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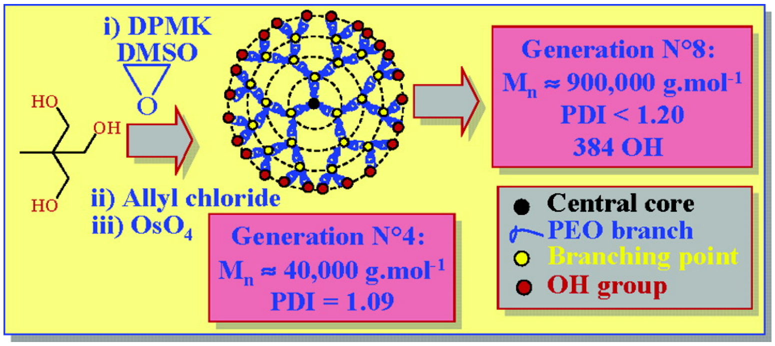

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Toward an Easy Access to Dendrimer-like Poly(ethylene oxide)s

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Abstract: Dendrimer-like poly(ethylene oxide)s (PEOs) were synthesized by an iterative divergent approach combining anionic polymerization of ethylene oxide from multi-hydroxylated precursors and branching reactions of PEO chain ends. Partial deprotonation of the hydroxyls ($<30\%$) and use of dimethyl sulfoxide as solvent proved crucial for a “controlled/living” polymerization of ethylene oxide at room temperature. These sequences of reactions allowed us to prepare a dendrimer-like PEO up to the eighth generation with a molar mass of 900 000 g mol^{-1} and 384 external hydroxyl functions. All samples from generation 1 to 8 were characterized by ^{1}H NMR spectroscopy, light scattering, and viscometry. The evolution of the intrinsic viscosity versus the generation number of these dendrimer-like PEO is similar to that of regular dendrimers.

Introduction

As stated by Flory, “architecture is a consequence of special atom relationships and just as observed for small molecules, different properties should be expected for new polymeric architectures”.[1] Such a pervasive statement has certainly inspired the efforts witnessed in the past two decades toward the synthesis of tree-like macromolecular structures such as dendrimers[2] and hyperbranched polymers.[3] Because of the high connectivity of their repeating units, which in turn shape them into globular structures, these highly branched macromolecules exhibit unique properties and have been extensively investigated for a wide range of applications, including catalysis,[4] biological molecular recognition, where dendrimers can engage in host−guest interactions,[5] energy and electron transfer,[6] and surface modification.[7]

It is well-documented, however, that a distinction should be made between “regular” dendrimers and hyperbranched polymers, although both exhibit similarities not only from a structural viewpoint (Figure 1) but also regarding their overall properties in solution or in bulk.[2,3] The former species are prepared in a stepwise fashion by repeating a sequence of coupling/modification reactions and exhibit a perfectly defined architecture with a degree of branching equal to unity. In contrast, hyperbranched polymers are generally synthesized in one-pot procedures from AB_n-type monomers, where A and B are antagonist functional groups. These architectures are characterized by a much lower degree of perfection (much higher polydispersity compared to dendrimers and degree of branching generally ranging from 0.5 to 0.6). Alternate synthetic developments have been, however, proposed toward better controlling both the branching pattern and the molar mass distribution in hyperbranched polymers.[3]

Dendrimers share with hyperbranched polymers properties such as a high solubility and a low viscosity. As illustrated in Figure 1, another common feature of both dendrimers and hyperbranched polymers is the presence of a repeating unit of monomeric size between the branching points, which implies the absence of chain entanglement. Compared to the numerous examples of regular dendrimers and hyperbranched polymers,

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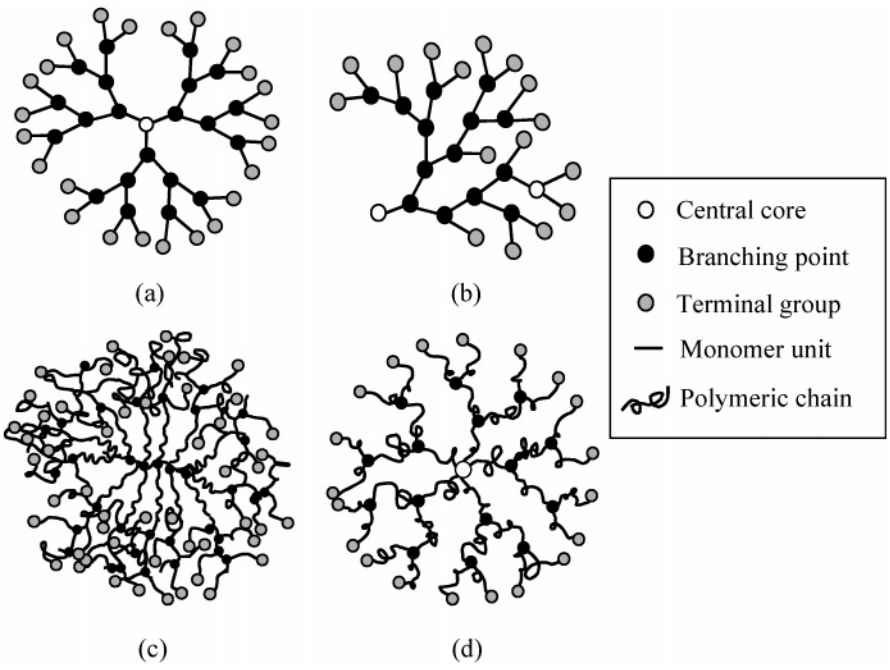

Figure 1. Representation of different tree-like macromolecular structures: (a) "regular" dendrimer; (b) hyperbranched polymer; (c) dendrigraft or arborescent polymer; and (d) dendrimer-like (star) polymer.

only a few branched architectures consisting of true oligomeric/polymeric segments between the branching points have been described in the recent literature.[8] Miscellaneous denominations such as comb-burst polymers,[9] arborescent graft polymers,[10] dendrigrafts,[10] polymers with dendritic branching,[11] and dendrimer-like polymers[12] have been proposed by authors who synthesized these architectures. Such branched polymers combine, in principle, some of the features of linear polymers such as crystallinity and chain entanglements with those of dendrimers, in particular a high number of functional end groups.

From a synthetic point of view, these branched polymers with true polymeric segments between the branching points are obtained by combination of "controlled/living" polymerization techniques[13] with selective branching reactions. In "*dendrigraft*" and "*comb-burst*" cases, a "graft-on-graft" approach based on the deactivation of linear "living" chains onto functional macromolecular backbones was followed, the linear chains becoming the grafts, and so on. As a matter of fact, branching points were introduced randomly in these structures. In contrast, "*dendrimer-like star polymers*" are synthesized by repeating two elementary steps, controlled/living chain polymerization from multifunctional precursors and chain end functionalization, to create at least two initiating sites per arm and from which upper generations could be grown. Dendrimer-like star polymers can be viewed as dendrimers with macromolecular size generations (Figure 1): they indeed share with "regular" dendrimers a number of common features, including the presence of a central core, a precise number of branching points, and outer terminal functions, differing only by the size of the generation. The term "dendrimer-like star polymers" was coined by Hedrick,[12] but the synthesis of such architectures was first contemplated by our group in 1995 in a report where we showed that polymeric chains could be connected between branching points regularly distributed within a dendritic structure.[14] Following a similar divergent approach, we recently described the synthesis of amphiphilic dendrimer-like copolymers based on poly(ethylene oxide) and polystyrene[15] and/or poly(acrylic acid) chains.[16] The same divergent strategy was adopted by the Hedrick group, who derived an entire array of dendrimer-like polyesters[17] and related core−shell copolymers composed of polylactone chains in the inner part and polymethacrylic blocks at the outer shell.[18] Percec and colleagues followed a similar synthetic methodology for the synthesis of dendrimer-like polymethacrylates of third generation:[19] starting from multifunctional initiators suitable for

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the copper-catalyzed controlled radical polymerization of methyl methacrylate, they used multipurpose compounds serving as irreversible chain terminators and multifunctional re-initiators to introduce their branching points. As for Hadjichristidis and colleagues, they followed a convergent approach to assemble anionically dendrimer-like copolymers of styrene and isoprene using a dual-functional compound as the branching agent and trichloromethylsilane or tetrachlorosilane as the central core.[20] Recently, Hirao and colleagues also proposed a convergent approach involving coupling reactions of living anionic poly(methyl methacrylate)s and functionalization of chain ends to derive dendrimer-like polymethacrylate-based systems.[21]

We wish to report here a versatile synthetic strategy affording dendrimer-like poly(ethylene oxide)s (PEOs) by a divergent approach. Our interest in such materials is motivated by the potential application of branched PEO in biomedical and pharmaceutical areas. PEO, often referred to as PEG for poly(ethylene glygol), exhibits specific properties such as chemical stability under basic or neutral conditions, water solubility, nontoxicity, ion-transporting ability, and presence of functional group(s) for the attachment of biologically active molecules.[22] In addition, the non-recognition of PEG by the immune system (PEG is “invisible” to macrophages) allows its circulation in the human body for a prolonged time (“stealth” effect).[23] For instance, the therapeutic efficacy of a protein can be improved by attaching it to PEG (PEGylation reaction), in vivo stability of the PEG-conjugated derivative being increased and its degradation being prevented by the protection offered by PEG.[24] Thus, PEGylation of biologically active molecules increases their water solubility and their stability against enzymatic degradation and facilitates their pharmacological administration.[25]

In addition to these biomedical applications, PEG is also well-known as an efficient and inert support for liquid-phase organic synthesis.[26]

The main limitation of all these applications, however, lies in the fact that low molar mass linear PEG precursors with a limited attachment capacity—one or two reacting sites depending on the chemical nature of the end groups—are generally employed. The solution might be to arrange PEG chains into a branched architecture carrying many reactive sites: better performance than for linear homologues was observed both in biomedical applications and in the use of such multifunctional PEGs as high-loading soluble supports.[27] It is therefore not surprising that studies have been dedicated to the synthesis of functionalized star-like PEOs,[28] hyperbranched PEOs,[29] or arborescent PEOs[30] in the recent literature. Hybrid block copolymers comprising linear or star-like PEO chains and rigid or flexible dendrons were also derived, with a view of developing unique stimuli-responsive micellar properties in the submicrometer size range, by self-assembly in solution or in bulk.[31] Polyester dendrons were also attached to three-arm PEO stars to produce branched water-soluble hybrid polymers used as scaffold for drug carriers.[32]

On the other hand, dendritic polyethers—polyols with physical properties analogous to those of highly branched PEG (water solubility, high loading capacity, biocompatibility, high molar masses)—were also described. For instance, regular dendritic polyethers with terminal hydroxy groups were obtained by convergent synthesis,[33] and hyperbranched polyglycerols were prepared by ionic ring-opening multibranching polymerization of OH-containing heterocycles (glycidol or 3-ethyl-3-(hydroxymethyl)oxetane) in a divergent way.[34]

As mentioned above, our group reported the synthesis of miscellaneous dendrimer-like polymers including a second generation dendrimer-like PEO that was derived by combination of both convergent and divergent methods.[35] The latter syntheses, however, suffered from a few disadvantages, including poor yields and aggregation phenomena of alkoxides during the polymerization of ethylene oxide, which prevented us from growing chains beyond the generation number 3.

Here we describe a novel and versatile synthetic approach to high molar mass dendrimer-like PEOs up to generation number 8, comprising not less than 384 peripheral hydroxy functions.

Experimental Section

Materials. Ethylene oxide (EO) (Fluka, 99.8%) was distilled over sodium into a buret. Diphenylmethylpotassium (DPMK) was prepared as described previously.[36] The concentration of DPMK was determined by titration with acetanilide and was equal to 4.5×10^{-4} mol mL^{-1}. 1,1,1-Tris(hydroxymethyl)ethane (Aldrich, 99%) and all PEO precursors were dried by freeze-drying from a dioxane solution. Dimethyl sulfoxide (DMSO, Aldrich, 99%) was distilled over CaH_2 prior to use.

Synthesis of PEOG1(OH)$_3$. In a 500 mL four-neck flask equipped with a magnetic stirrer, an inlet, and three graduated burets containing

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DMSO, ethylene oxide, and DPMK, the anhydrous trifunctional precursor 1,1,1-tris(hydroxymethyl)ethane (0.36 g, 3.0 mmol) was dissolved in dry DMSO (120 mL) under a slight nitrogen overpressure. A solution of DPMK in THF (2.7 mmol) was slowly introduced; the orange-red color was lost as the alkoxides were formed. The solution remained homogeneous and took a yellowish color. Ethylene oxide (10.2 mL, 0.21 mol) was then added. The solution was stirred at 30 °C for 48 h. The alkoxides were deactivated by adding a few drops of a concentrated solution of HCl in methanol. The solution was concentrated and precipitated with an excess of diethyl ether. After the first precipitation, as DMSO was still present in the polymer, the latter was re-precipitated twice in a large excess of diethyl ether from a dichloromethane solution. The yield was 90% after three precipitations; $\overline{M}_n = 2900$ g mol^{-1} as determined by ^{1}H NMR in DMSO-d_6 (400 MHz).

Synthesis of PEOG1(allyl)$_3$. To a solution of tetrabutylammonium bromide (135 mg, 0.42 mmol) and NaOH (1.68 g, 42 mmol) in 1.7 mL of water were added PEO-G1(OH)$_6$ (4.1 g, 4.2 mequiv) and THF (4 mL). After the solution was stirred for 30 min at 50 °C, allyl chloride (3.4 mL, 42 mmol) was added under N_2. The solution was kept for 24 h at 50 °C under vigorous stirring. The volatiles were removed and the residues extracted with dichloromethane. The solution was dried and concentrated. The product was obtained by precipitation with excess cold diethyl ether (3.4 g, 85%). ^{1}H NMR (δ_{ppm}, CDCl$_3$): 6.03−5.79 (m, 3H, CH=CH$_2$), 5.33−5.11 (m, 6H, CH=CH_2), 4.01 (d, 6H, OCH_2-CH=CH$_2$), 3.64 (PEO, broad peak), 0.91 (s, 3H, CH_3).

Synthesis of PEO-G1(OH)$_6$. To a solution of PEO-G1(allyl)$_3$ (3.4 g, 3.4 mequiv C=C), *N*-methylmorpholine-*N*-oxide (1.2 g, 10.2 mmol) in acetone (4.5 mL), distilled water (4.5 mL), and *tert*-butyl alcohol (1 mL) was added 200 μL of a 4 wt % OsO$_4$ solution in water under N_2. The mixture was stirred for 24 h at 20 °C. After removal of the organic solvents, the residue was extracted with CH$_2$Cl$_2$ and concentrated. The solution was precipitated in cold diethyl ether. The product (3.1 g, 90%) was isolated after drying in a vacuum at room temperature. ^{1}H NMR (δ_{ppm}, DMSO-d_6): 4.61 (d, 3H, CHOH), 4.45 (t, 3H, CH$_2$OH), 3.50 (PEO, broad peak), 0.83 (s, 3H, CH_3).

Synthesis of PEOG2(OH)$_6$. To a two-neck 250 mL flask charged with the dried precursor PEO-G1(OH)$_6$ (1.9 g, 3.6 mequiv OH) was added dry DMSO (60 mL) under vacuum. DPMK (1.1 mmol) was introduced at −20 °C, the temperature was slowly raised to room temperature, and the solution was stirred. The flask was again chilled, and about 10% of the EO (4.5 mL, 90 mmol) was added. After this addition, the system was stirred for 12 h at room temperature and the rest of the monomer was added. The polymerization was carried out at room temperature for 3 days. The alkoxides were deactivated with methanol. The solvent was distilled under vacuum, and the polymer (5.8 g) was obtained by double precipitation with diethyl ether from a dichloromethane solution. ^{1}H NMR (δ_{ppm}, DMSO-d_6): 4.65 (s, 6H, CH$_2$-CH$_2$OH), 3.50 (PEO, broad peak), 0.83 (s, 3H, CH_3).

Characterization. ^{1}H NMR spectra were recorded on a Bruker AC 400 spectrometer. The molar masses were determined by *size exclusion chromatography* (SEC) with tetrahydrofuran (THF) as eluent (1 mL/min) at 25 °C, a refractive index detector (Varian RI-4), and a PSS column (8 × 300 mm, 5 μm). Comparison was made with a second SEC apparatus fitted with three TSK-gel columns (7.8 × 30 cm, 5 μm, G 2000, 3000, and 4000 HR with pore sizes of 250, 1500, and 10 000 Å, respectively) and a refractive index (RI) detector (Jasco, RI-1530) with DMF as eluent (0.7 mL/min). Both SECs were calibrated using linear polystyrene or linear poly(ethylene oxide) samples, with no significant difference observed between the two types of standards. The absolute molar masses of PEO were calculated using a multiangle laser light scattering (MALLS) detector (Wyatt Technology, ASTRA Software) connected to the SEC line. The (d*n*/d*c*) values of samples were assumed to be that of linear PEO: $(dn/dc) = 0.062$ cm^3 g^{-1}.

MALDI-TOF mass spectrometry was performed using a Micromass TofSpec E spectrometer equipped with a nitrogen laser (337 nm), a delay extraction, and a reflector. The MALDI mass spectra represent averages over 100 laser shots. This instrument operated at an accelerating potential of 20 kV. The polymer solutions (10 g L^{-1}) were prepared in THF. The matrix solution (1,8-dithranol-9(10H)-anthracenone, dithranol) was dissolved in THF. The polymer solution (2 μL) was mixed with 20 μL of the matrix solution, and 2 μL of a sodium iodide solution (10 g L^{-1} in methanol) was added to favor ionization by cation attachment. The final solution (1 μL) was deposited onto the sample target and allowed to dry in air at room temperature. The detection was done in the reflector mode.

Viscosities were measured in methanol at 25 °C with a Ubbelohde viscometer. The solvent flow time was 218 s. Huggins and Kraemer plots were used to determine the intrinsic viscosities.

Dynamic light scattering (DLS) experiments were performed using an ALV laser goniometer, which consists of a 22 mW HeNe linear polarized laser with 632.8 nm wavelength and an ALV-5000/EPP multiple tau digital correlator with 125 ns initial sampling time. The samples were kept at constant temperature (25.0 °C) during all experiments. The accessible scattering angular range varied from 40° to 150°. The solutions were introduced into 10 mm diameter glass cells. The minimum sample volume required for the experiment was 1 mL. The data acquisition was done with the ALV Correlator Control Software, and the counting time varied for each sample from 300 to 600 s. Millipore water was thoroughly filtered through 0.1 μm filters and directly employed for the preparation of the solutions. All the solutions showed a monomodal distribution with a translational diffusive mode. The hydrodynamic radius (R_H) could be calculated from the diffusion coefficient using the Stokes−Einstein relation.

For *atomic force microscopy* (AFM), a dilute solution (0.01 wt %) was spin-cast on a 1 × 1 cm^2 freshly cleaved mica. Samples were analyzed after complete evaporation of the solvent at room temperature. All AFM images were recorded in air with a Dimension microscope (Digital Instruments, Santa Barbara, CA), operated in the tapping mode. The probes were commercially available silicon tips with a spring constant of 40 N/m, a resonance frequency in the 270−320 kHz range, and a radius of curvature in the 10−15 nm range.

Results and Discussion

Synthesis of Dendrimer-like PEOs. Our previous attempts to prepare dendrimer-like PEOs met with synthetic difficulties associated with the aggregation of the multiple alkoxides carried by each dendritic molecule.[14,16] Although the anionic ring-opening polymerization (AROP) of ethylene oxide (EO) is free of side reactions and follows a living path, this aggregation phenomenon prevented us from preparing samples beyond the third generation. AROP of EO, indeed, involves primary propagating alkoxides whose tendency to self-aggregate is well-known.[37,38] Depending upon the metallic countercation that is associated, aggregation can be alleviated and the reactivity of these alkoxides modulated (the higher the ionic radius of the metal, the higher the reactivity of the propagating alkoxides: $Na^+ < K^+ < Cs^+$). Aggregation is responsible for the sluggish polymerization of EO, which proceeds through a minute concentration of active non-aggregated alkoxides in equilibrium with non-reactive aggregated ones. When multiple alkoxides are used as initiators, the possibility exists that the equilibrium between reactive and inactive species shifts toward the latter ones and no polymerization occurs at all.[36,37] This is why polar solvents such as tetrahydrofuran (THF) are preferred to apolar ones like toluene to minimize the aggregation of alkoxides.

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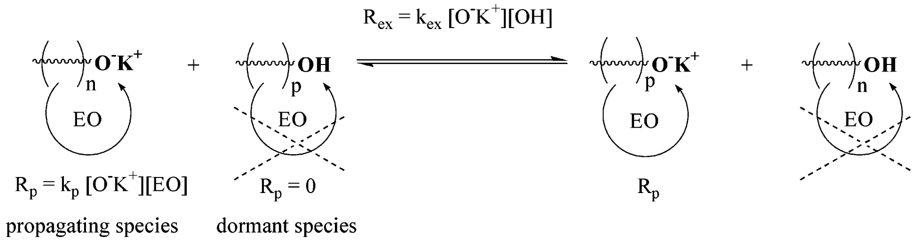
[37] Boileau, S. *Comprehensive Polymer Science*; Pergamon Press: Oxford, 1989; Vol. 3 p 467.

[38] Hsieh, H. L.; Quirk, R. P. *Anionic Polymerization. Principles and Practical Applications*; Marcel Dekker Inc.: New York, 1996.

Scheme 1. Exchange of Protons between Dormant and Active Species during the AROP of EO ($R_{ex} \gg R_p$)



Another way to avoid multiple alkoxides just precipitating in the form of a solid lump is to deprotonate only partially the multihydroxylated precursors and take advantage of the fast exchange of protons between active alkoxides and dormant hydroxylated species (Scheme 1), as shown by Flory in 1940.[39] In this case, the extent of aggregation is limited, and because the rate of exchange (R_{ex}) is much faster than that of propagation (R_p), the synthesis of PEOs with accurate control of molar masses and OH end-group functionality, exhibiting in addition narrow molar mass distribution, can normally be achieved. These conditions work for low generation dendrimer-like PEOs but failed to produce higher generation samples because aggregation could not be efficiently curbed.

A new strategy was thus developed to overcome the difficulties encountered previously and gain readily access to PEO-based dendrimers of higher generations. The synthetic scheme contemplated relied on the reiteration of the two steps of AROP of EO from multifunctional precursors and the chemical modification of the PEO chain ends, the latter sequence of reactions being carried out to introduce the branching points and multiply by two the number of initiating sites for the next generation to grow (Schemes 2 and 3).

The first step of the synthesis thus involved the preparation of star-shaped PEOs with a precise control of their size and functionality. We turned to a commercially available reagent, namely 1,1,1-tris(hydroxymethyl)ethane (**1**), as a trifunctional precursor and synthesized hydroxy-ended three-arm PEO stars, denoted PEOG1(OH)$_3$. The three hydroxyls of **1** were first deprotonated with a solution of diphenylmethylpotassium (DPMK). To prevent a too strong aggregation of propagating alkoxides, dimethyl sulfoxide (DMSO) was chosen as the solvent for polymerization instead of THF, because of its more dissociating properties at room temperature and the much higher rate of propagation it implies. A potential problem associated with the use of DMSO, however, is the occurrence of chain transfer of propagating alkoxides to this solvent, a reaction known to yield “dimsyl” carbanions ($CH_3(SO)CH_2^-$) that are capable of initiating polymerization.[36,40] In other words, the larger the concentration of propagating alkoxides in the medium, the higher the probability of forming linear chains by their chain transfer to DMSO.[41]

Bearing this in mind, the extent of deprotonation of hydroxyls by DPMK was limited to a minimum value, and the amount of DPMK was adjusted to deprotonate only 30% of the hydroxyls of the trifunctional precursor for the growth of the first generation. Such an approach was followed systematically for the subsequent generations to grow. Due to the rapid exchange of protons between dormant hydroxyls and propagating alkoxides, all three arms grew at the same rate.[28,39] The obtainment of PEOG1(OH)$_3$ with a very low polydispersity index and excellent control of their molar masses confirmed the living/controlled character of AROP of EO under these conditions. A typical ^{1}H NMR spectrum recorded in DMSO-d_6 of such a three-arm PEO star is shown in Figure 2. The signal of the terminal hydroxyl protons (CH$_2$O*H*) appears at 4.6 ppm, and the methyl protons of the core are clearly detected at 0.8 ppm.

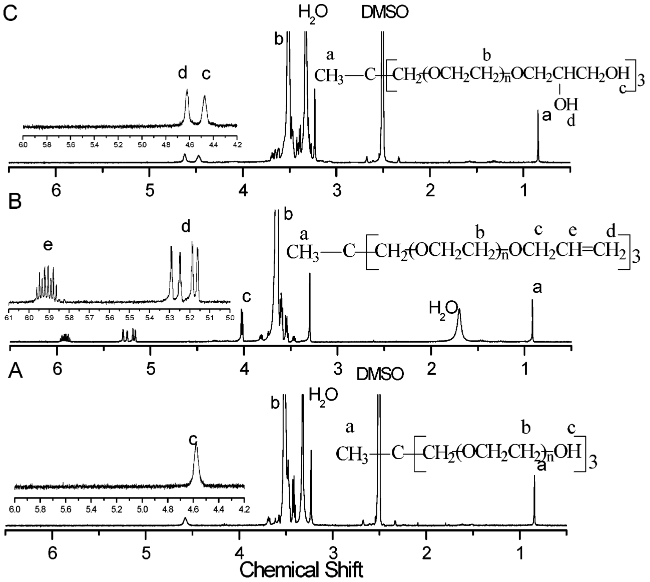


Figure 2. ^{1}H NMR spectra of PEOG1(OH)$_3$ (A, DMSO-d_6), PEOG1(allyl)$_3$ (B, CDCl$_3$), and PEOG1(OH)$_6$ (C, DMSO-d_6).

Next, the three end-standing hydroxyls of these PEOG1(OH)$_3$ stars were derivatized into twice as many hydroxyl groups. In our previous work, we resorted to a branching agent containing two geminal OH groups, protected in the form of a ketal ring, to modify the termini of the PEO branches under the conditions of a Williamson reaction. After a final step of hydrolysis carried out under acidic conditions, two geminal hydroxyls could be released at the end of each PEO arm.[14] Although functioning satisfactorily, this “branching” method proved inappropriate for the growth of generations higher than 3 because the two geminal alkoxides generated after deprotonation tended to precipitate in THF and remained inactive. We therefore reinvestigated the branching reaction of the PEO chain ends. A simple two-step sequence of reactions based on the use of commercially available reagents was developed (Scheme 3). This procedure of chemical modification of hydroxyl groups was first described by Haag and colleagues[42] in the case of their dendritic polyether polyols, and it was adapted here to the case of multiarm PEO stars, as

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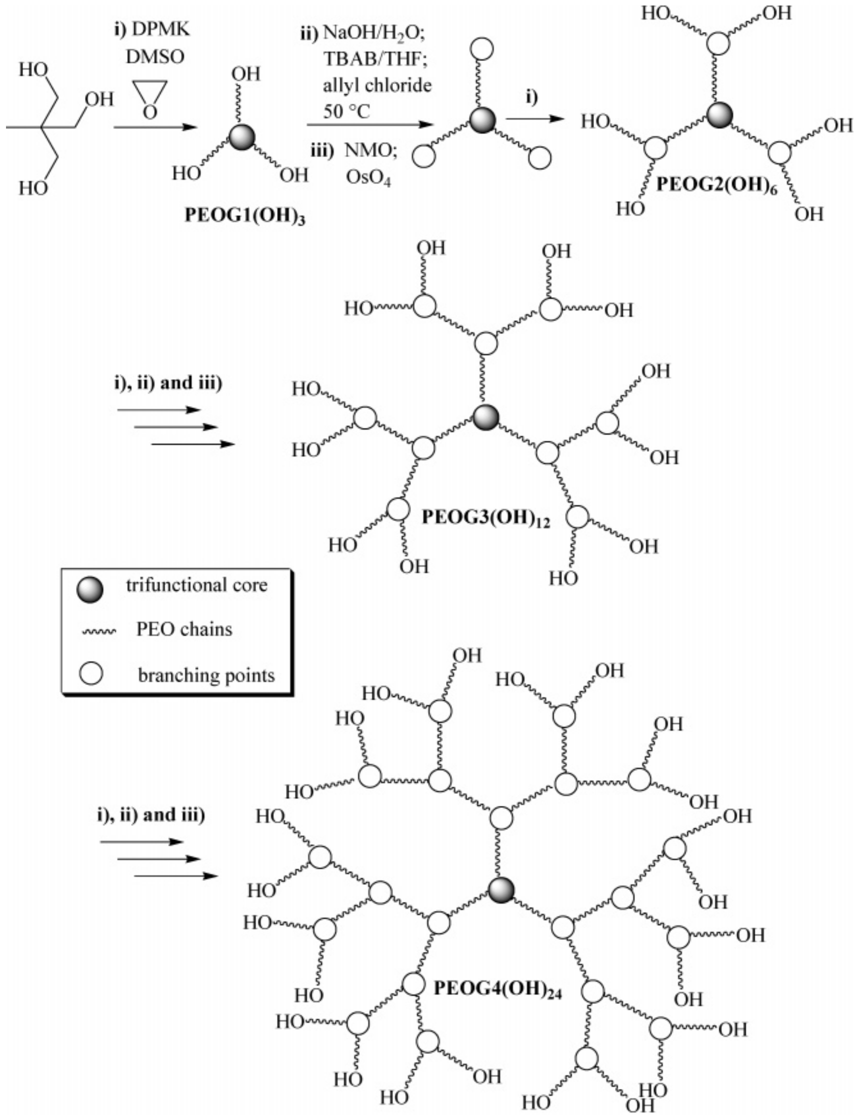
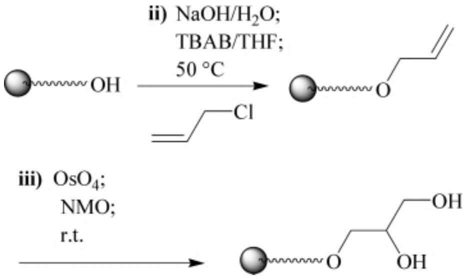
(39) Flory, P. J. *J. Am. Chem. Soc.* **1940**, *62*, 1561.
(40) Quirk, R. P.; Lizarraga, G. M. *Macromol. Chem. Phys.* **2000**, *201*, 1395.
(41) Jannasch, P. *Polymer* **2000**, *41*, 6701.
(42) Haag, R.; Sunder, A.; Stumbé, J.-F. *J. Am. Chem. Soc.* **2000**, *122*, 2954.

Scheme 2. Overall Synthetic Strategy toward Dendrimer-like PEOs[a]



[a] Details of the branching reactions (ii) and (iii) are shown in Scheme 3.

Scheme 3. Branching Reaction onto PEO Arm Ends Involving Steps (ii) and (iii)



follows. First, allyl chloride was reacted with PEOG1(OH)$_3$ in a mixture of water and THF, in the presence of a phase-transfer catalyst (TBAB), affording a three-arm PEO star, denoted PEOG1(allyl)$_3$, with allylic end groups. The latter star compound was in turn submitted to a bis-hydroxylation reaction using OsO$_4$ and *N*-methylmorpholine-*N*-oxide in a mixture of acetone, water, and *tert*-butyl alcohol. This allowed us to obtain three-arm PEO stars, denoted PEOG1(OH)$_6$, that were end-functionalized with primary and secondary hydroxyl groups at each arm (Scheme 3).

Because of the respective position of these two hydroxyls at the arm ends, precipitation of the initiating sites could be avoided upon deprotonation, a uniform growth of novel PEO chains being observed as discussed below. The effectiveness of this two-step branching reaction was monitored by ^{1}H NMR spectroscopy and by MALDI-TOF mass spectroscopy. Figure 2 shows the ^{1}H NMR spectra of the three-arm PEO derivatives, PEOG1(OH)$_3$, PEOG1(allyl)$_3$, and PEOG1(OH)$_6$, respectively. The peak around 0.8 ppm due to the methyl protons of the star core was taken as a reference for integration. After the treatment with allyl chloride, a complete disappearance of the terminal OH protons can be clearly noted, while the protons characteristic of the allylic double bonds of PEOG1(allyl)$_3$ are detected between 5 and 6 ppm. When comparing the intensity of the peaks due to the $-CH_3$ protons of the core with that corresponding to the allylic protons of the chain ends ($CH_2{=}CH-CH_2-$ and $CH_2{=}CH-CH_2-$), a 1:2:1 ratio is obtained, in very good agreement with the expected values, attesting to a quantitative functionalization. After the treatment with OsO$_4$ and *N*-methylmorpholine-*N*-oxide, both protons of primary and secondary hydroxyls of PEOG1(OH)$_6$ ($HOCH_2-CH(OH)-$

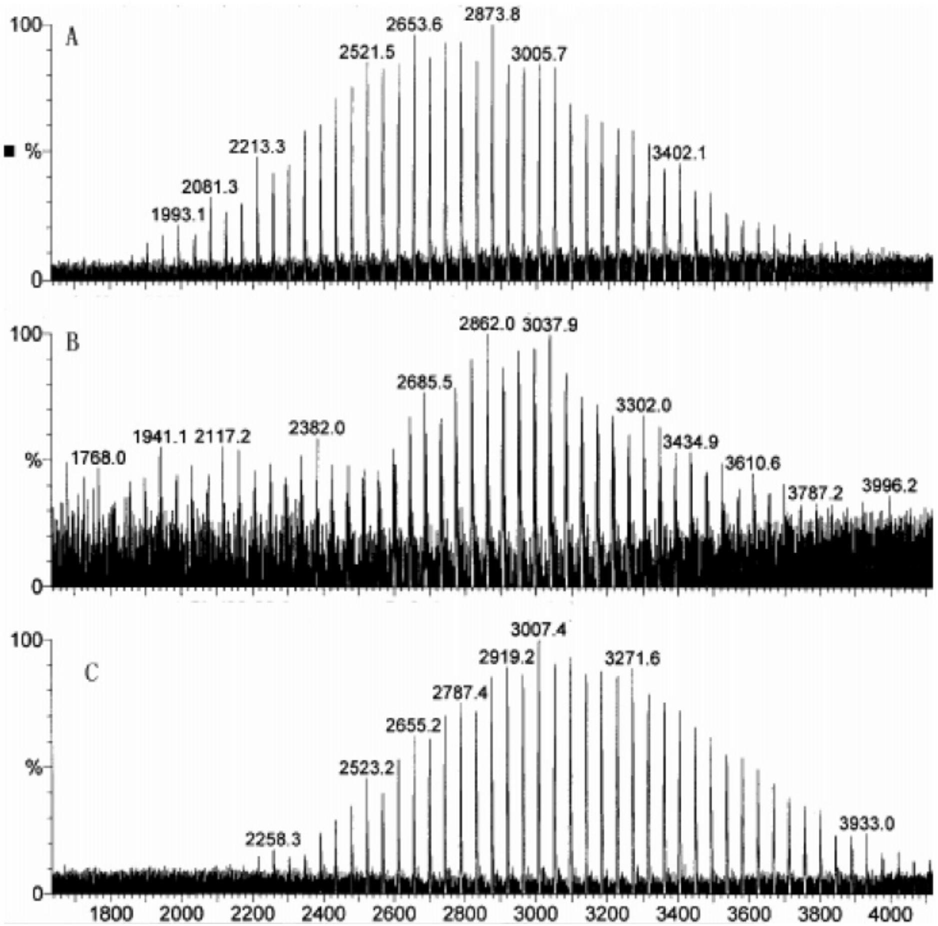


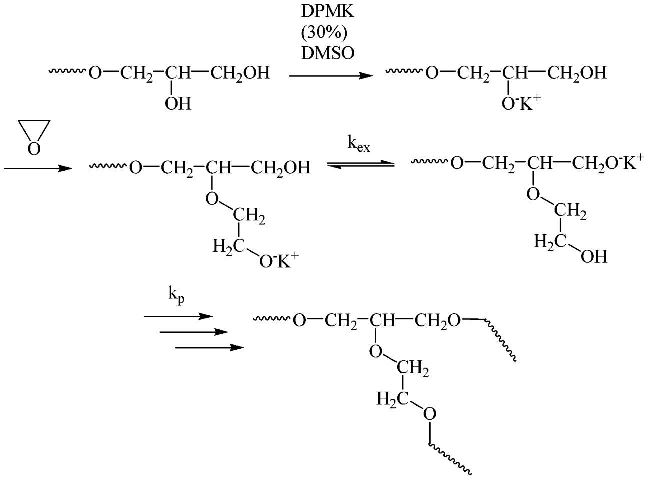
Figure 3. From the top MALDI-TOF MS of PEOG1$(OH)_6$, PEOG1$(allyl)_3$, and PEOG1$(OH)_6$.

CH_2- and HOCH$_2-$CH(OH)$-$CH$_2-$, respectively) can be distinguished and the allylic protons completely vanish. This attests to a quantitative bis-hydroxylation step.

MALDI TOF mass spectroscopy proved also powerful for monitoring the branching reaction. Figure 3 shows the MALDI-TOF mass spectra of PEOG1$(OH)_3$, PEOG1$(allyl)_3$, and PEOG1$(OH)_6$. In all cases, a single distribution is observed with a peak-to-peak mass increment of 44.05 g mol^{-1}, corresponding to the molar mass of one EO unit. The distribution obtained could be perfectly accounted for, taking into account the molar mass of the chain ends and that of the core. The peaks, indeed, appeared at $m/z = 44.05n + M_{\text{termi}} + 23$, where n is the degree of polymerization, 23 the molar mass of the sodium ion generated during the ionization process, and M_{termi} the molar mass of the end groups and the core. M_{termi} is equal to 120.15 for PEOG1$(OH)_3$, 240.34 for PEOG1$(allyl)_3$, and 342.39 for PEOG1$(OH)_6$. For instance, the peak appearing at 2873.8 corresponds to a PEO star of total degree of polymerization of 62 for the three arms. These results bring further evidence that PEOG1$(OH)_3$ could be quantitatively modified and the branching points selectively introduced at the arm ends of three-arm PEO stars.

The same sequence of reactions (i), (ii), and (iii) was then repeated starting from PEOG1$(OH)_6$ used as precursor. Again, only 30% of the OH groups carried by PEOG1$(OH)_6$ were deprotonated using DPMK. From a practical viewpoint, EO was added dropwise over several hours. Such conditions permitted the uniform growth of PEO chains from the two types of hydroxyls carried by the branching points (Scheme 4).

Scheme 4. Growth of Two PEO Branches from a Branching Point Containing a Primary and a Secondary Hydroxyl



The dendrimer-like PEO sample of second generation was obtained after 48 h of reaction in near-quantitative yields, with the polydispersity index (PDI) revolving around 1.05$-$1.15. Its experimental molar mass, determined by ^{1}H NMR as explained below ($M_n = 9000$ g mol^{-1}), is close to the theoretical value ($M_n = 8400$ g mol^{-1}).

Thus, the choice of DMSO as a solvent in combination with a low degree of titration of hydroxyls provides the best conditions for performing the AROP of EO with no visible formation of aggregates. In contrast, insoluble aggregates were

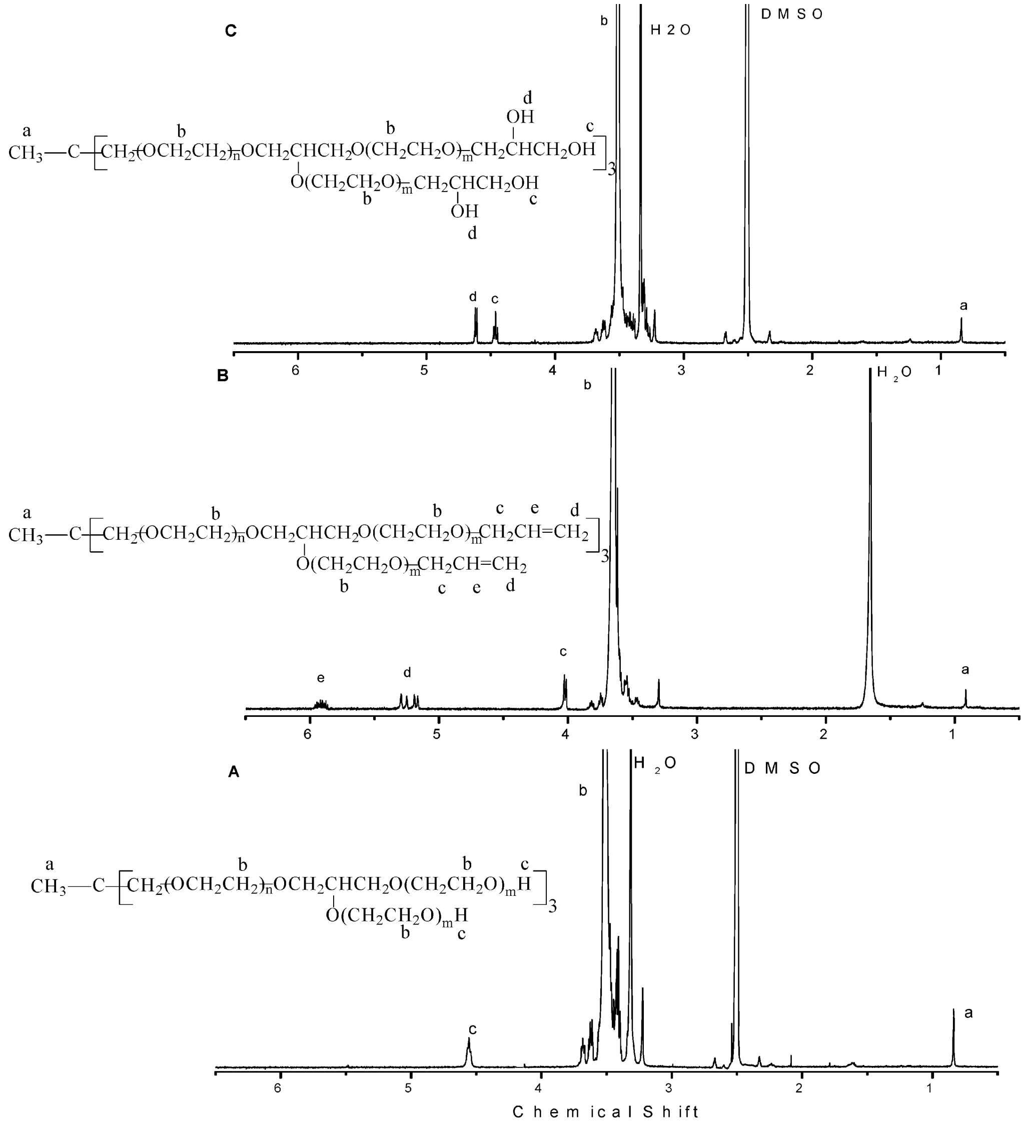


Figure 4. ^{1}H NMR spectrum of PEOG2(OH)$_6$ (A, DMSO-d_6), PEOG2(allyl)$_6$ (B, $CDCl_3$), and PEOG2(OH)$_{12}$ (C, DMSO-d_6).

Table 1. Data for Dendrimer-like PEOs

PEO	$M_{n\,theor}$[a] ×10^3	$M_{n\,NMR}$[b] ×10^3	$M_{n\,SEC\,THF}$ ×10^3 (PDI)	$M_{n\,SEC\,DMF}$ ×10^3 (PDI)	$M_{n\,MALLS\,THF}$ ×10^3 (PDI)	OH[e]
PEOG1	2.80	2.90[b]	3.40 (1.08)	6.40 (1.04)	4.74 (1.18)	3
PEOG2	8.40	9.00[b]	9.00 (1.09)	18.5 (1.05)	11.0 (1.13)	6
PEOG3	20.5	23.0[b]	18.0 (1.08)	34.9 (1.05)	24.0 (1.18)	12
PEOG4	39.9	48.5[c]	35.0 (1.09)	50.4 (1.05)	46.1 (1.16)	24
PEOG5	80.4	100 [c]	45.0 (1.09)	74.7 (1.07)	90.2 (1.19)	48
PEOG6	185	221[c]	65.0 (1.15)	115 (1.13)	211 (1.10)	96
PEOG7	410	401[c]	*d*	163 (1.18)	419 (1.08)	192
PEOG8	852	921[b]	*d*	243 (1.28)	650 (1.18)	384

[a] Theoretical molar mass obtained by gravimetry. [b] Calculated by ^{1}H NMR using the peak of methyl protons as a reference. [c] Calculated by ^{1}H NMR on (PEO)G$_n$(allyl)$_{3\times 2^{n-1}}$ ($n = 4-8$) using the double bond as a reference. [d] PEOG7 and PEOG8 could not be analyzed by SEC in THF because of interactions of these two samples with the chromatographic support. [e] Theoretical value.

formed when THF was used instead of DMSO, and a longer time was required to reach completion in THF (15 days compared to 2 days in DMSO), after which only 30% of the hydroxyls were deprotonated.

The ^{1}H NMR spectrum of the second generation dendrimer-like PEO, denoted PEOG2(OH)$_6$, was recorded at 400 MHz in DMSO-d_6 to quantify the terminal hydroxyls. This spectrum revealed all the expected signals, including the signal of the methyl protons of the core at 0.8 ppm, that of the terminal hydroxyls (CH_2OH) at 4.6 ppm, and the peak due to the protons of ethylene oxide units around 3.5 ppm (Figure 4A). The integration ratio of the these signals provided us with an estimation of the molar mass of this PEOG2(OH)$_6$ dendritic sample (see Table 1), using the following equation:

$$\overline{M_n} = \frac{I_{3.5\,ppm}/4}{I_{0.8\,ppm}/3} \times 44.05$$

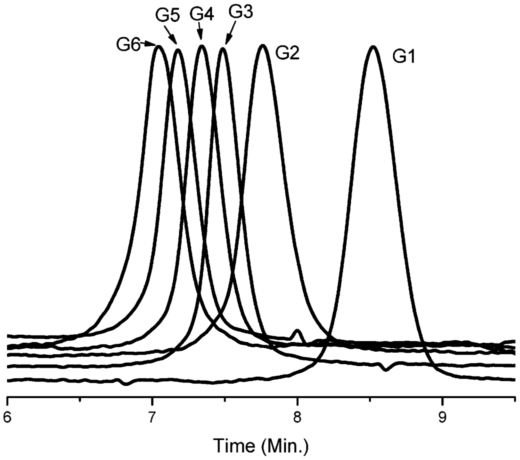


Figure 5. SEC traces (THF, RI detector) of dendrimer-like PEOs from generations 1 to 6 (see also Table 1).

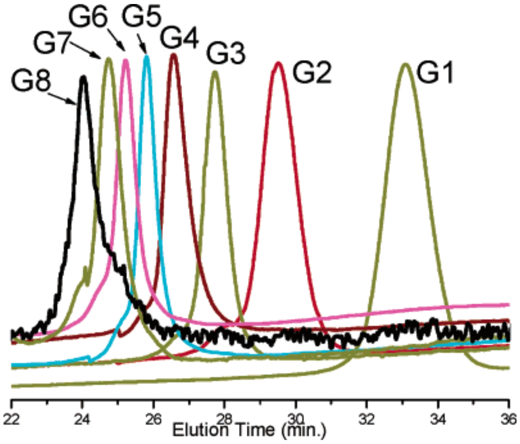


Figure 6. SEC traces in DMF of dendrimer-like PEOs from generations 1 to 8.

where $I_{3.5\text{ ppm}}$ is the integration of the peak due to the protons of ethylene oxide units (CH_2CH_2O) appearing at 3.5 ppm, $I_{0.8\text{ ppm}}$ is the integration of the peak due to the methyl protons of the core at 0.8 ppm, and 44.05 is the molar mass of one ethylene oxide unit.

As discussed above, PEOG2$(OH)_6$ was subjected to the sequence of reactions (ii) and (iii). The transformation of the six primary hydroxyls of PEOG2$(OH)_6$ into 12 peripheral hydroxyls in two steps (six primary + six secondary OH) obtained after allylation and bis-hydroxylation reaction with OsO_4 was checked by ^{1}H NMR. These data are presented in Figure 4B,C, respectively.

For the purpose of an accurate characterization by ^{1}H NMR, the PEO arms grown generation after generation were limited to the size of oligomers (DP_n per arm $\approx$ 25). Samples generated under these conditions and characterized by ^{1}H NMR all exhibit molar masses very close to the targeted values. As shown in Figure 5, the SEC traces of the different generations of dendritic PEOs with THF as eluent reflect monomodal and narrow molar mass distributions (polydispersities were lower than 1.15) free of any side population. This indicated that the transfer of alkoxides to DMSO, if existing, was negligible since linear chains of lower molar mass were not detected in these SEC traces. These results were confirmed with DMF as the eluent for SEC (see Table 1 and Figure 6).

Next, the growth of successive generations was also monitored using a multi-angle laser light scattering (MALLS) detector fitted at the outlet of the SEC columns with THF as eluent (see Table 1). Our aim here was to access the absolute molar masses of the prepared dendrimer-like PEOs. For these analyses, the d*n*/d*c* values of these PEO samples were taken to be identical to the value reported for a linear PEO of high molar mass: d*n*/d*c* = 0.062 cm^3 g^{-1}, that measured for a sixth generation sample being very close to 0.062 cm^3 g^{-1}. Except for low molar mass species, that is, for the two first generations, an excellent agreement can be observed between absolute values of molar masses delivered by MALLS and the expected ones. In contrast, values obtained for low molar mass samples may be slightly overestimated because the intensity of the LS response is proportional to the product Mc, where M is the molar mass and c the concentration of the solution, and therefore less sensitive to low molar mass species. For instance, the MALLS/SEC of PEOG2$(OH)_6$ was rather noisy. For this reason, M_n values of the first generations of dendrimer-like PEOs drawn from ^{1}H NMR characterization (from G1 to G3) are certainly more reliable; in contrast, molar masses determined by the MALLS/SEC characterization for higher generations (from G4 to G8) are more trustworthy (see Table 1). For these samples, indeed, the peak at 0.9 ppm was too weak to be used as the internal reference. Nevertheless, molar masses of dendrimer-like PEOs from G4 to G8 could be estimated from the allylic protons appearing at 5.2 ppm, using the following formula:

$$\overline{M_n} = \frac{I_{3.5\text{ ppm}}/4}{I_{5.2\text{ ppm}}/2y} \times 44.05$$

where y is the number of terminal allylic functions (24 for G4, 48 for G5, etc). In such a case, it should be stressed that an assumption was made that all the dendrimer-like PEOs contained the expected number of branches and that all OH groups were derivatized into allylic ones.

In no case could a side population be detected in the MALLS/SEC traces. In particular, no visible intermolecular aggregates of dendritic PEOs taking the form of a shoulder or a separate peak in the SEC traces could be seen. A typical MALLS/SEC trace is shown in Figure 7, confirming the monomodal shape of the distribution observed by RI detector from Figures 5 and 6. Another way to account for the well-defined character of these dendritic PEOs is to plot the cumulative mass fraction of each sample as a function of the molar mass. This is represented in Figure 8, where the molar masses were obtained by MALLS/SEC in THF for dendrimer-like PEOs from generation 2 to generation 7. The observation of almost vertical lines in each case is indicative of very narrow molar mass distribution for each of these dendritic PEO species.

For instance, a dendrimer-like PEO of generation 8, carrying up to 384 OH functions at the periphery and exhibiting a molar mass of approximately 900 000 g mol^{-1}, could be obtained with no major difficulty (Table 1). All these facts substantiate the idea that well-defined dendrimer-like PEO samples of high generation were obtained by a chemistry involving AROP of EO and selective branching reactions.

Characterization of the Size and Shape of Dendrimer-like PEOs. An accurate means to evaluate the degree of compactness of these dendrimer-like PEOs is to investigate their

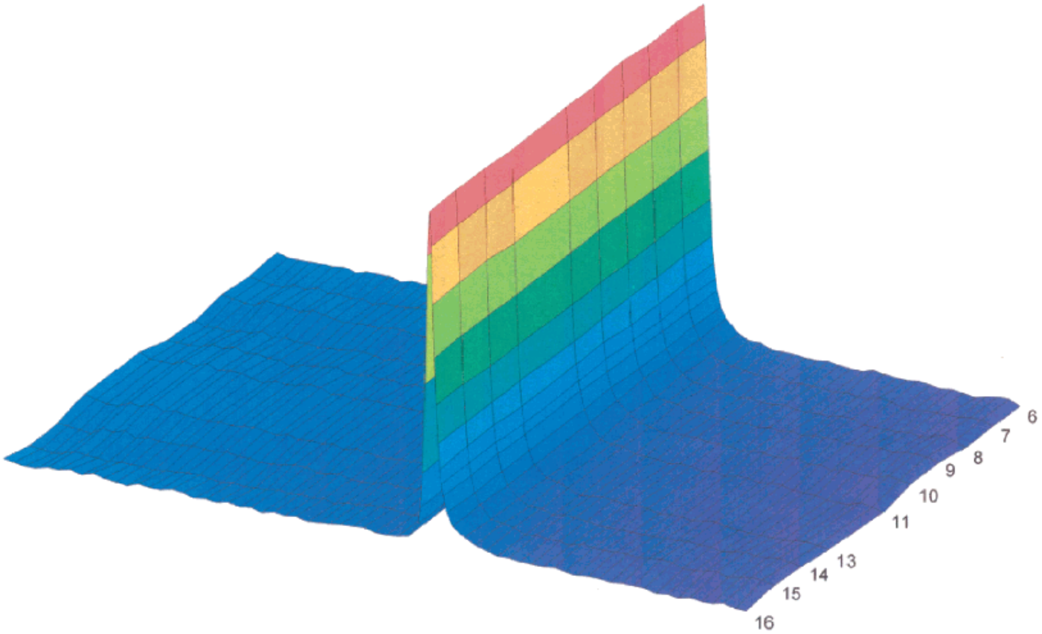


Figure 7. LS/SEC trace in THF of dendrimer-like PEOG6(OH)$_{96}$ shown in three dimensions at different angles as a function of the elution volume (low angles at the back of the figure).

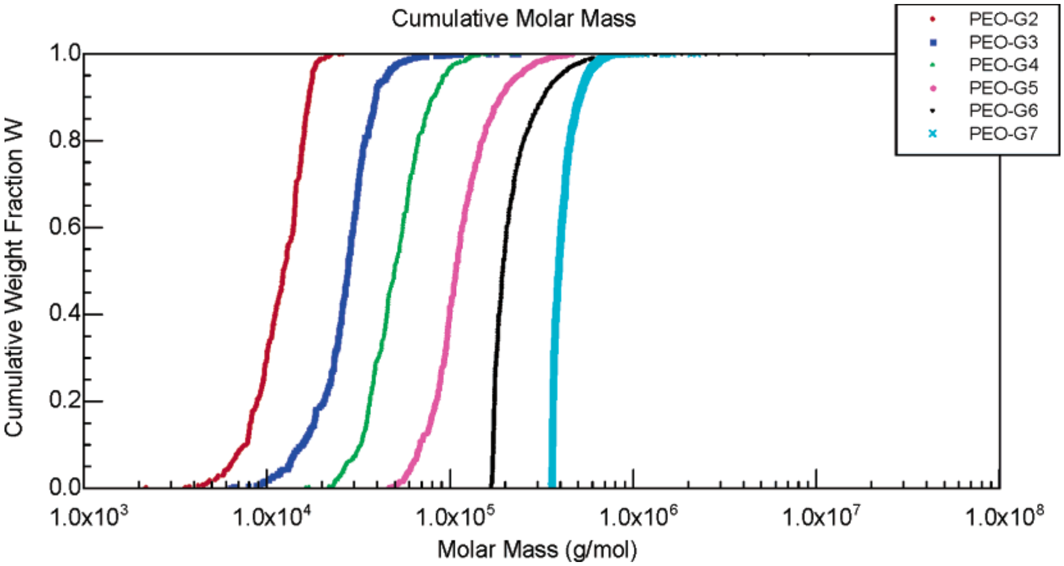


Figure 8. Cumulative mass fraction as a function of the molar mass obtained by MALLS/SEC in THF of dendrimer-like PEOs from generations 2 to 7.

intrinsic viscosity [η], a function of their molar mass. Dendrigrafts are known to behave as globular objects, and their intrinsic viscosity is independent of their molar mass, whereas regular dendrimers exhibits a bell-shaped curve for their [η] versus molar mass variation.[2,3,8,10] Since [η] is proportional to the ratio V_H/M, where V_H is the hydrodynamic volume, such a peculiar variation slightly mirrors the different dependence of hydrodynamic volumes and molar masses with the number of generations grown one after the other. The intrinsic viscosity of our dendrimer-like PEOs was determined at 25 °C in methanol as solvent (Figure 9). As expected, their Log [η] versus Log M profile is strikingly different from those observed for regular star polymers or other branched architectures. The peculiar profile of Log [η]—which also represents the reciprocal of the hydrodynamic density—for these dendrimer-like PEOs is reminiscent of that reported for regular dendrimers of lowest generations. Unlike the latter structures, however, no maximum of Log [η] could be observed for dendrimer-like PEOs of higher generations, but the trend exhibited by the Log [η] vs Log M curve, which tends to flatten as g increases, indicates that such a maximum is likely shifted beyond the eighth generation. Such a profile of [η], and thus the profile density, is unique when compared to all other branched systems synthesized so far.

Dynamic light scattering (DLS) experiments were performed on aqueous solutions of dendrimer-like PEO samples of the seventh generation. From the analysis of the normalized intensity autocorrelation function $C(q,t)$, where q is the scattering vector, the z-average diffusion coefficient D_z can be determined and used to calculate R_H on the basis of the Stokes−Einstein equation, $R_H = kT/6\pi\eta D_z$, where η is the solvent viscosity and kT the Boltzman energy factor. The R_H value was determined using the cumulant and CONTIN method (Figure 10). A unimodal and narrow size distribution is observed independently of the scattering angle considered, which suggests that PEOG7-

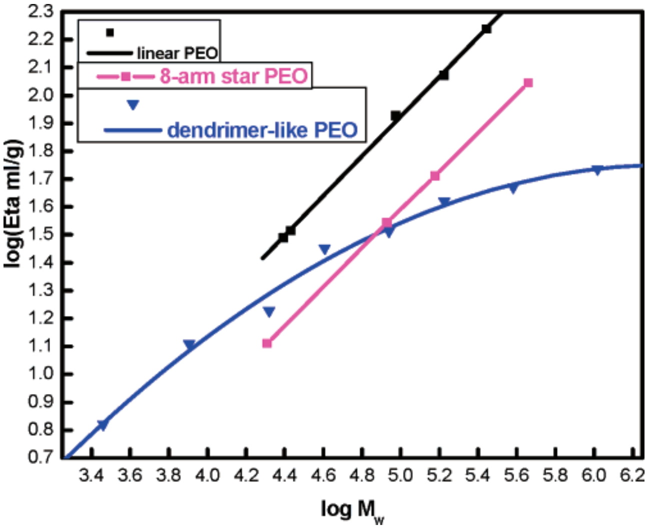


Figure 9. Evolution of Log [η] versus Log M of dendrimer-like PEOs from generations 1 to 8, eight-arm PEO stars and linear PEO (data from ref 28).

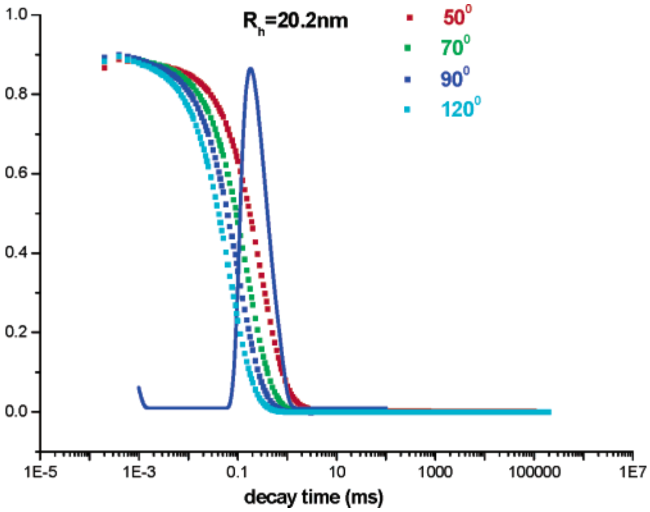


Figure 10. Dynamic light scattering on PEOG7$(OH)_{192}$ in water.

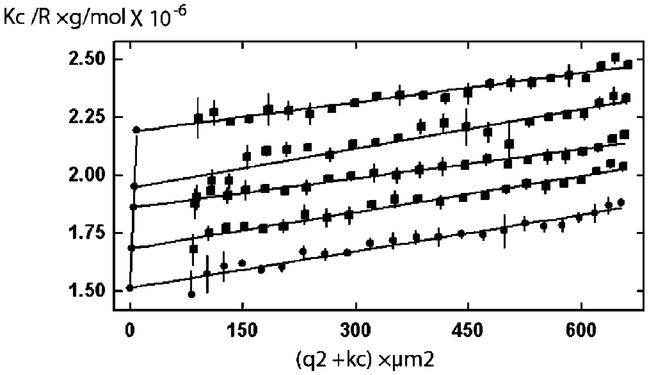


Figure 11. Zimm plot obtained by static light scattering on PEOG7$(OH)_{192}$ in water. $R_g = 32.2$ nm.

$(OH)_{192}$ adopts a spherical shape in solution. An R_H value of 20.2 nm was found. In addition to DLS, the same PEO sample of the seventh generation was analyzed by static light scattering (SLS). From the intensities measured, a Zimm plot could be drawn (Figure 11) which yielded a mass-average molar mass of 400 000 g mol^{-1}, in rather good agreement with the value determined by MALLS/SEC. SLS gave a z-average radius of gyration (R_g) of 32 nm for that particular sample. The R_g/R_H ratio of 1.6 found indicates that PEOG7$(OH)_{192}$ behaves as a loose sphere that is hydrodynamically draining in water. Finally, this sample could be directly visualized by atomic force microscopy (AFM) using a tapping mode: a spherical particle can be clearly seen with an average diameter of 40 nm, in accordance with values obtained by DLS.

Conclusion

The main objective of this study is to propose an easy access to well-defined dendrimer-like PEOs. The strategy contemplated to synthesize these highly functionalized hydrophilic materials relies on an iterative divergent method combining the "living" anionic ring-opening polymerization of ethylene oxide and chain end functionalization/branching reactions that were repeated several times. To reach that goal, the conditions best suited to polymerize ethylene oxide from multifunctional hydroxylated precursors were thoroughly investigated. Partial deprotonation of the hydroxyls (below 30%) was found to be crucial for a successful polymerization of ethylene oxide at room temperature using DMSO as a solvent. Under such conditions, near-quantitative yields were obtained and aggregation of propagating alkoxides could be prevented. The straightforward introduction in two steps of 1,2-propanediol units as branching points at chain ends also contributed efficiently to the success of these syntheses.

The reiteration of these three elementary steps afforded dendrimer-like PEOs up to the eighth generation, carrying 384 hydroxyl end groups. Following such a strategy, not only could the size of each generation be varied but also high molar mass dendrimer-like samples could be obtained in a few steps. Characterization of these dendrimer-like PEOs in solution revealed an extremely narrow size distribution of their molar masses; these samples behave as solvated spheres whose density is unevenly distributed from the core to the periphery.

Such well-defined functionalized branched PEOs should meet requirements such as solubilizing properties, mechanical properties, biocompatibility, dimensional stability, and presence of functional groups for attachment of molecules with specific properties. These dendrimer-like PEOs are currently modified to be used for the recognition of specific molecules and more generally for biomedical applications. Work is also in progress to design new branching reagents with the aim toward functionalizing the interior of these dendrimers with macromolecular generations.

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