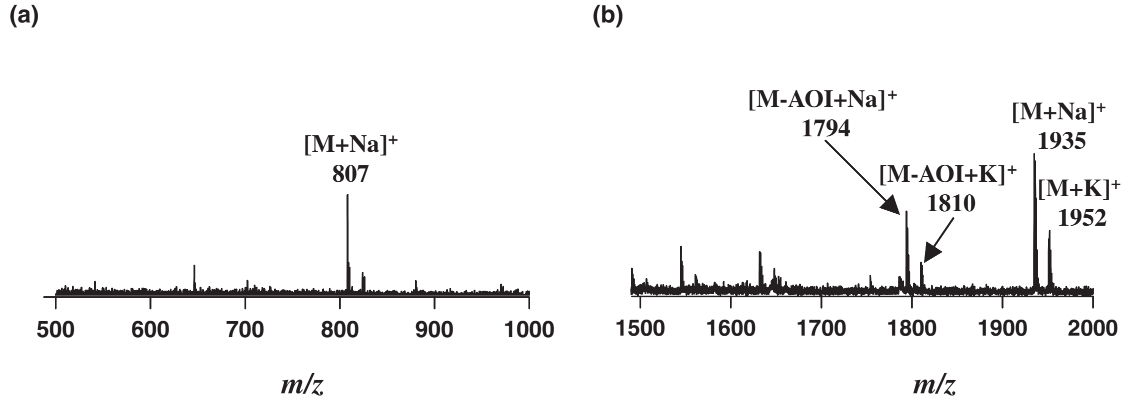
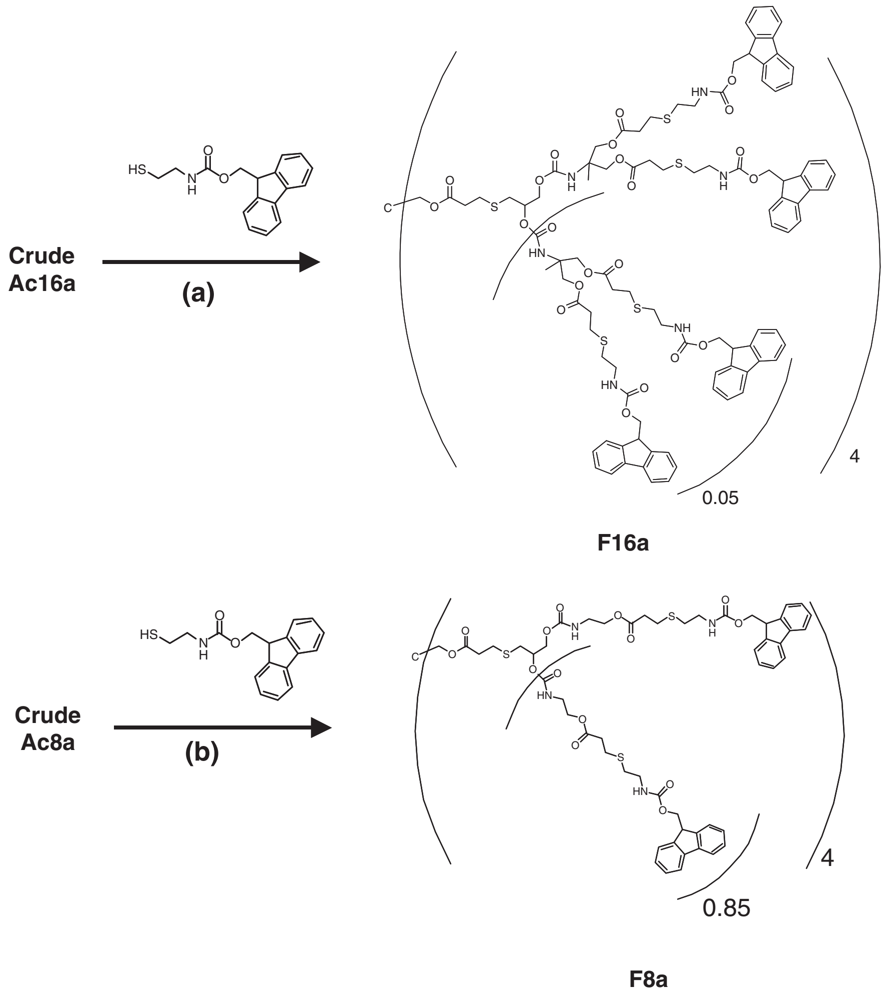


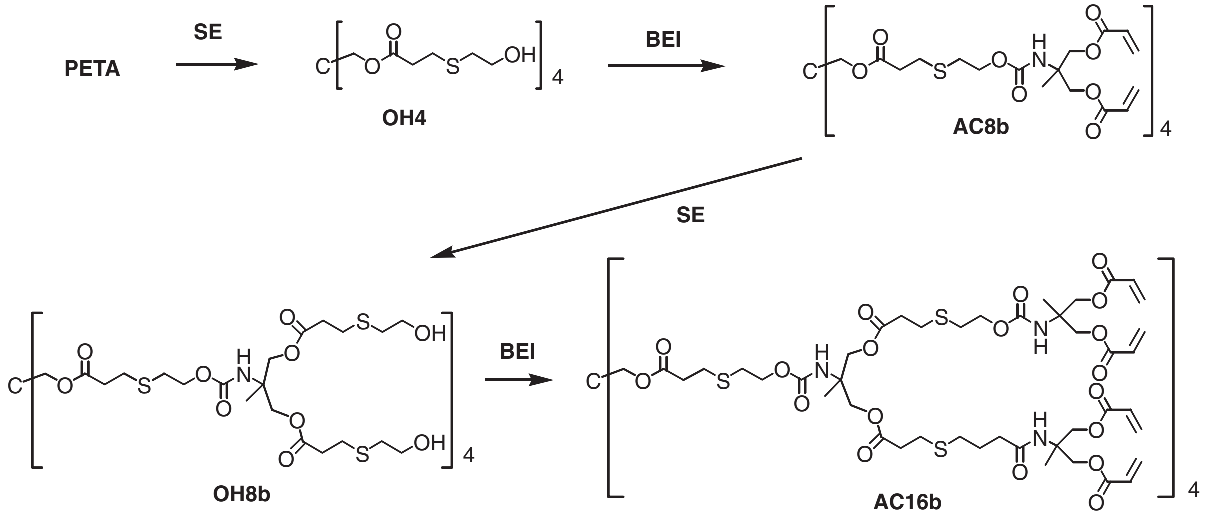
Figure 3. MALDI-TOF/MS spectra of (a) **OH8a**, (b) crude mixture of **Ac8a**, and defective species. α-Cyano-4-hydroxycinnamic acid (**CHCA**) was used as matrix.



Scheme 3. Terminal modifications of crude (a) **Ac16a** and (b) **Ac8a** by **Fmoc-SH** to give crude **F16a** and **F8a**.

Accordingly, the level of conversion of OH groups into urethane linkage was estimated by means of the addition of **Fmoc-SH** in the same manner as described above. UV spectral analysis revealed that the molecular weight per Fmoc unit of the product is 547, whereas the theoretical value is 539, indicating that 7.4 of Fmoc groups are introduced to each molecule (Scheme 3). This value corresponds to an 85% conversion of secondary OH groups.

Dendrimers Derived from PETA, SE, and BEI. To summarize the results shown above, the employment of **TG** as a branched building block is not satisfactory due to the lower reactivity of the secondary OH group for our final goal to synthesize dendrimers in a one-pot manner as a result of the repetition of two different addition reactions, even though dendritic structures are partially constructed. This situation led us to use the combination of **SE** as a spacer depicted as N_1–N_2



Scheme 4. Synthetic pathways of dendrimers using **PETA**, **SE**, and **BEI**.

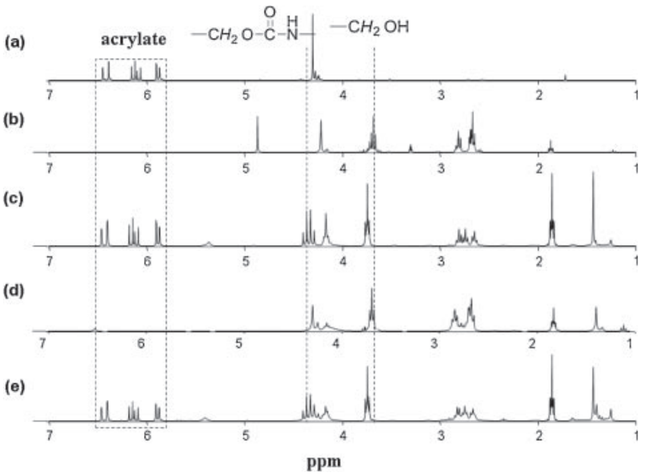


Figure 4. ^{1}H NMR spectra of (a) **PETA**, (b) **OH4**, (c) **Ac8b**, (d) **OH8b**, and (e) **Ac16b**.

and **BEI** as a branched building block E_2–$(E_1)_2$ to prepare specialty dendrimers according to Scheme 4.[27] The first step consists of the Michael addition of **PETA** with 4-molar equivalents of **SE** to give the tetraol (**OH4**). The reaction proceeded quantitatively under the same conditions employed for **PETA** and **TG** system. As shown in Figures 4a and 4b, the acrylate peaks of **PETA** at ca. 5.9, 6.1, and 6.4 ppm disappeared entirely, accompanied by the appearance of a signal due to CH_2–OH at 3.68 ppm. MALDI-TOF/MS spectra showed a single parent peak due to the sodium-additive form of **OH4** at $m/z = 687$, as shown in Figure 5a. The second step is the urethane formation between the primary OH groups of **OH4** and 4-molar equivalents of **BEI** in THF under reflux in the presence of **DBTDL** and cupferron. As seen in ^{1}H NMR spectrum in Figure 4c, a new signal at ca. 4.3 ppm due to CH_2–OCONH appeared with the perfect disappearance of the CH_2–OH signal, indicating the quantitative formation of the dendritic octaacrylate (**Ac8b**). The structure of **Ac8b** was also supported by the MALDI-TOF/MS spectra (Figure 5b) having two peaks at $m/z = 1643$ and 1659, which correspond to the sodium- and the potassium-additive forms of **Ac8b**, respectively. The yield of crude product after sufficient concentration and drying exceeded 100% due to the encapsulation of THF molecules in the internal cavities of **Ac8b**. The amount of THF remaining in the products was estimated to be 17 wt % by an intensity ratio of $-CH_2CH_2O-$ protons of THF at 1.83 and $CH_2{=}CHCO_2-$ of the dendrimer at 6.44. Note that the number of the terminal acrylate groups increase twice through the alternate addition reactions. Besides, it is worthy to mention that the reaction is complete stoichiometrically so that no starting compound remains in the crude product, gratifying our strategy as stated above. Encouraged by the results, crude **Ac8b** was treated subsequently with 8 equivalents of **SE** to give the dendritic octaol (**OH8b**). ^{1}H NMR spectral features during the reaction were quite similar to those of the first cycle, exhibiting the disappearance of acrylate signals and the appearance of the signal due to CH_2–OH, as shown in Figure 4d. A single peak at $m/z = 2268$ due to the sodium-additive form of **OH8b** (Figure 5c) were observed in MALDI-TOF/MS, suggesting that the crude adduct is satisfactorily pure. Subsequently, **OH8b** was reacted with 8 equivalents of **BEI** for the generation growth to give the dendritic hexadecylacrylate (**Ac16b**). The molecular structure was in line with the thorough disappearance of the ^{1}H NMR signals due to CH_2–OH (Figure 4e) and the observation of a parent peak at $m/z = 4180$ due to the sodium-additive form of **Ac16b** in MALDI-TOF/MS spectrum (Figure 5d). There are smaller peaks with a constant difference in m/z below the parent peak in the range of $m/z = 3200$–3900. Taking $m/z = 239$ of **BEI** into account, **Ac16b** is assumed to be contaminated with dendrimers missing one, two, and three **BEI** units. It is very probable that the imperfection comes from the steric hindrance of NCO group of **BEI** at the tertiary position. Accordingly, the results may lead us to achieve the next step to improve the dendrimer synthesis by employing a nucleophilic building block having a primary NCO group.

Noting the facile reactivity of SH with acrylate, **Ac8b** and **Ac16b** were subjected to the reaction with 2-naphthalenethiol

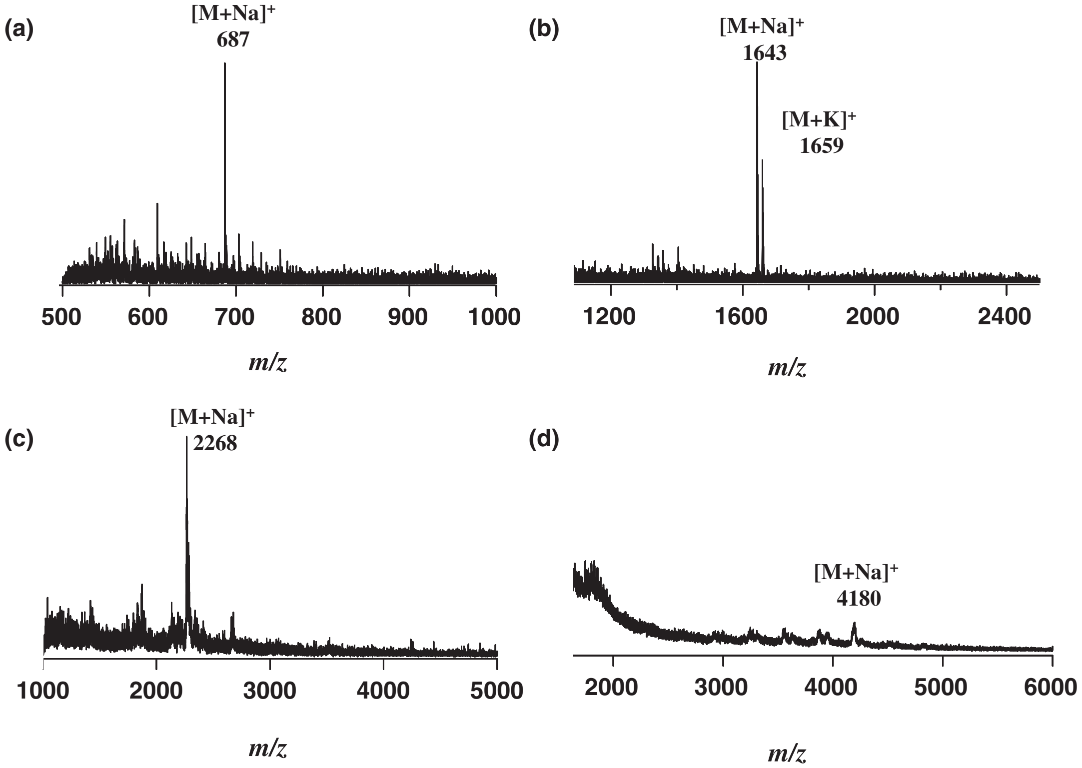
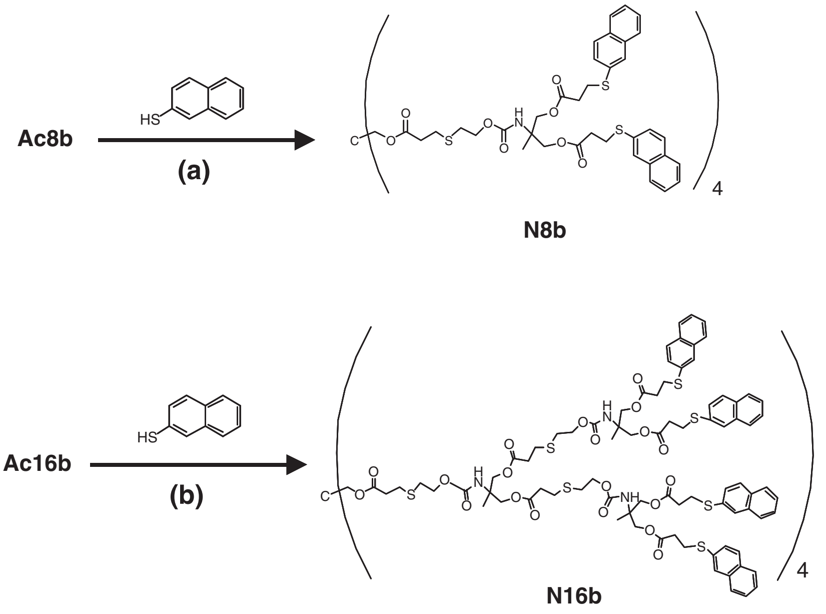


Figure 5. MALDI-TOF/MS spectra of (a) **OH4**, (b) **Ac8b**, (c) **OH8b**, and (b) **Ac16b**. **CHCA** or dithranol was used as matrix.



Scheme 5. Terminal modification of (a) **Ac8b** and (b) **Ac16b** by **NT** to give **N8b** and **N16b**.

(**NT**) to afford the corresponding 2-naphthylthio-terminated derivatives (Scheme 5; **N8b** and **N16b**). The purpose was twofold. The first was to determine the purity of the dendrimers after chromatographic separation because it was difficult to purify polyacrylates by means of column chromatography owing to ready polymerizability in the absence of an inhibitor. Besides, the naphthalene moieties can act as a convenient UV probe for gel-permeation chromatography (GPC) analysis. The second was to confirm the reasonable chemical modification of polyacrylate dendrimers by using aromatic thiols. Since the uniqueness of dendrimers originates from the local condensation of various functional moieties tethered to chain termini, a generic method to introduce functional groups is of fundamental as well as practical significance. The addition of the aromatic thiol to acrylate groups of **Ac8b** and **Ac16b** was carried out in the presence of a basic catalyst to give the

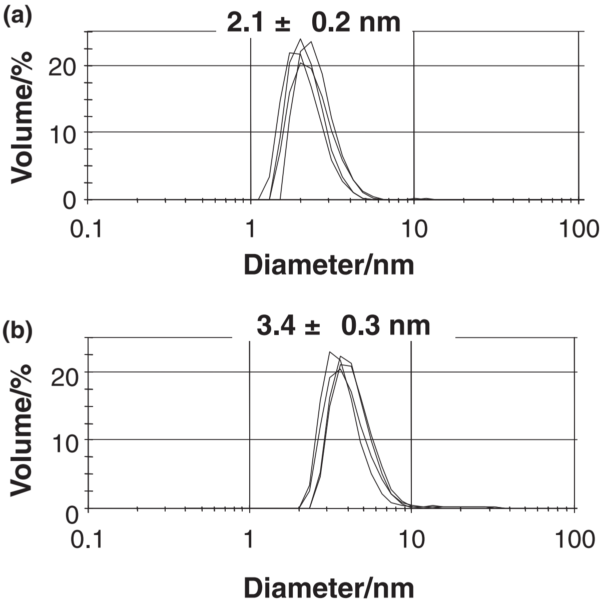


Figure 6. Dynamic light scattering (DLS) spectra of the THF solutions of (a) **Ac8b** and (b) **Ac16b** in the concentration of 5% (w/w).

corresponding naphthylthio-terminated dendrimers (Scheme 5; **N8b** and **N16b**), respectively. Both compounds were subjected to silica column chromatography. GPC analysis revealed that purified **N8b** exhibited $M_w = 2.7 \times 10^3$ and $M_w/M_n = 1.04$, whereas the theoretical M_w is 2904, supporting that **Ac8b** is sufficiently monodispersed. On the other hand, M_w and M_w/M_n of **N16b** with theoretical $M_w = 6724$ were 5.5×10^3 and 1.06, respectively, suggesting that the purity of **Ac16b** is slightly reduced in accord with the MALDI-TOF/MS data. The purity of **N8b** and **N16b** was also checked by means of UV spectral measurements to estimate molar equivalent weights (i.e., molecular weights per naphthylthio unit) by using molar absorption coefficient ($\varepsilon = 9.74 \times 10^4\,\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$ at 254 nm) of tetranaphthylthio derivative (Scheme 1; **N4**)[31] as a model compound. The estimated molar equivalent weights of **N8b** and **N16b** were 365 and 442, respectively, indicating that the numbers of the terminal naphthylthio moieties are 7.8 for **N8b** and 14 for **N16b**, respectively, on average. It follows that the purity of **N8b** and **N16b** are 98% and 88%, respectively.

It is of great interest to know three-dimensional molecular shapes or conformation of the polyacrylate dendrimers in solutions. Dynamic light scattering (DLS) analysis provides us valuable information on average diameters of such spherical molecules.[32] Figure 6 shows molecular size distributions of **Ac8b** and **Ac16b** in THF solution (5%, w/w) obtained by DLS measurements. The diameters were estimated to be 2.1 ± 0.2 nm for **Ac8b** and 3.4 ± 0.3 nm for **Ac16b**, being irrespective of the concentration of the dendrimers ranging from 2.5 to 10% (w/w), while the theoretical diameters of the thoroughly stretched structures was estimated to be ca. 3.6 nm for **Ac8b** and ca. 6.0 nm for **Ac16b**, respectively. Although quite strict discussion of molecular size is difficult to make from DLS measurement, we estimated that each branch of the dendrimers is folded to shrink to some extent in solution.

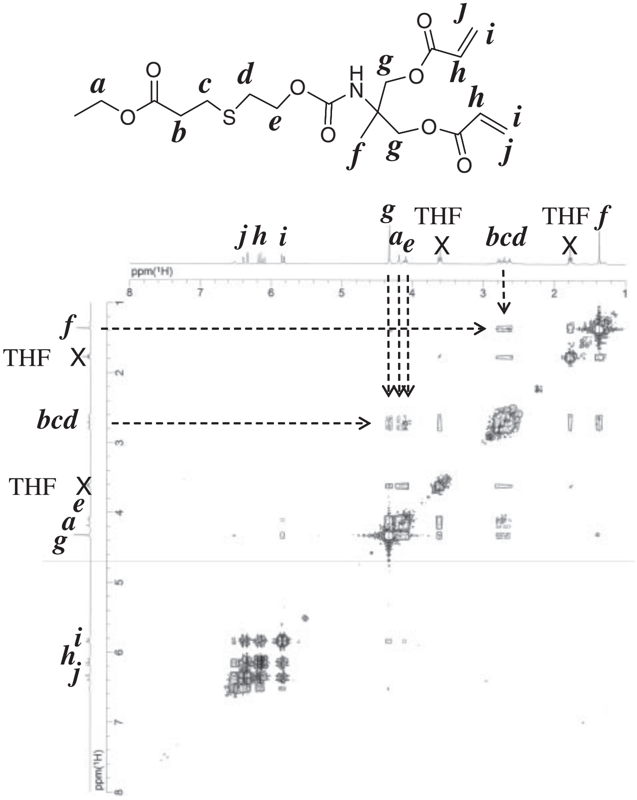


Figure 7. 2D NOESY spectrum of **Ac8b** dissolved in THF-d_8 in a concentration of 5% (w/w).

We made further detailed conformational analysis based on proton–proton nuclear Overhauser effect (NOE) interactions, which can supply significant information on spatial correlations among protons of dendritic chains.[31,33] Figure 7 shows a 2D NOESY spectrum of **Ac8b** dissolved in THF-d_8 in the concentration of 5% (w/w). Strong NOE correlation signals were observed between inner protons (*b*, *c*, *d*) and middle layer protons (*e*, *f*, *g*), while outer acrylate protons of *h*, *i*, and *j* exhibited no NOE correlation with inner protons. These results suggest that the inner (*b*, *c*, *d*) and the middle layer protons (*e*, *f*, *g*) are located closely to each other due to the shrinkage of dendritic chains, while acrylate moieties are exposed to the outermost positions of the molecules without suffering from backfolding. In this manner, the acrylate groups of **Ac8b** are placed in the most activated positions so that they exhibit high Michael addition reactivity with 2-sulfanylethanol. The same tendency was confirmed in a 2D NOESY spectrum of **Ac16b** dissolved in THF-d_8. Assuming that C=O and NH moieties of **Ac8b** form hydrogen bonds with each other in a intramolecular manner, we can estimate three dimensional conformation of **Ac8b** in THF solution based on the result of 2D NOESY analysis, as depicted in Figure 8. The diameter was calculated to be ca. 2.4 nm, which is in line with the forgoing result derived from DLS analysis (2.1 ± 0.2 nm).

In summary, the results obtained by using **PETA**, **SE**, and **BEI**, which are all commercially available, support the validity of our strategy based on the AMA process to perform the quantity synthesis of dendrimer without the formation of any by-product and weight loss owing to the employment of two

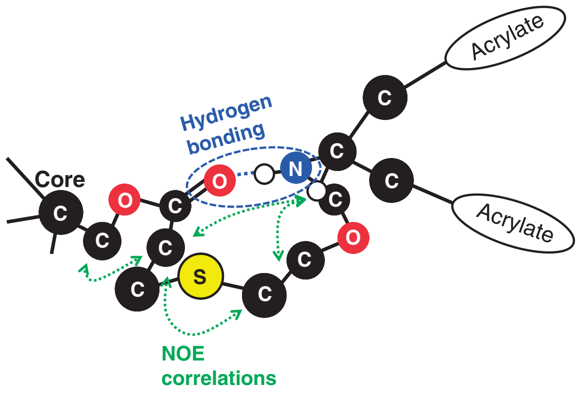


Figure 8. Feasible conformation of a branched chain of **Ac8b** in THF solution. Black, red, blue, yellow, and white circles represent carbon, oxygen, nitrogen, sulfur, and hydrogen atoms, respectively, and redundant hydrogen atoms are omitted. Hydrogen bonds between C=O and NH moieties and NOE correlations are depicted by blue and green dotted lines, respectively.

kinds of addition reactions; the Michael addition and urethane formation. It was also clarified that the appropriate choice of building blocks is crucial for the AMA process in order to skip tedious purification steps. **TG** as a trifunctional building block gave insufficient results owing to the retarded reactivity with NCO of the secondary OH groups. We believe that the dendrimers shown here play a role as specialty chemicals and precursors in developing functional dendrimers by tailor-made chemical modification, followed by final purification, as exemplified by the Michael addition of **NT** and **Fmoc-SH** to terminal acrylate residues. In addition, **Ac8b** and **Ac16b** are of practical significance as UV-curable materials because of the enhanced photosensitivity and low polymerization shrinkage, and the results will be reported elsewhere.

Conclusion

The synthetic method for dendrimers potentially usable as specialty chemicals is proposed on the basis of the AMA process accompanied by no formation of by-product and no weight loss, and requirements for the AMA process are presented. The Michael addition of thiol to acrylate and the urethane formation between NCO and OH groups were employed. Three combinations of commercially available compounds were examined to achieve the process. The first system consisted of the Michael addition of **TG** to acrylate groups of **PETA** to give the corresponding octaol (**OH8a**) quantitatively, followed by the urethane formation of the polyol with **BEI**. It was revealed that the reaction of the secondary OH groups with **BEI** bearing tertiary NCO is markedly retarded due to the steric hindrance. Second, the replacement of **BEI** by **AOI** having a primary NCO group was carried out to improve the urethane formation, but the reactivity was influenced still by the steric effect of secondary OH. Third, **PETA** was treated with **SE** as a difunctional spacer to achieve the Michael addition to afford the corresponding tetraol (**OH4**), which was subsequently subjected to the reaction with **BEI** stoichiometrically to result in the formation of the dendritic octaacrylate (**Ac8a**). Further generation growth was possible by the repetition of the alternate addition reactions, giving the dendritic hexadecylacrylate (**Ac16b**) in a large scale. The Michael addition of **NT** or **Fmoc-SH** to the dendritic acrylates was carried out to achieve the modification of chain termini in order to determine the purity of the acrylated dendrimers after chromatographic separation and to confirm the ease for the conversion into various functional dendrimers. GPC as well as UV-spectroscopic analysis of these modified dendrimers supported the well-defined, monodispersed structure of **N8b**, whereas the purity of **N16b** is slightly reduced.

Experimental

Materials. The chemical structures used here are shown in Scheme 1. 2-Isocyanatoethyl acrylate (**AOI**) and 1,1-bis(acryloyloxymethyl)ethyl isocyanate (**BEI**) were kindly gifted by Showa Denko Co., Ltd., whereas pentaerythritol tetraacrylate (**PETA**) was gifted by Shin-Nakamura Chemical Co., Ltd. α-Thioglycerol (**TG**), 2-sulfanylethanol (**SE**), and dibutyltin dilaurate (**DBTDL**) were purchased from Tokyo Kasei Kogyo Co., Ltd. Triethylamine (**TEA**), *N*,*N*-dimethylaminoethanol (**DMAE**), 2-naphthalenethiol (**NT**), ammonium salt of *N*-nitrosophenylhydroxylamine (cupferron), dicyclohexylamine, and dithranol were purchased from Wako Pure Chemical Industries, Ltd. 9-Fluorenylmethanol and α-cyano-4-hydroxycinnamic acid (**CHCA**) were obtained from Aldrich. All of the materials were of reagent grade and used without further purification. **Fmoc-SH** was prepared according to our previous report.[29]

Physical Measurements. ^{1}H- and NOESY 2D NMR measurements were carried out at 25 °C by using a Bruker AVANCE 300 MHz spectrometer. NOESY 2D NMR experiments were carried out with an acquisition time of 0.334 s, a pulse (90°) width of 12 µs, a relaxation delay of 2 s and a mixing time of 100 ms. MALDI-TOF/MS spectra were taken on an Applied Biosystems Voyager-DE Pro by using α-cyano-4-hydroxycinnamic acid (**CHCA**) or dithranol as a matrix. UV–vis spectra were taken on a Shimadzu Multi-Spec 1500. GPC was conducted on a Shimadzu system comprised of an LC-10ADvp pump unit, an SPD-10Avp UV detector, a CTO-10Avp column oven and an SCL-10Avp controller. The molecular weights of the dendrimers were determined with reference of polystyrene standards in THF solutions. Dynamic light scattering (DLS) measurements were performed by using a Malvern Zetasizer Nano ZS system. The sample solutions were filtered through membrane filters with 0.1 µm pores before DLS analyses.

Synthetic Procedures for Dendrimers. **Synthesis of OH8a:** A solution of **TG** (46.4 g, 429 mmol) in 40 mL of THF was added to a solution of **PETA** (37.7 g, 107 mmol) in 160 mL of THF, followed by adding **TEA** (3.00 g, 29.7 mmol) and was stirred at room temperature for two days. **OH8a** was isolated after the removal of the solvent under a reduced pressure for 24 h at room temperature to give 89.2 g of viscous oil. ^{1}H NMR (300 MHz, D_2O): δ 2.4–2.8 (m, 24H, $–COCH_2CH_2SCH_2–$), 3.35–3.7 (m, 16H, $–CHOH–CH_2OH$), 4.23 (s, 8H, $C–CH_2–O$). MALDI-TOF/MS (m/z): 807 ($[M + Na]^+$). The product contained 8.1% THF, as revealed by the intensity ratio of $–CH_2CH_2O–$ protons of THF at 1.83 ppm and $–CH_2OH$ at 4.23 ppm of the polyol dendrimers. The yield of **OH8a** was estimated to be 98%.

Ac16a: A solution of **BEI** (14.7 g, 61.5 mmol) in THF (150 mL) was added to a solution of **OH8a** (5.00 g, 6.37 mmol), **DBTDL** (0.768 g), and cupferron (0.633 g) dissolved in 100 mL of THF, and the mixture was heated under reflux for 10 h. Subsequently, **DMAE** (1.16 g, 13.0 mmol) in 2 mL of THF was added to the reaction mixture and refluxed for 10 h. After cooling at ambient temperature, the solution was evaporated, followed by the dilution with chloroform. The solution was washed three times with 2 M HCl, once with a saturated sodium bicarbonate solution and a saturated NaCl solution, respectively, and finally dried over magnesium sulfate. Evaporation and drying under a reduced pressure for 12 h at room temperature gave 21.3 g of a pale orange oil. The weight of the crude product was almost equal to that of the sum of the starting materials. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.43 (s, 24H, –CH_3), 2.5–2.9 (m, 31H (theoretical: 24H), –OCOCH_2CH_2SCH_2–), 3.9–4.5 (m, 54H (theoretical: 52H, C–CH_2–COO, –SCH$_2$CH(OCO–)CH_2OCO–, –CH_2-acrylate), 5.8–5.9 (m, 5.4H (theoretical: 8H), –NH–COO), 5.8–6.0 (m, 16H, acrylate-H), 6.1–6.2 (m, 16H, acrylate-H), 6.4–6.5 (m, 16H, acrylate-H).

Synthesis of Ac8a: A solution of **AOI** (8.6 g, 78 mmol) in THF (150 mL) was added to a solution of **OH8a** (5.00 g, 6.37 mmol), **DBTDL** (0.768 g), and cupferron (0.633 g) dissolved in 100 mL of THF, and a mixture was heated under reflux for 10 h. Subsequently, **DMAE** (1.16 g, 13.0 mmol) in 2 mL of THF was added to the reaction mixture and refluxed for 10 h. After cooling at an ambient temperature, the solution was evaporated, followed by the dilution with chloroform. The solution was washed three times with 2 M HCl, once with a saturated sodium bicarbonate solution and a saturated NaCl solution, respectively, and finally dried over magnesium sulfate. Evaporation and drying under a reduced pressure for 12 h at room temperature to gave crude **Ac8a** as a viscous oil (5.3 g, a crude yield of 44%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.4–3.0 (m, 26H (theoretical: 24H), –OCOCH_2CH_2SCH_2–), 3.4–3.6 (m, 21H (theoretical: 16H, NH–CH_2–), 4.0–4.4 (m, 36H, (theoretical: 36H), C–CH_2–COO, –SCH$_2$CH(OCO–)-CH_2OCO–, –CH_2-acrylate), 5.3–5.8 (m, 6H (theoretical: 8H), –NH–COO), 5.8–5.9 (m, 8H, acrylate-H), 6.1–6.2 (m, 8H, acrylate-H), 6.4–6.5 (m, 8H, acrylate-H). MALDI-TOF/MS (*m*/*z*): 1935 ([M + Na]$^+$), 1952 ([M + K]$^+$), 1794 ([M − **AOI** + Na]$^+$), 1810 ([M − **AOI** + K]$^+$).

Synthesis of OH4: A solution of **SE** (16.8 g, 215 mmol) in 50 mL of THF was added slowly to a solution of **PETA** (18.9 g, 53.6 mmol) in 120 mL of THF and **TEA** (1.52 g, 15 mmol) below 5 °C, followed by stirring at 0 °C for 2 h and at room temperature for 24 h. The removal of the solvent at 50 °C under a reduced pressure at 50 °C for 10 h gave 37.8 g of **OH4** as a colorless oil. ^{1}H NMR (300 MHz, MeOD): δ 2.6–2.7 (m, 16H, OCO–CH_2, S–CH_2–), 2.82 (t, $J = 6.0$ Hz, 8H, S–CH_2–), 3.68 (t, $J = 6.0$ Hz, 8H, CH_2–OH), 4.22 (s, 8H, CH_2–COO). MALDI-TOF/MS (*m*/*z*): 687 ([M + Na]$^+$). The product contained 7.2% of THF, as revealed by intensity ratio of –CH_2CH$_2$O– protons of THF and –CH$_2$COO– at 4.22 ppm for the product, so that the yield was estimated to be 99%.

Synthesis of Ac8b: A solution of **BEI** (28.8 g, 120.4 mmol) in 200 mL of THF was added slowly to a THF (200 mL) solution containing the crude **OH4** (20.0 g, 30.1 mmol), **DBTDL** (1.5 g, 2.38 mmol), and cupferron (0.5 g, 1.1 mmol) under reflux for 10 h and cooled at room temperature. The removal of the solvent under reduced pressure for 12 h at room temperature to gave 58.1 g of **Ac8b** as a viscous oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.41 (s, 12H, –CH_3), 2.6–2.8 (m, 24H, OCO–CH_2, S–CH_2–), 4.1–4.2 (m, 16H, (C=O)–O–CH_2–), 4.31 (d, 8H, $J = 12$ Hz, CH_2–OCONH), 4.38 (d, 8H, $J = 12$ Hz, CH_2–OCONH), 5.37 (s, 4H, OCO–NH), 5.88 (d, 8H, $J = 9.0$ Hz, acrylate-H), 6.0–6.2 (m, 8H, acrylate-H), 6.44 (d, 8H, $J = 18.0$ Hz, acrylate-H). MALDI-TOF/MS (*m*/*z*): 1643 ([M + Na]$^+$), 1659 ([M + K]$^+$). The product contained 17% THF, as revealed by ^{1}H NMR, so that the yield was estimated to be 102%.

Synthesis of OH8b: The synthesis was carried out in a manner similar to that of **OH4** from the crude **Ac8b** (25.0 g) to give **OH8b** as a viscous oil (36.6 g) after drying under a reduced pressure at 50 °C for 10 h: ^{1}H NMR (300 MHz, THF-d_8): δ 1.34 (s, 12H, –CH_3), 2.6–2.8 (m, 72H, OCO–CH_2, S–CH_2–), 3.62 (t, $J = 6.0$ Hz, 16H, –CH_2–OH), 4.0–4.3 (m, 32H, CH_2–OCO, CH_2–OCONH). MALDI-TOF/MS (*m*/*z*): 2268 ([M + Na]$^+$). The product contained 6.1% of THF, as revealed by ^{1}H NMR, so that the yield was estimated to be 97%.

Synthesis of Ac16b: The synthesis was carried out in a manner similar to the preparation of **Ac8b** from the crude **OH8b** (50.4 g) to give **Ac16b** as viscous oil (104.6 g). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.44 (s, 36H, –CH_3), 2.6–2.9 (m, 72H, OCO–CH_2, S–CH_2–), 4.1–4.2 (m, 32H, (C=O)–O–CH_2–), 4.2–4.5 (m, 48H, CH_2–OCONH), 5.40 (s, 12H, OCO–NH), 5.90 (d, 16H, $J = 9.0$ Hz, acrylate-H), 6.1–6.2 (m, 16H, acrylate-H), 6.44 (d, 16H, $J = 18.0$ Hz, acrylate-H). MALDI-TOF/MS (*m*/*z*): 4180 ([M + Na]$^+$). The product contained 13.1% THF, as revealed by ^{1}H NMR, so that the yield was estimated to be 100% under assumption that **Ac16b** possesses the ideal structure.

Reaction of Ac16a with Fmoc-SH: A solution containing crude **Ac16a** (2.0 g, 0.74 mmol), **Fmoc-SH** (5.3 g, 18 mmol), and dicyclohexylamine (180 mg, 0.92 mmol) in 50 mL of chloroform was stirred at room temperature for 3 days. The solution was washed twice with 2 M HCl, once with a saturated sodium bicarbonate solution and a saturated NaCl solution, respectively, and finally dried over magnesium sulfate. After the removal of the solvent, a residue was subjected to column chromatography on silica gel with a 1:5 (v/v) mixture of ethyl acetate and dichloromethane and subsequently with a 1:1 (v/v) mixture of acetone and dichloromethane as eluents, followed by the removal of the solvents under reduced pressure for 12 h at room temperature to give 3.4 g (a 61% yield) of crude **F16a** as a yellowish powder. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.33 (s, 32H (theoretical: 24H), –CH_3), 2.1–3.0 (m, 61H (theoretical: 72H, –COO–CH_2–CH_2–S–CH_2–), –CH_2–NH–COO–), 3.2–3.4 (m, 30H (theoretical: 32H), –CH_2–NH–COO–), 4.0–4.6 (m, 102H (theoretical: 100H), C–CH_2–COO, –S–CH$_2$(–CH)–CH_2–, NH–C–CH_2–, NH–COO–CH_2–CH–), 5.2–5.7 (s, 24H, –CONH–), 7.2–7.4 (m, 64H, aromatic C–H), 7.5–7.6 (m, 32H, aromatic C–H), 7.7–7.8 (m, 32H, aromatic C–H).

Reaction of Ac8a with Fmoc-SH: The conversion of **Ac8a** to Fmoc-terminated derivatives was carried out in a manner similar to that of **F16a** from the **Ac8a** (1.0 g, 0.52 mmol) and **Fmoc-SH** (1.87 g, 6.4 mmol) to give **F8a** as a yellowish powder (0.90 g, a 40% yield) after drying under a reduced pressure for 12 h at room temperature. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.5–2.9 (m, 130H (theoretical: 120H, –COO–CH_2–CH_2–S–CH_2–), –CH_2–NH–COO–), 3.0–3.6 (m, 32H (theoretical: 32H), –CH_2–NH–COO–), 4.0–4.7 (m, 52H (theoretical: 60H), C–CH_2–COO, –S–CH$_2$(–CH)–CH_2–, NH–COO–CH_2–CH–), 4.9–5.8 (m, 15H (theoretical: 8H), –CONH–), 7.2–7.4 (m, 32H, aromatic C–H), 7.5–7.6 (m, 16H, aromatic C–H), 7.7–7.8 (m, 16H, aromatic C–H).

Reaction of Ac8b with NT: A solution of **NT** (4.4 g, 27.5 mmol) in 60 mL of THF was added slowly to a THF solution of **Ac8b** (5.0 g, 3.08 mmol, 10 wt %) containing **TEA** (0.36 g, 3.56 mmol) at room temperature and kept stirring for 3 days. After the removal of the solvent, residue was subjected to column chromatography on silica gel (eluent: first dichloromethane, followed by a mixture of acetone and dichloromethane (v/v 1:1)), followed by the removal of the solvents under reduced pressure, to give 7.55 g of **N8b** (an 84% yield) as a viscous oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.35 (s, 12H, –CH_3), 2.56–2.72 (m, 40H, OCO–CH_2, S–CH_2–), 3.23 (t, 16H, $J = 6.0$ Hz, CH_2–OCO, CH_2–OCONH), 5.20 (s, 4H, OCO–NH), 7.39–7.48 (m, 24H, naphthalene-H), 7.72–7.77 (m, 32H, naphthalene-H). MALDI-TOF/MS (m/z): 2926 ([M + Na]$^+$), 2942 ([M + K]$^+$).

Reaction of Ac16b with NT: This was prepared in a way similar to that for **N8b** to give viscous oil (3.2 g, a 66% yield). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.35 (s, 36H, –CH_3), 2.58–2.75 (m, 104H, OCO–CH_2, S–CH_2–), 3.23 (t, 32H, $J = 6.0$ Hz, CH_2–OCO, CH_2–OCONH), 5.20 (s, 12H, OCO–NH), 7.40–7.48 (m, 48H, naphthalene-H), 7.72–7.77 (m, 64H, naphthalene-H). MALDI-TOF/MS (m/z): 6747 ([M + Na]$^+$).

UV-Spectroscopic Determination of Molar Equivalent Weight of Fmoc Unit of F8a and F16a. Crude **F16a** (47.36 mg) was dissolved in chloroform to give a 10 mL of solution. 25 µL of the solution was taken out and diluted with chloroform to obtain a 5 mL of sample solution to be subjected to UV-spectral measurement. A molar equivalent weight (i.e., molecular weight per Fmoc unit) was estimated by using molar absorption coefficient ($\varepsilon = 1.69 \times 10^4\,\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$ at 268 nm) of 9-fluorenylmethanol to be 513. Suppose that the crude mixture of **F16a** is composed of **OH8a** (MW: 784.98) and x of (**BEI** + 2 × **Fmoc-SH**) (MW: 838.0), the average molecular weight is calculated as $784.98 + 838.0x$, and the following equation is given: $[784.98 + 838.0x] = 513 \times 2x$. Since $x = 4.2$, the number of Fmoc moieties was 8.4 in average. The molar equivalent weight and the number of the terminal moieties of **F8a** were estimated in a similar manner.

UV-Spectroscopic Determination of Molar Equivalent Weight of 2-Naphthylthio Unit of N8b and N16b. **N8b** (47.77 mg) was dissolved in THF to give a 10 mL of solution. A 25 µL of the solution was taken out and diluted with THF to obtain a 10 mL of sample solution. The molar equivalent weight (i.e., molecular weight per Fmoc unit) was estimated by using molar absorption coefficient ($\varepsilon = 9.74 \times 10^4\,\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$ at 254 nm) of **N4** to be 365. Supposing that **N8b** is composed of **OH4** (MW: 664.87) and x of (**BEI** + 2 × **NT**) (MW: 559.70) moieties, the molar equivalent weight and the number of the terminal moieties were calculated. This method was also applied to **N16b**.

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