Dendrimer-like polymers: a new class of structurally precise dendrimers with macromolecular generations†

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A new class of highly branched polymers referred to as dendrimer-like polymers has been developed in the last decade, the first synthetic example dating back to 1995. Dendrimer-like polymers exhibit molecular features similar to those of regular dendrimers, such as the presence of a central core, a precise number of branching points and terminal functions, but comprise of generations of macromolecular size between their branching junctions. In this highlight article synthetic strategies to dendrimer-like polymers are reviewed as well as some of their characteristic properties. A special emphasis is placed on synthetic methodologies designed in our group to generate dendrimer-like homopolymers and block copolymers by iterative divergent approaches based on anionic ring-opening polymerization of ethylene oxide and atom transfer radical polymerization. Are also thoroughly described the methods used for selectively branching polymeric chain-ends and introducing ω-geminal functionalities from which further macromolecular generations could be grown.

1. Introduction

Both regular dendrimers[1] and hyperbranched polymers[2] exhibit very unique properties compared with those of their linear analogues. Because of the high connectivity of their repeating units which in turn shape them in globular structures, these highly branched macromolecules exhibit unique properties and have been extensively investigated as speciality polymers for a wide range of potential applications including catalysis,[3] biological molecular recognition—where dendrimers can engage in host–guest interactions—,[4] energy and electron transfer,[5] or surface modification.[6] Dendrimers share with hyperbranched polymers properties such as a high solubility and a low viscosity but also the inability to entangle owing to the generations of monomeric size between their branching points. Besides these regular dendrimers and hyperbranched polymers, a novel class of dendritic macromolecules whose branching points are linked to each other by true polymeric chains has emerged in the literature.[7] Different names have been proposed to christen them depending upon the architecture designed and the synthetic method used: comb-burst® polymers,[8] arborescent graft polymers,[9–12]

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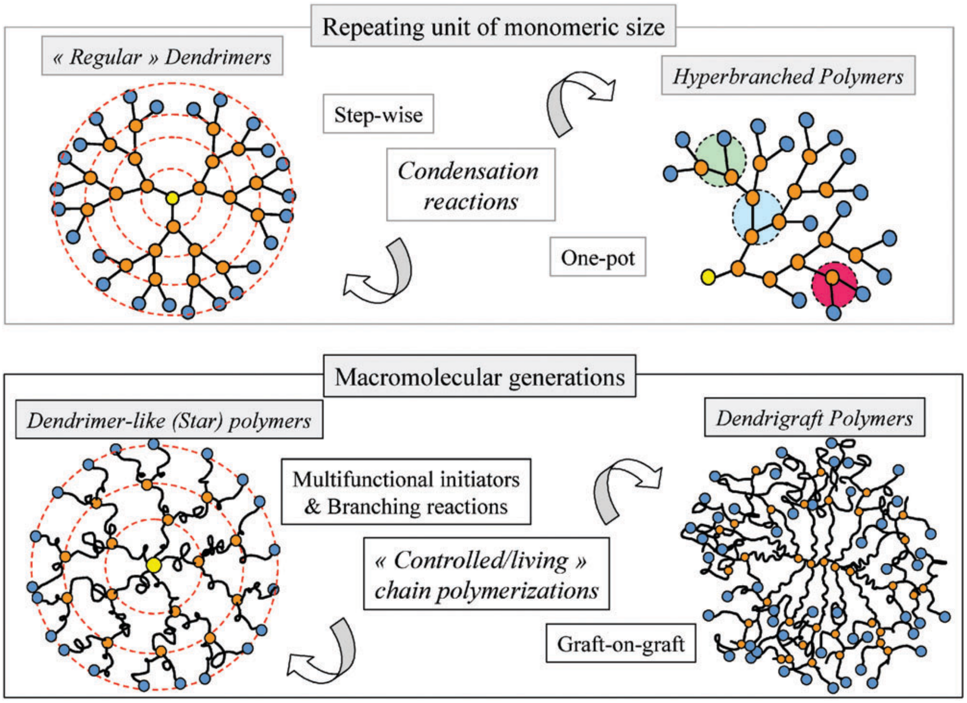

Fig. 1 Different types of dendritic architectures.

dendrigrafts,[9] polymers with dendritic branching,[13] hyper-Macs,[14] and finally dendrimer-like (star) polymers[15] to which this highlight is devoted. Such highly branched polymers comprise true polymeric arms between their branching points and combine, in principle, features of linear polymers such as crystallinity and chain entanglements with those of regular dendrimers such as a high number of functional end-groups.

From a synthetic point of view, these materials are generally obtained by combination of "controlled/living" polymerization (C/LP) techniques[16] with selective branching reactions. In "dendrigraft" and "comb-burst®" cases, for instance, a "graft-on-graft" approach based on the deactivation of linear "living" chains onto functional macromolecular backbones is followed, the linear chains becoming the grafts, and so on.[7] However, branching points are randomly introduced in these structures. In contrast, "dendrimer-like (star) polymers" are synthesized by reiterating two elementary steps that are C/LP from multifunctional precursors and selective chain end branching reactions. A rapid increase in molar masses and size are characteristic of the formation of the successive generations of dendrimer-like polymers. For instance, we have reported a dendrimer-like poly(ethylene oxide) of generation N°7 with a theoretical number of hydroxyl end groups equal to 192, a hydrodynamic radius in water of 20 nm, and a total molar mass of approx. 400 kg mol^{-1}, each polymeric branch being only of 1500 g mol^{-1} for each generation.[17] Dendrimer-like polymers can thus be viewed as dendrimers comprising a central core, a precise number of branching points and outer terminal functions but whose generations are of macromolecular size (Fig. 1). The term "dendrimer-like star polymers" was coined by Hedrick[15] but the synthetic access to these structures was first contemplated by our group in 1995.[18] We have subsequently developed versatile synthetic tools to assemble traditional polymers such as polystyrene (PS), poly(acrylic acid) (PAA) or poly(ethylene oxide) (PEO) in a dendrimer-like architecture.

In this perspective article, we describe how C/LP techniques could be successfully combined with branching reactions for the design of dendrimer-like homo- and copolymers, with a special emphasis on our own contribution. Works by other groups in this field are also briefly described. For complementary information, readers can refer to the review article by Gauthier and Teerstra[7] on "dendrigraft polymers" as well as to the recent highlight by Hirao and coworkers[19] on "precise synthesis of well-defined dendrimer-like star-branched

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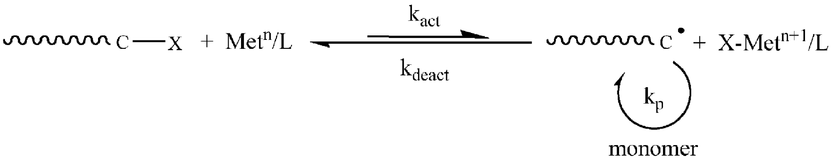


Scheme 1 Reversible termination assisted by a transition metal-based complex in ATRP.

polymers by iterative methodology based on living anionic polymerization" focusing on their own work.

2. Iterative divergent strategy to dendrimer-like polymers

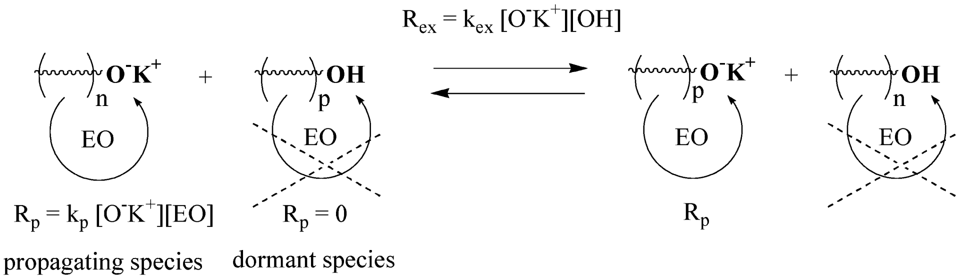
Atom transfer radical polymerization (ATRP)[20] of vinylic monomers and anionic ring opening polymerization (AROP)[21] of ethylene oxide (EO) are two C/LP that we extensively used for the synthesis of dendrimer-like polymers. Both ATRP and AROP mechanisms are based on a dynamic equilibrium between propagating active chains and so-called dormant species. ATRP is a reversible termination process brought about by a transition metal-based complex in which the metal centre undergoes redox reactions.[20] The control of the polymerization is achieved by maintaining a very low steady state concentration of radical growing chains which are reversibly transformed in a dormant halogenated (or pseudo-halogenated) form by recurrent exchange of halide (or pseudo halide) groups between polymer chain ends and the metallic complex (Scheme 1). As for AROP of EO, it involves a reversible (or degenerative) transfer of proton between propagating alkoxides and hydroxylated chains behaving as dormant species (Scheme 2).[21] As shown by Flory in 1940,[22] this exchange is fast, *i.e.* the rate of exchange, R_{ex}, is much higher than that of propagation, R_p. The AROP of EO can also be carried out with all the growing chain ends in the form of active alkoxides, but aggregation of the latter species slows down the polymerization of EO. One solution to this problem is to deprotonate only partially the hydroxylated precursor that most often plays the role of the initiating precursor and take advantage of the fast exchange mentioned above.[17,21,22]

When initiated from multifunctional precursors, C/LP of a given monomer results in the formation of regular star polymers whose chain ends are subjected to derivatization and selective branching reactions so as to generate and multiply the initiating sites of the next generation to grow. Following the same polymerization mechanism as the one used to obtain the star precursor or another one, a novel macromolecular generation can be added in this way. In Scheme 3 is shown the divergent route generally used to grow dendrimer-like homo- and copolymers, combining repetitive C/LP and chain-end branching reaction.[15,18]

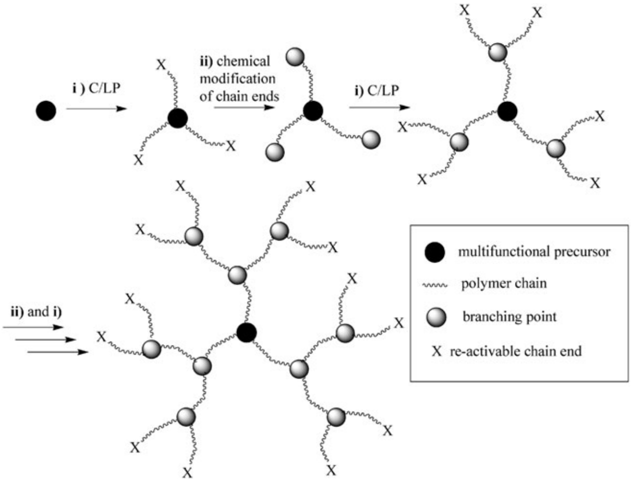
2.1 Multifunctional precursors for core-first star polymers synthesis

First in such an endeavour is thus the synthesis of star polymers with a precise number of arms using multifunctional initiators by C/LP.[23] Representative multifunctional precursors used to this end are shown in Fig. 2. We employed commercially available or readily accessible multifunctional precursors (**1–5**) for the synthesis of core-first star polymers by ATRP and by AROP of EO.[24] The group of Hedrick resorted to the ring-opening polymerization (ROP) of cyclic esters, mainly ε-caprolactone (ε-CL) initiated from multihydroxy-functional precursors such as **6**; the latter was derived from 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) and activated with stannous 2-ethylhexanoate.[15] As for Percec and coworkers, they typically used the trifunctional precursor **7** carrying three aryl sulfonyl chlorides for synthesizing multi-arm poly(methylmethacrylate) (PMMA) stars by ATRP.[25]

Depending on the polymerization method, growing polymeric chains in multiple directions may be a challenging task. For instance, the tendency of propagating anionic species (alkoxides, carbanions) to aggregate and their limited solubility make living anionic polymerization difficult to use for star synthesis by the core-first approach. As discussed in detail in previous works,[17,18,21] the conditions the best suited to polymerize EO from multifunctional hydroxylated precursors require that the latter be partially deprotonated (below 30%) by a solution of diphenylmethyl potassium (DPMK) and that AROP be carried out in dimethylsulfoxide as solvent. By preventing the aggregation of propagating alkoxides and promoting a rapid exchange of protons with dormant



Scheme 2 Reversible transfer of protons between dormant hydroxyls and active alkoxides during the AROP of EO ($R_{ex} \gg R_p$).



Scheme 3 The divergent synthetic strategy to dendrimer-like polymers.

hydroxylated species, such conditions were favourable for AROP of EO to proceed in a controlled way, yielding PEO star samples of targeted molar masses and low polydispersities.

With multifunctional precursors designed for free radical polymerization, one has to avoid that the growing arms undergo irreversible terminations. We demonstrated that the extent of these side reactions are not only correlated to kinetic parameters such as the equilibrium constant (K_{eq}) between the radical active sites and the dormant species and the ratio between k_p/k_t, where k_p and k_t are the rate constant of propagation and that of termination, but also to the actual concentration of stars in the reaction medium.[26] It is therefore essential to maintain the lowest possible concentration of propagating radicals because any irreversible recombination between growing arms would result in the loss of control of the star functionality. It was also observed that the probability for intermolecular coupling is enhanced whenever the concentration of stars crosses their critical overlapping concentration [C*]. In addition, the higher the functionality of the PS stars, the higher the probability of stars to get coupled (8 > 6 > 4). For instance, star-shaped PS containing precisely 3, 4, 6 or 8 arms can be generated by the core-first approach, using commercial reagents containing 3 or 4 bromobenzyl groups or from *tert*-butylcalix[*n*]arene derivatives as multifunctional initiators for ATRP (**1–3** in Fig. 2).[26] The polymerization was typically carried out in bulk at 110 °C, in the presence of CuBr–bipyridyl as the catalytic system. Under such conditions, good control over molar masses and polydispersities could be achieved. However, in the case of the octafunctional initiator, the polymerization of styrene had to be limited to conversion <20% in order to obtain stars with the expected functionality.[26]

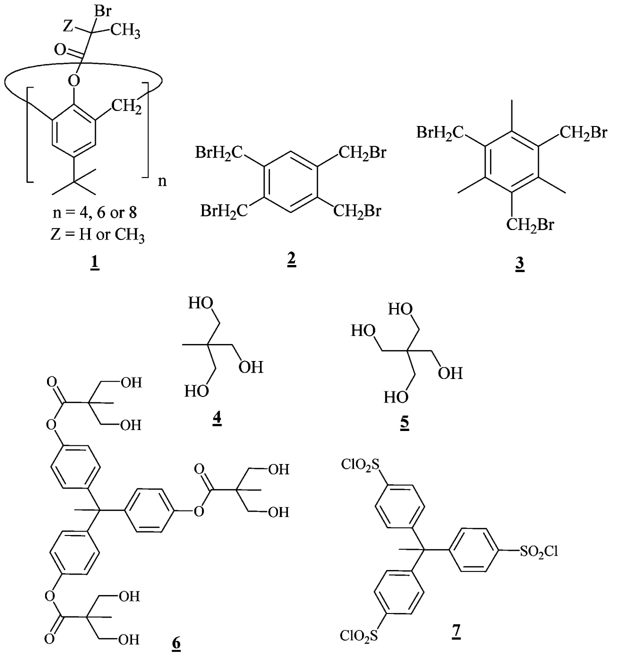
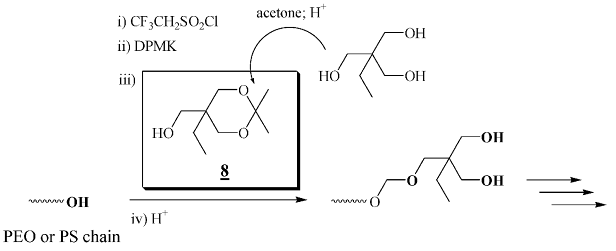


Fig. 2 Multifunctional initiators for core-first star polymers synthesis by ATRP (**1–3** and **7**),[24–26,28–31] AROP of EO (**4** and **5**)[17,18,33–36] or ROP of ε-CL (**6**).[15,43–46,48–51]

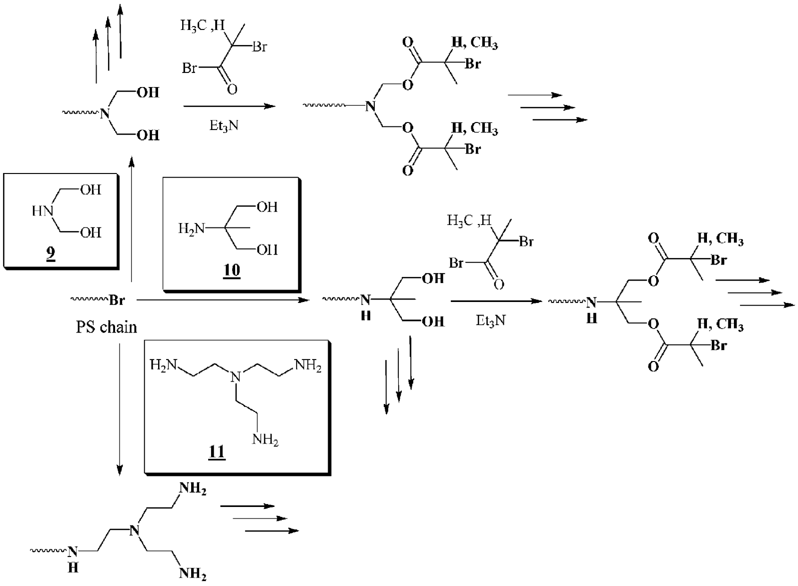
2.2 Branching reactions of polymer chain-ends

Branching reactions consist in transforming the end-groups carried by star or dendrimer-like polymers into at least twice as many initiating sites for the growth of the next generation which can be based on either the same or another monomer. Schemes 4–7 show representative branching agents and branching reactions used by us to introduce geminal functionalities at PS or PEO chain ends and from which additional polymer branches could be grown. Generally speaking, quantitative displacement of ω-end groups could be evidenced by NMR spectroscopy as well as by MALDI-TOF mass spectrometry.

We originally developed an AB_2-type branching agent, namely, 2,2-dimethyl-5-hydroxymethyl-1,3-dioxane, **8**, containing two geminal OH groups protected in the form of a ketal ring (Scheme 4). This compound was found efficient to derivatize hydroxy-ended multiarm PS stars grown initially by "living" cationic polymerization[27] and also hydroxy-ended multiarm PEO stars obtained by AROP of EO.[18] The hydroxyl functions carried at PS or PEO arms had to be transformed, first, into trifluoroethanesulfonyl groups, before being reacted with the branching agent **8** under its alkoxide form which resulted in the nucleophilic displacement of the trifluoroethanesulfonate groups. Acidic cleavage of the ketal functions finally afforded PS or PEO with two geminal hydroxyls per PS or PEO branch. This branching method, however, proved inappropriate for the growth of generations of PEO higher



Scheme 4 Branching of ω-hydroxy PEO or PS chains for AROP.[18,27]

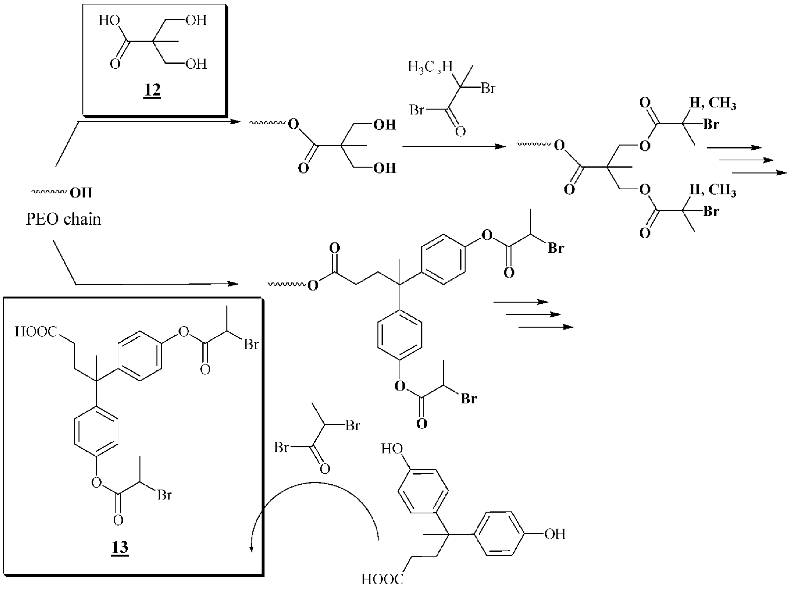


Scheme 5 Branching of ω-bromo PS chains for ATRP and AROP.[28–32]

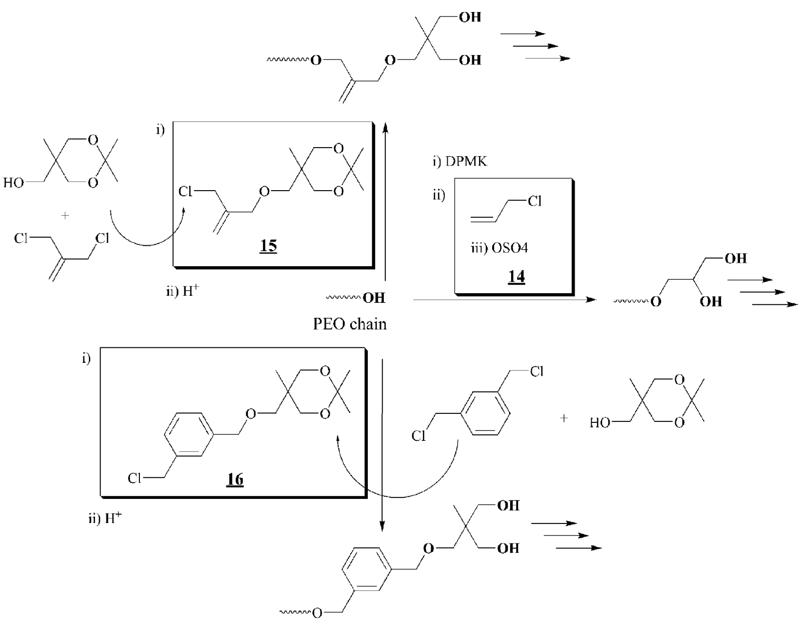
than 3 because the two geminal alkoxides generated after deprotonation tended to precipitate in THF and remained inactive.[18]

Alternatively, bromo-end groups of PS branches derived by ATRP could be quantitatively transformed into twice as many hydroxyls by nucleophilic substitution using a large excess of commercially available AB_2-type reagents such as serinol (**9**)[28,29] or diethanolamine (**10**).[30–32] Such branching reactions (Scheme 5) were particularly suitable to grow outer PEO layers, since these branching agents did not contain any electrophilic functions (such as ester groups) that could interfere with the AROP of EO.[30] Furthermore, esterification of the geminal OH groups thus introduced at the termini of ATRP-derived PS branches could be readily achieved using 2-bromoisobutyryl bromide in the presence of triethylamine.[28–32] Such ω,ω′-dibromo PS could then be used as macroinitiator for the growth of either an additional layer of PS or of another polymer, *eg* poly(*tert*-buylacrylate) (P*t*BA), following standard ATRP conditions.[28,32] Also, the commercially available A_3-type tris-amine **11** (Scheme 5) could be used to derivatize ω-bromo PS derived by ATRP into ω,ω′-primary amino groups, as previously reported.[32]

To derivatize hydroxyls of PEO termini into ATRP bromo-end groups, appropriate AB_2-type branching agents were designed (Scheme 6). For instance, 2,2-bis(hydroxymethyl) propionic acid (bis-MPA) (**12**) were treated with PEO arms in the presence of dicyclohexyl carbodiimide and *N*,*N*-dimethylamino pyridine *p*-toluene sulfonic acid.[33] The geminal OH groups generated were then esterified using 2-bromopropionyl bromide in the presence of triethylamine. Alternatively,



Scheme 6 Branching of ω-hydroxy PEO chains for ATRP.[33,34]



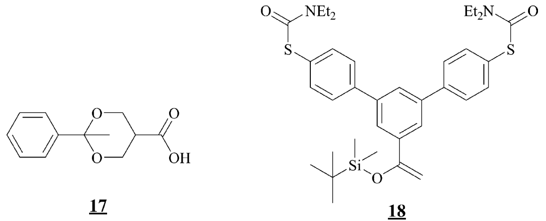
Scheme 7 Branching of ω-hydroxy PEO chains for AROP.[17,36]

the branching agent **13** could be synthesized following a two-step sequence and be readily attached to hydroxy-ended PEO chains by a simple esterification reaction.[34]

Recently, we revisited the branching reaction of PEO chains with a view of generating dendrimer-like PEO's of much higher generation number than those obtained in first instance.[17] A straightforward two-step sequence of reactions (Scheme 7) based on the use of commercially available reagents (**14**) was thus developed to introduce 1,2-propanediol units as branching points at PEO chain ends, instead of using our former branching agent **8**. First, allyl chloride was reacted with OH end-groups of PEO chains in the presence of a phase transfer catalyst, affording a PEO derivative with allylic end groups, which in turn was submitted to a bis-hydroxylation reaction, using OsO_4 and *N*-methylmorpholine-*N*-oxide.[17] Interestingly, it was shown that MALDI-TOF mass spectroscopy could be used for the analysis of dendrimer-like PEO's of second generation with molar masses higher than 10 000 Da.[35] Detailed analysis of the isotope distributions confirmed that the terminal hydroxyl groups of PEO branches could be multiplied by a factor of 2 in a quantitative way after carrying out the branching steps mentioned above. According to MALDI-TOF results, not only narrow molar mass distributions were obtained but the expected 12 peripheral functions were quantitatively introduced at PEO chain ends.[35]

More recently,[36] we designed an original AB_2C-type branching agent for PEO chains, **15**, containing (i) a chloromethyl group (A) for the hooking reaction with the hydroxyl groups of PEO arms, (ii) two hydroxyls (B_2) masked under a ketal form to be released for the growth of the next generation by the AROP of EO and (iii) an allylic group (C) for derivatization purpose into ATRP sites. Allyl moieties were chosen as C groups because they are insensitive to alkoxides present in both the AROP of EO and during chain end branching. Moreover, allyl functions are known to readily undergo chemical modification into hydroxyls or carboxylic groups. For this purpose, methallyl dichloride (MDC) was used as starting material to derive the AB_2C-type branching agent, namely, 2-(2′-chloromethyl-propenyloxymethyl)-2-methyl-5,5-dimethyl-1,3-dioxane (DBBA) (**2**), as described in Scheme 7. The branching reaction utilizing **15** as branching agent combined with trimethylolpropane (**5**, Fig. 2) initiated by AROP of EO allowed us to prepare dendrimer-like PEO's of fourth generation functionalized with allylic groups in their inner part (see Section 2–3–6– below). A fifth generation of PEO chains with not less than 48 PEO branches was grown by AROP of EO from this parent dendrimer-like PEO using a "conventional" AB_2-type branching agent, **16** (Scheme 7).

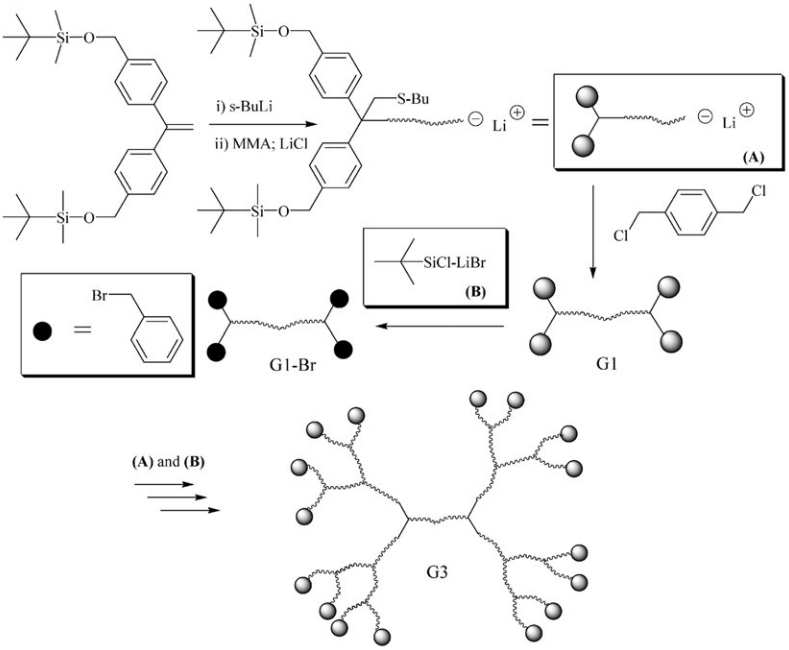
Fig. 3 shows branching agents employed by other groups for the synthesis of dendrimer-like polymers. The group of Hedrick mainly used bis-MPA as synthon of branching agents such as **17** to obtain their dendrimers based on aliphatic polyesters. Additionally, AB_4-type and AB_8-type dendrons derived from bis-MPA were also used to generate dendrimer-like polylactone isomers differing only on the location of their branching junctions. As for Percec and collegues, they designed multipurpose compounds such as **18** that they named TERMINI serving as irreversible chain TERMInator of



17

18

Fig. 3 Representative branching agents used by Hedrick and collegues (**17**)[15,43–46,48–51] and Percec and collegues (**18**)[25] for the synthesis of dendrimer-like PCLs and dendrimer-like PMMAs, respectively.



Scheme 8 Synthetic strategy to dendrimer-like PMMAs developed by Hirao and collegues.[19]

growing chains and masked multifunctional INItiator for the next generation to grow.[25]

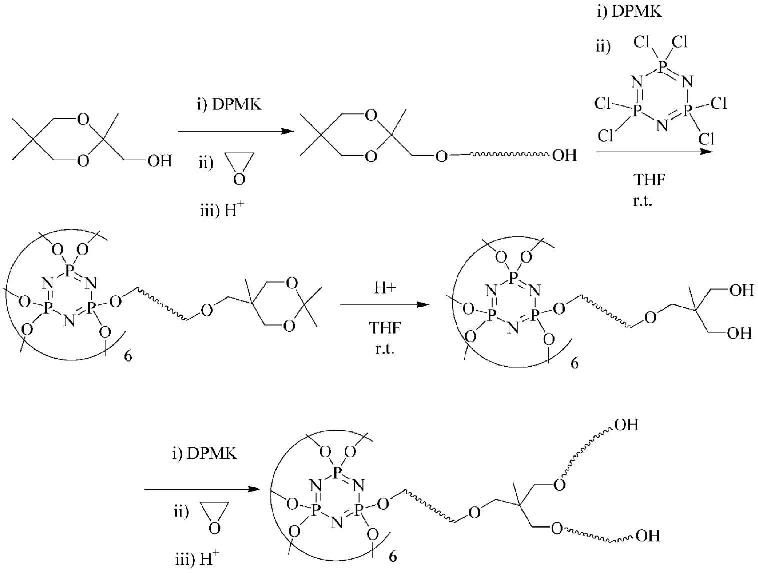
To obtain their dendrimer-like polymers based on poly (methyl methacrylate) (PMMA), the group of Hirao developed an iterative method relying on both divergent and convergent pathways, involving the deactivation/linking reaction of living PMMA chains functionalized in α-position with at least two *tert*-butyldimethylsilyloxymethylphenyl groups (Scheme 8) followed by the chemical transformation the latter functions into benzyl bromides (BnBr).[37] These BnBr functionalities could subsequently serve for the deactivation of new living PMMA chains. This concept of PMMA chain-end branching is discussed in more detail in ref. 16.

2.3 Dendrimer-like polymers and core-shell dendrimer-like block copolymers

2.3.1 Dendrimer-like poly(ethylene oxide)s. PEO exhibits unique properties such as chemical stability, water solubility, non-toxicity, ion-transporting ability, non-recognition by the immune system (stealth™ effect) and presence of functional group(s) that permits the covalent attachment of biologically active molecules (PEGylation reaction).[38,39] This has been exploited to increase the *in vivo* stability and therapeutic efficacy of biologically active molecules after their conjugation. Linear PEO chains, however, has a limited loading capacity for the PEGylation of biomolecules. The solution might be to arrange PEO chains into a dendrimer-like architecture that could thus carry many terminal reactive sites so that the loading capacity of PEO could be dramatically augmented. In 1995, our research group described the first example of dendrimer-like polymers which was based on the reiteration of AROP of EO and arborization of PEO chain ends based on the use of **8** as branching entity. Later on, we reported on the synthesis of a second generation dendrimer-like PEO derived by combination of both convergent and divergent methods.[40] A six-arm PEO star was first synthesized by the arm-first approach through deactivation of a 6-fold excess of a α-ketal, ω-hydroxy PEO linear precursor onto hexachlorocyclophosphazene which served to build the core (Scheme 9). Acidic treatment of the corresponding six-arm PEO stars with their six terminal ketal rings afforded six arm PEO stars with twelve peripheral hydroxyls. The latter compound was subsequently deprotonated and used for the AROP of EO following a divergent approach; a dendrimer-like PEO consisted of a first generation of six PEO arms and a second generation of twelve hydroxy-ended PEO branches could be obtained in this way.

The advantages provided by the dendritic structure, in particular the high loading capacity due to the multiplicity of OH terminal groups could thus be combined with the unique features of PEO, namely its stealth effect™. We, indeed, derivatized such second generation dendrimer-like PEO's with glycosidic end units.[41] The corresponding materials were found to exhibit better anti-inflammatory activity *in vivo* than their linear and even their star glycosidic counterparts.

The syntheses of these dendrimer-like PEO's, however, suffered from a few disadvantages,[18,27] including poor yields and aggregation phenomena of alkoxides during AROP of EO, which prevented us from growing generations beyond the third one. We therefore revisited our synthetic strategy to dendrimer-like PEO's. In our novel approach, we significantly improved the branching steps (Scheme 7) as well as the control of the polymerization itself. In particular, the partial deprotonation of hydroxyls ($<30\%$) and the use of dimethylsulfoxide as solvent proved crucial for a "controlled/living" AROP of EO at room temperature. Under such conditions near quantitative yields were obtained and aggregation of propagating alkoxides were prevented. The straightforward introduction in two steps of 1,2-propanediol units as



Scheme 9 Combining arm-first and core-first strategies to synthesize a second generation dendrimer-like PEO[40].

branching points at chain ends also contributed efficiently to the success of these syntheses (Scheme 7). A series of dendrimer-like PEO's up to the eighth generation was thus generated, the final compound having a molar mass of 900 kg mol^{-1} and 384 external hydroxyl functions (Fig. 4). Samples from generation 1 to 8 were thoroughly characterized by ^{1}H NMR spectroscopy, light scattering and viscometry (see Fig. 5 for details). For instance, the evolution of the intrinsic viscosity [η] *versus* the generation number of these dendrimer-like PEO reminded that of regular dendrimers. Indeed, a peculiar profile of [η]—which is also inversely proportional to the hydrodynamic density—with respect to the number of generations/molar mass was observed for these dendrimers based on PEO generations,[17] *i.e.* a bell-shape curve like regular dendrimers (Fig. 6).[42] The relation between [η] and the hydrodynamic volume (V_{H}) is as follows: $[\eta] = 2.5\ N_{\mathrm{a}}\ V_{\mathrm{H}}/M = 10\ \Pi/3\ N_{\mathrm{a}}\ R_{\mathrm{H}}{}^{3}/M$ where R_{H} is the hydrodynamic radius and N_{a} the Avogadro number. Unlike the cases of arborescent[7] or hyperbranched polymers,[2] the variation of [η] with respect to the number of generations in the case of regular dendrimers mirrors the different dependence of hydrodynamic volumes and molar masses with the number of generations (g). Indeed, molar masses in regular dendrimers increase exponentially with g according to 2^{g-1} and their hydrodynamic volume grows with g^3; [η] varying proportionally to $g^3/2^{g-1}$, it passes therefore through a maximum with increasing g. The progression of molar masses with the number of generations for dendrimer-like PEO's follows the same exponential trend in 2^{g-1}, the two families of dendrimers exhibiting common molecular features.

Characterization of these dendrimer-like PEO's in water or tetrahydrofurane solutions revealed extremely narrow size distribution of their molar masses. Dynamic light scattering in water showed that these samples behave as unimolecular solvated spheres whose density is unevenly distributed from the core to the periphery.

2.3.2 Dendrimer-like polystyrenes. The branching procedure of PS termini described in Scheme 5 was applied to multiarm PS stars grown from calixarene-based cores in order to derive dendrimer-like PS exclusively by ATRP.[29] Thus, four-, six- and eight-arm PS core-first stars were derivatized so as to generate PS stars carrying 8, 12 or 16 geminal bromoisobutyrate groups, respectively. These PS precursors

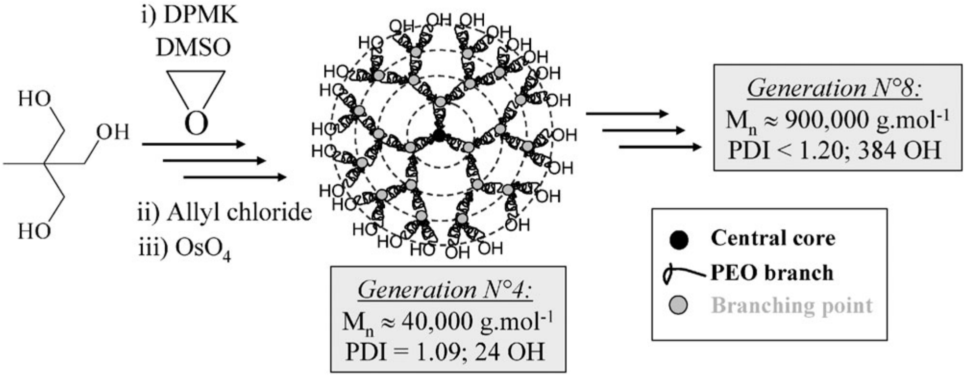


Fig. 4 Synthetic strategy to dendrimer-like PEO's up to generation 8 (see also Scheme 7).

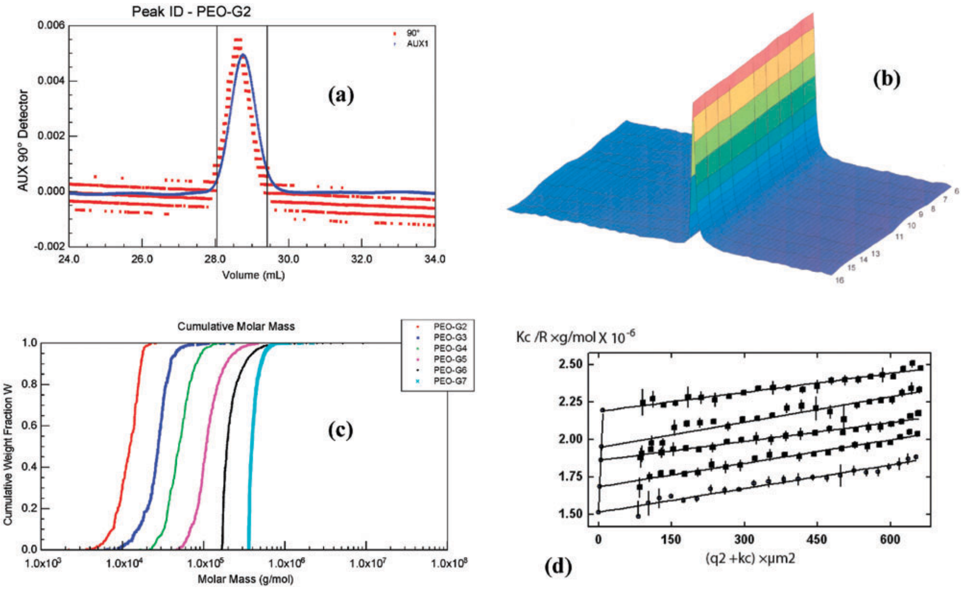


Fig. 5 Characterization of dendrimer-like PEO's in solution (see also Scheme 7). (A) refractometric (blue) and LS (red) responses by SEC in THF of a dendrimer-like PEO of generation 2, PEOG2$(OH)_6$. Although the LS signal is noisy due to the low molar mass sample, the signals show uniform and narrow molar masses distribution; (B) LS/SEC trace in THF of dendrimer-like generation 6 PEOG6$(OH)_{96}$ shown in three dimension at different angles as a function of the elution volume (low angles at the back of the figure) showing a monomodal shape; (C) cumulative mass fraction as a function of the molar mass obtained by MALLS/SEC in THF of dendrimer-like PEO's from generation 2 to generation 7. Vertical lines in each case are indicative of narrow molar mass distribution; (D) Zimm plot obtained by static light scattering on dendrimer-like PEOG7$(OH)_{192}$ in water; the mass average molar mass (M_w) is equal to 400 kg mol^{-1} and the radius of gyration to 30 nm.

served as multifunctional macroinitiators for the formation of a second generation of PS by ATRP. Reiteration of the aforementioned sequence afforded dendrimer-like PS of third generation constituted of 16, 24 or 32 outer arms, respectively, as depicted in Fig. 6. The ester linkages present at the core and at the branching junctions of such dendrimer-like polymers were then subjected to cleavage under basic conditions so that the molar mass of each generation and its uniformity could be checked. The actual polymer architecture and the functionality of dendrimer-like PS could thus be confirmed by analysis of the individual arms after hydrolysis.[29]

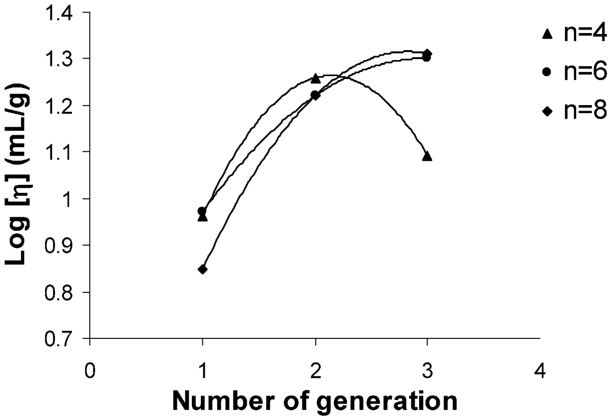


Fig. 6 Evolution of Log[η] as a function of the number of generation (*G*) for dendrimer-like PS prepared using tetrafunctional (*n* = 4), hexafunctional (*n* = 6), or octafunctional (*n* = 8) initiators (see **1** in Fig. 2).

In addition, the intrinsic viscosity [η] of these dendrimer-like PS determined at 35 °C in toluene gave much lower values than those observed for linear homologues. The same peculiar profile of [η] with respect to the number of generations/molar mass was observed for these dendrimers based on PS generations as in the case of dendrimer-like PEO's,[17] *ie* a bell-shape curve (Fig. 7). This, again, indicated that [η] was not independent of the molar mass for these dendrimer-like PS as in the case of hyperbranched polymers.

2.3.3 Dendrimer-like polycaprolactones. The group of Hedrick also adopted a divergent strategy based on the ROP of ε-CL and the use of **17** as a branching agent to derive an entire

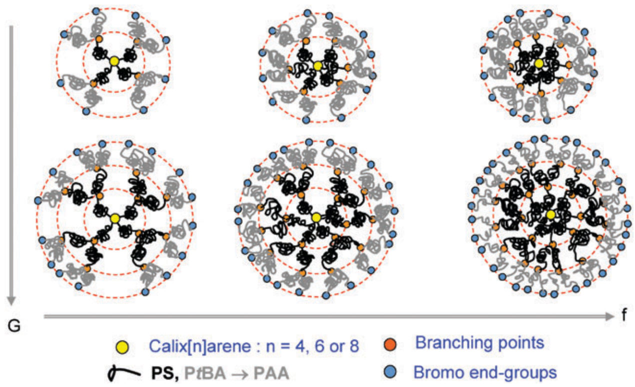


Fig. 7 Description of dendrimer-like PS homopolymers, PS/P*t*BA and PS/PAA block copolymers synthesized by ATRP using **1** (Fig. 2) and **9** and **10** (Scheme 5); from the left to the right the functionality increases from 4 to 6 to 8 and, from the top to the bottom the generation number increases from G2 to G3.

array of dendrimer-like poly(ε-caprolactone)s (PCLs),[15,43] for instance well-defined dendrimer-like PCLs of generation 2 possessing 24 outer chains arms. Iteration of the same procedure led to a third generation polymer with 42 PCL chains. The crystalline and moisture transport properties of these compounds were reported in a subsequent publication.[44] Films obtained from dendrimer-like PCLs gave a higher diffusivity of water vapour than that of linear homologues, which was ascribed to a higher density of hydroxyl groups in the branched polymers and a film porosity estimated by differential scanning calorimetry (DSC) at 10% and facilitating the transport of water. Micropores in films could be eliminated by crystallization under pressure, leading to the same bulk density as the linear analogue. DSC characterization also showed that the size of the PCL crystallites was consistent with the length of the PCL segments in a fully extended conformation. It was also hypothesized that chains of the outer generation could intramolecularly fold into crystals of the lower generation. Interestingly, Hedrick and collegues also investigated the physical properties in bulk and in solution of constitutional isomers of dendrimer-like PCLs: all samples had roughly the same total molar mass (M_n = 80 kg mol^{-1}), a number of branching junctions equal to 45 and a number of terminal hydroxyls equal to 48.[45] These dendrimer-like PCLs isomers were divergently synthesized using AB_2, AB_4 and AB_8-type dendrons described above as branching agents. Thermal analysis showed that the placement of the branching units had no influence on the glass transition temperature (T_g) which was the same for all isomers. In contrast, the melting enthalpy and the melting point decreased upon increasing the generation number at constant molar mass. This was indicative of a decreased crystallinity in a more compact architecture containing chains that are shorter and are separated by a larger number of evenly distributed branching points for the higher generation compounds. Solution properties of these dendrimer-like PCL isomers were investigated using SEC calibrated with linear PS standards and by dynamic light scattering (DLS).[45] SEC analysis showed a decrease in the apparent molar mass for high generation compounds mirroring their higher compact structure. In addition, the R_g/R_h ratio, where R_g is the radius of gyration determined by small-angle X-ray scattering and R_h is the hydrodynamic radius obtained from DLS, showed that the radial density of the dendrimer-like isomers were in agreement with that described for star-branched polymers. These findings differ from those described above for dendrimer-like PEO's and dendrimer-like PS whose profile of the hydrodynamic density—reciprocal to that of [η]—with respect to the number of generations gave a bell-shape curve. However, both the functionality of the core and the number of generations were not exactly the same between the different dendrimer-like polymers.

In a subsequent contribution, Hedrick and collegues used their dendrimer-like PCLs as pore templates for the preparation of nanoporous organosilicate networks.[46] The corresponding materials exhibited a lower dielectric constant than in the case of non-porous organosilicates, which might find applications in microelectronics. After formation of the cross-linked organosilicate, the dendrimer-like PCLs were sacrificed by thermolysis to generate nanopores that were of lower sizes (approx. 30 nm) than those generated from linear PCL homologues (approx. 100 nm). This was explained by a limited phase separation with the dendritic materials and their better affinity towards the organosilicate gel, due to their numerous chain ends and their globular topology, as compared to linear homologues.

2.3.4 Dendrimer-like poly(methyl methacrylate)s (PMMAs). As already mentioned, Hirao and coll. proposed a hybrid method based on both convergent and divergent approaches involving the coupling reactions of living anionic PMMAs carrying 1,1-bis(3-*tert*-butyldimethylsilyloxy methylphenyl)-ethylene in α-position. Dendrimer-like polymethacrylates could be obtained using this chain-end branching as shown in Scheme 8 and extensively described in ref. 16.

Percec and coworkers also reported the divergent synthesis of dendrimer-like PMMAs. In their case, these authors developed an iterative methodology involving copper-mediated ATRP and a chain-end modification using multifunctional agents named TERMINI (*e.g.* **18**). Dendrimer-like PMMAs up to the fourth-generation with a total molar mass of 464 kg mol^{-1} and a precise control of the PMMA chain length were thus prepared by this procedure.

2.3.5 Core-shell dendrimer-like copolymers. When synthesizing dendrimer-like copolymers, the divergent approach is certainly the most appropriate as it allows switching from one polymerization mechanism to another (*eg* from ATRP to AROP of EO or *vice versa*) or the simple sequential C/LP of two monomers using the same polymerization mechanism. In both cases, the arm tips of the parent generation first formed have to be derivatized and branched so as to grow the next generation. For instance, switching from ATRP to the AROP of EO through introduction of appropriate branching agents such as **9** or **10** afforded amphiphilic dendrimer-like block copolymers with a core-shell architecture.[30] As a matter of fact, we not only developed a synthetic route to block copolymer composed of an inner PEO generation and an outer generation based on PS[33] or poly(acrylic acid)[34] segments but also the reverse architecture, *ie* with a hydrophobic PS generation covered by a hydrophilic PEO layer.[30] Based on ^{1}H NMR spectroscopy characterization, the amphiphilic PEO_3-b-PS_6 dendrimer-like copolymers were found to self-associate into micellar structures including unimolecular micelles.[33] For instance, the ^{1}H NMR spectra obtained in $CDCl_3$ for copolymers $(PEO)_n$-b-$(PS)_{2n}$ displayed well-resolved peaks for both the PS and PEO parts. In a mixture of $CDCl_3$ and CD_3OD (70 : 30, v/v), a solvent selective for the inner PEO chains, peaks associated with the PS chains were no longer detected, which indicated that inner PEO segments were able to wrap around the hydrophobic PS segments in a polar environment. In a subsequent work, it was shown that some of these amphiphilic core-shell architectures self-assemble spontaneously at the air/water interface on a Langmuir trough, forming thin films. Circular domains representing 2D micelle-like aggregated molecules were also visualized by AFM after transfer from the Langmuir trough onto mica at various surface pressures.[47]

In another contribution, we reported the divergent synthesis of dendrimer-like copolymers composed of an inner generation based on PS and an outer P*t*BA generation by sequential ATRP of styrene and *t*BA combined with selective PS chain ends using **9** or **10** as branching agents (see also Fig. 6).[31] The data and the size exclusion chromatograms unambiguously showed an efficient cross-over reaction from PS blocks to P*t*BA ones, these second generation dendritic samples being free of any PS precursor. Their molar mass distributions remained relatively narrow ($M_w/M_n < 1.3$) and M_n values were close to the expected ones, indicating a controlled polymerization process. Symmetrical and narrow multi-angle laser light scattering (MALLS)/SEC traces were indicative of the absence of high molar mass side-products. PS_nPAA_{2n} ($n = 2$, 4, 6 or 8) amphiphilic structures based on PS and poly(acrylic acid) (PAA) were subsequently generated by selective cleavage of the *tert*-butylester groups of the P*t*BA blocks using trifluoroacetic acid (CF_3COOH) in dichloromethane. However, such dendrimer-like copolymers based on PS and PAA could hardly be solubilized in water. Upon addition of aqueous NaOH, poly(sodium acrylate) (PANa) blocks were formed helping the resulting copolymer (denoted PS_nPANa_{2n}) to become water-soluble. The ^1H NMR spectrum of PS_nPANa_{2n} in D_2O showed signals corresponding to the sodium acrylate blocks (δ = 1.2–2.0 ppm) whereas aromatic signals corresponding to the PS blocks could not, indicating that the PS part collapsed into the micellar core with the hydrophilic PANa blocks extending outward. In contrast, the ^1H NMR spectrum of PS_8PAA_{16} in DMSO-d_6, a good solvent for both PS and PAA blocks, resulted in well-resolved signals for the two blocks.

In the continuity of their works on dendrimer-like PCLs, the group of Hedrick also resorted to sequential block copolymerization of ε-caprolactone and lactide to prepare PCL_6-b-PLA_{12} dendrimer-like copolymers with a total molar mass equal to 46.5 kg mol^{-1}.[48,49] Dynamic mechanical analysis of these copolymers evidenced microphase-separation, as expected. Various layered dendrimer-like block copolymers based on PCL and polymethacrylate were also derived by switching from ROP to ATRP after chain-end arborisation using the AB_2 or AB_4 branching agents described above, which yielded 12 and 24 reactive hydroxyl functions, respectively.[50] Esterification of these hydroxyls with 2-bromo-2-methylpropionyl bromide afforded as many ω,ω′-bromoester functions which served to trigger the ATRP of methyl methacrylate. Using dibromobis(triphenylphosphine)nickel(II) as catalyst, dendritic copolymers exhibiting microphase-separation could be obtained, as evidenced by DSC and DMA. Partially deuterated samples could be prepared from d_5-methyl methacrylate in order to investigate the solution properties of dendrimer-like copolymers by SANS, as a function of the core structure.[51] Using mixtures of hydrogenated and deuterated toluene, neutron scattering arises from the PCL core only. In the dilute solution regime, fractal dimensions in the range 1.45–1.92 were determined for the core, comparable to those predicted for swollen gels or network structures. Liquid-like short-range ordering of the molecules was observed in the semi-dilute solution regime (5–15 wt%). The decreased order observed for generations 1 and 2 was attributed to the core interpenetration, due to the size of chains between branching junctions. Finally, 2-hydroxyethyl methacrylate and/or PEO-methacrylate were also randomly copolymerized with MMA to produce dendrimer-like copolymers with amphiphilic character which also gave rise to microphase separation.[50]

2.3.6 Functionalizing the interior of dendrimer-like poly (ethyleneoxide)s. The incorporation of functional groups at the interior of regular dendrimers has already been exploited to finely tune their physical properties[52] and target specific applications in Nanoscience such as light harvesting[53] or catalysis.[54] Very recently, we reported the first example of functionalization of the interior of dendrimer-like polymers. A dendritic PEO scaffold could be functionalized, indeed, with short inner PAA chains located at the branching junctions. While PEO and PAA usually form pH-sensitive aggregates through non-covalent interactions when associated in a block copolymeric structure, such dendrimer-like PEO's with PAA chains at the interior of the dendritic scaffold formed pH-responsive unimolecular systems; the intermolecular complexation between acrylic acid and ethylene oxide units leading to macroscopic aggregation or a even mesoscopic micellizations could be avoided in favour of the sole intramolecular complexation. The sensitivity of such interactions to pH was exploited to generate dendrimer-like PEOs that could reversibly shrink and expand with the pH, as illustrated in Fig. 8.[36] In particular, the AB_2C-type branching agent **15** was designed as described above (Scheme 7). Reiteration of AROP of EO and derivatization of PEO branches allowed us to prepare a dendrimer-like PEO of fourth generation with a total molar mass of 52 kg mol^{-1}, containing 24 external hydroxyl functions and 21 inner vinylic groups in the interior. A specific AB_2-type branching agent was then attached to the tips of the fourth generation before growing the 48 PEO branches of the fifth generation which served as a shield for the internal allylic groups. The 48 outer hydroxy-end groups of the fifth generation dendrimer-like PEO obtained were subsequently quantitatively converted into inert benzylic groups using benzyl bromide. The 21 internal vinylic groups carried by the PEO scaffold were then chemically modified in a two-step sequence into bromoester groups. The latter functions served to introduce PAA chains by ATRP of *tert*-butylacrylate, followed by a final step of hydrolysis. In this way, molecular features such as the size of each generation and the position of functional

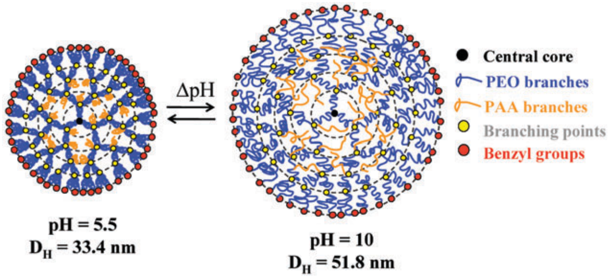


Fig. 8 pH-sensitive dendrimer-like PEO's of generation 5 functionalized by 21 branches of PAA at the branching points within the dendritic scaffold up to generation 4 (see also Scheme 7).

groups at the periphery or at the branching junctions could be precisely controlled. DLS was used to determine the size of these double hydrophilic dendrimer-like copolymers in water and to investigate their response to pH variation. Formation of unimolecular micelles in the nanometer size range was demonstrated with a capacity to shrink at low pH and expand at high pH. This remarkable feature is the direct result of the particular dendritic arrangement of PAA and PEO, which prevented their intermolecular complexation and the formation of large aggregates. Such inner functionalized dendrimer-like PEO's are expected to meet requirements such as solubilizing properties, mechanical properties, biocompatibility, dimensional stability, presence of functional groups for attachment of bioactive molecules with specific properties and pH-responsiveness.

3. Convergent strategy to dendrimer-like polymers

As reviewed by Teerstra and Gauthier, the convergent approach involving CLP and "grafting-onto" techniques were thoroughly exploited to prepare highly branched polymers including macromolecular generations (*e.g.* dendrigrafts, "pom-pom"-like structures, *etc.*). In contrast, this approach has received less attention than the divergent strategies described previously to synthesize true dendrimer-like polymers, *i.e.* possessing a precise number of branching points. One can consider, however, that the contribution of Hirao and coworkers to this field utilizes a mixed methodology based on both convergent and divergent approaches (see Scheme 8).[19] An advantage of the convergent strategy to synthesize dendrimer-like (co)polymers is that linear chains can be sampled out and independently characterized. These pre-formed "living/controlled" polymer chains also guarantees uniform length of the arms. Also, the coupling reaction can be monitored using SEC and other methods to compare the absolute molar masses of the starting materials with those of the intermediates and of the final compounds. One main drawback in this approach, however, is the necessity to use an excess of linear chains to obtain samples with the expected number of arms; hence, a final fractionation step is required to remove unreacted linear precursors. In this context, Knauss and coll. reported a series of papers on the convergent synthetic approach to hyperbranched polymers exhibiting structural analogies to dendrimer-like polymers.[13] To this end, 4-(chlorodimethylsilyl)styrene served as a terminating/copolymerizing agent to introduce the branching points and was slowly added onto living polysstyryllithium chains to form a star-shaped polymeric carbanion. The latter species was subsequently used as a macro-initiator to grow a PS chain, followed by a slow addition of 4-(chlorodimethylsilyl) styrene again. This afforded a second-generation dendrimer-like PS, althrough the coupling of the living chains with the branching agent was not perfectly uniform. The final compound therefore exhibited a less perfect structure than those obtained divergently as described above. Hadjichristidis and collegues resorted to a similar convergent approach to assemble anionically dendrimer-like homo- and copolymers of styrene and isoprene, *i.e.* using also 4-(chlorodimethylsilyl)styrene as branching agent but trichloromethylsilane or tetrachlorosilane as central core.[55] Addition of living anionic PS onto 4-(chlorodimethylsilyl)styrene resulted in the formation of styryl-ended macromonomers whose reaction with living PS, followed by the anionic polymerization of isoprene generated the dendronized precursor to the final dendrimer-like polymer. The latter was indeed obtained upon deactivation of such living dendrons onto the above mentioned central cores. Such stepwise synthesis provided good control over the structural and compositional homogeneity of the samples, the molar masses of the dendritic materials reaching M_n up to 200 kg mol^{-1} depending on the chain length of the individual arms and the core functionality. Four different dendrimer-like (co)polymers were derived based exclusively on PS or PI branches, or combining both polymers. Such a methodology was recently extended to the synthesis of dendrimer-like block copolymers of a third generation.[56]

As for Hutchings and collegues, they designed α,ω,ω'-trifunctionalized macromonomers based on PS that were used as polymeric AB_2-type building blocks to prepare either hyperbranched polymers by polycondensation or dendrimer-like PS.[14] A first-generation was first obtained by reacting the two phenol functions of the macromonomer with alkyl chloride-terminated PS. The remaining primary hydroxyl group was then converted into a chloride function. A second generation PS could be synthesized following the same methodology. In a subsequent step, 1,1,1-tris(4-hydroxyphenyl)ethane was used as a core to attach the PS-based dendron, giving rise to dendrimer-like PS of second and third generations.

4. Conclusion—perspectives

Unlike regular dendrimers, dendrimer-like polymers are composed of macromolecular generations and as such they represent a new class of highly branched polymeric architectures. They share, however, with regular dendrimers similar features such as a precise number of branching points and functions but differ from them by the possibility to entangle or crystallize. Advantages provided by the dendritic structure, in particular the multiplicity of reactive sites, can thus be combined with the properties of specific polymers, *e.g.* PEO for its stealth™ effect, poly(ε-caprolactone) for its biodegradation, poly(acrylic acid) for its pH-responsiveness. The iterative synthetic strategy that was applied to generate dendrimer-like homo- and copolymers mainly follows a divergent pathway which combines two elementary steps that are "controlled/living" polymerization from multifunctional precursors and polymer chain-end branchings. This permits not only to vary the size of branches between the branching junctions but also to associate macromolecular generations of different nature and distinct properties, providing access to highly functionalized, highly branched and shape-persistent materials of mesoscopic dimensions. This may be exploited to finely tune the physico-chemical properties of dendrimer-like (co)polymers, which holds great promise to target specific applications in Nanoscience, for instance as nanocarriers in drug and gene delivery or as organic supports for catalysis. Only a few research groups, however, have directed their efforts to these new architectures. This field is still in infancy and, indeed, several issues still remain unanswered. Obviously, there is a need for deeper investigations to establish reliable structure—property relationship for dendrimer-like (co)polymers. A few potential applications have already been put forward in the recent literature, for instance in microelectronics, or in the biomedical field. Considering the wide range of dendrimer-like (co)polymers potentially accessible, other applications should be suggested.

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