Articles

Hyperbranched Polyglycerols with Elevated Molecular Weights: A Facile Two-Step Synthesis Protocol Based on Polyglycerol Macroinitiators

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ABSTRACT: Hyperbranched polyglycerol (PG) is established as one of the few hyperbranched polymers that offer the possibility to control molecular weight up to $M_n = 6000$ g/mol. This work introduces a facile 2-step strategy that relies on the use of a low molecular weight PG ($M_n = 500$ and 1000 g/mol) as a macroinitiator for the slow addition of glycidol, permitting to overcome previous limitations concerning molecular weights and molecular weight control. A systematic investigation of the effect of the degree of deprotonation on the control of the polymerization reaction has been carried out. A series of hyperbranched PGs with molecular weights up to $M_n = 24000$ g/mol has been obtained under fully controlled conditions. The polydispersities of the samples prepared were in the range of 1.3 to 1.8. In summary, we present the first example of a synthetic strategy for a hyperbranched polymer that is now accessible over a broad range of molecular weights (300−24000 g/mol) without the ubiquitous problem of large polydispersities or the necessity for solid supports. In addition, the samples permitted a systematic study of the degree of branching DB of the hyperbranched PGs of elevated molecular weight. Values of DB = 0.60 to 0.63 were obtained, approximating the theoretical limit of 0.66 for slow monomer addition.

Introduction

Enormous interest has been generated by highly branched polymers in the last two decades. Dendrimers have long been the focus of numerous studies and as a result several fascinating applications related to their unique molecular architecture have been developed.[1] Within the last two decades, also hyperbranched polymers have obtained increasing academic and industrial interest, primarily due to their advantageous commercial viability. Hyperbranched polymers are associated with fast and convenient preparative accessibility.[2] Most synthetic approaches are based on one-pot syntheses via polymerization of AB_m-type monomers that leads to the formation of randomly branched structures, which at least qualitatively mimic dendrimers in a variety of their properties. A major drawback of hyperbranched macromolecules obtained from the classical AB_m polycondensation or the elegant self-condensing vinyl polymerization introduced by Fréchet et al. in the mid-1990s[3] is constituted by the relatively broad molecular weight distributions. This problem is long known from the work of Flory within the scope of his seminal considerations[4] as well as by subsequent theoretical and experimental investigations by Burchard.[5] Although structural perfection is not a strict requirement for a variety of possible applications of dendritic polymers,[6] the lack of control over molecular weight, polydispersity and thus materials properties represents a clear disadvantage for most of these purposes. In the early 1990s, it was first shown that hyperbranched polymers can be prepared in a controlled manner by ring-opening polymerization of cyclic, latent AB_2-type monomers, wherein the B groups of the monomer are only activated for polymerization after preceding reaction of the A group.[7] Several works by Moore and co-workers as well as our group have meanwhile demonstrated the feasibility of hyperbranched polymers with low polydispersity, since this procedure permits pseudo chain-growth kinetics.[8] Combining the use of an *f*-functional initiator B_f with slow addition of an AB_2 compound, the monomer concentration in the reaction mixture remains very low and ideally results in exclusive reaction of the monomer with the growing polyfunctional macromolecules.[6] The first example of a controlled hyperbranching polymerization based on a simple commercially available monomer compound was introduced in 1999 with the anionic ring-opening multibranching polymerization of glycidol, which afforded well-defined branched polyglycerols in a "living" type of chain polymerization under slow monomer addition (SMA) conditions.[9] Vandenberg had previously published a seminal paper on the characterization of anionically prepared polyglycerols, including a brief description of the branched structure in 1985[10] before Dworak and Penczek carried out a detailed study of the cationic polymerization of glycidol.[11]

Owing to its dendritic architecture, high end-group functionality, thermal stability and a fully biocompatible[12] polyether scaffold, hyperbranched polyglycerol is currently being used for various biomedical purposes[13] and has even been discussed as a substitute for the linear poly(ethylene glycol) (PEG) in several applications.[14] Particularly in this area highly pure, well-defined materials are required that do not contain any residual low molecular weight impurities. Control of molecular weight distributions over a broad range of molar masses thus represents

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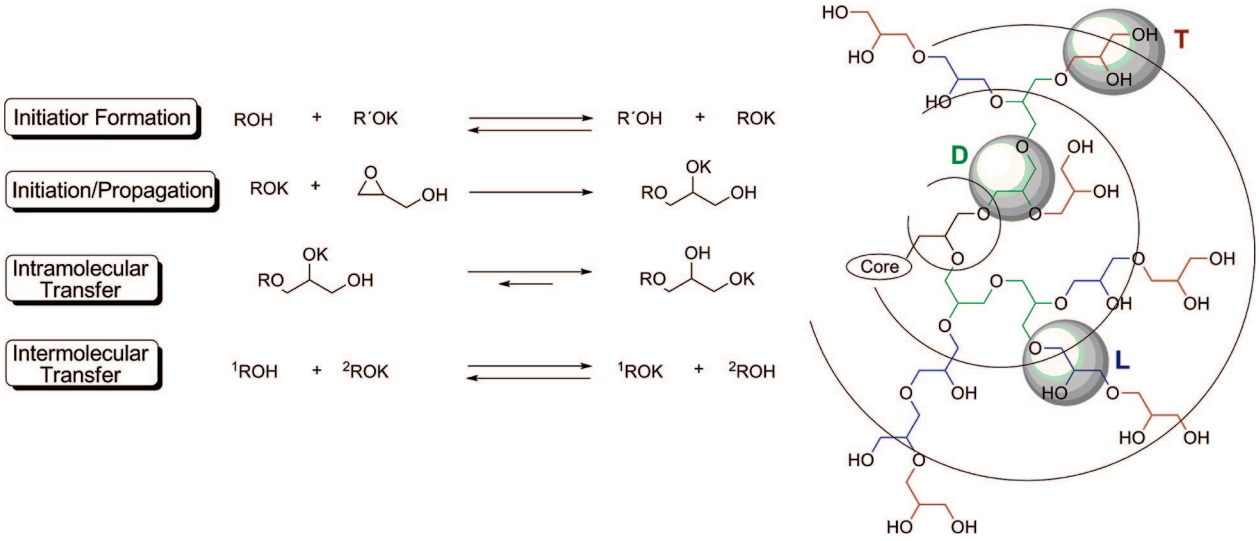
Scheme 1. Mechanism of the Anionic Ring-Opening Polymerization of Glycidol, Employing a Partially Deprotonated Alcohol as Initiator[a]



[a] A proton exchange equilibrium affords primary and secondary alkoxide sites and thus leads to a hyperbranched polyether scaffold with multiple hydroxyl groups. D, L, and T refer to the dendritic, linear, and terminal units of the polymer structure, respectively.

Table 1. Molecular Weight and Polydispersity Control in the Synthesis of Hyperbranched PG

Molar Mass / g mol^{-1}	< 6,000	6,000 - 150,000	> 150,000
Molecular Weight Control	✓	×	×
Low Polydispersity	✓	×	✓

a crucial issue in polyglycerol chemistry at present. To date, precise polymerization control with respect to narrow and monomodal molecular weight distributions at exact compliance with target molar masses has only been reported for molecular weights up to 6000 g/mol.[9] Recent progress in this molecular weight range also involved the preparation of low-molecular weight hyperbranched polyglycerols (M_n < 1500 g/mol) in a continuous flow setup.[15] In another approach, Brooks and co-workers described the formation of PGs with surprisingly high molecular weights (M_n between 350000 and 700000 g/mol), when using dioxane as an emulsifying agent in the ring-opening polymerization of glycidol.[16] The authors explained the unexpected high molecular weights with the comparably low polarity of dioxane and the accordingly accelerated cation exchange. A multistep grafting-from process based on the repeated polymerization and deprotection of a protected glycidol monomer was described by Dworak and co-workers.[17] Haag et al. very recently presented an elegant pathway to hyperbranched polyglycerol analogues with remarkably large diameters up to 90 nm by a facile cross-linking technique using "click"-chemistry.[18] Despite these interesting advances, the *controlled* synthesis of hyperbranched PGs with medium molecular weights exceeding 6000 g/mol has remained a challenge due to the inherent complications arising from solubility problems. The state of the art concerning the availability of hyperbranched polyglycerol is summarized in Table 1.

In the current paper, we have studied the correlation between the degree of deprotonation of the alkoxide initiator, the growing macromolecule and the properties of the resulting polymers. Our aim was to develop a simple and efficient synthetic approach that avoids the necessity for product dialysis or preparative size exclusion chromatography (SEC) subsequent to the polymerization, which is widely used to lower the polydispersity of hyperbranched polymers. On the basis of these requirements and the aforementioned theoretical studies, a synthetic strategy that relies on a low molecular hyperbranched polyglycerol macroinitiator has been developed. To the best of our knowledge, this new approach represents the first example of a hyperbranching polymerization that affords moderate to narrowly distributed ($M_w/M_n \leq 1.7$) material from low molecular weight oligomers to polymers with molecular weights of more than 20000 g/mol with high degrees of branching (DB).

Experimental Section

Instrumentation. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC and were referenced internally to residual proton signals of the deuterated solvent. ^{13}C NMR spectra were recorded at 100.15 MHz and referenced internally to solvent signals.

For SEC measurements in DMF (containing 1 g/L of lithium bromide as an additive), an Agilent 1100 series was used as an integrated instrument including a PSS Gral column ($10^4/10^4/10^2$ Å porosity) and a RI detector. Calibration was achieved with poly(styrene) or poly(ethylene glycol) standards provided by Polymer Standards Service (PSS).

Reagents. All chemicals were purchased from Acros Organics and used as received, unless otherwise stated. Diglyme (99%) and glycidol were purified by vacuum distillation over CaH_2 directly prior to use. Tetrahydrofuran (THF) was refluxed with sodium/benzophenone before distillation.

General Procedures. *Synthesis of Macroinitiators PG-0.5 and PG-01.* Polymerization was carried out in a glass reactor equipped with a mechanical stirrer under argon atmosphere. 1,1,1-Tris(hydroxymethyl)propane (TMP) was partially deprotonated (10%) with potassium methylate and methanol was distilled off from the melt under reduced pressure. The initiator was dissolved in diglyme (10 mL per mL monomer) and transferred to the reactor via cannula. The required amount of glycidol (20 wt % in THF) was slowly added at 120 °C over 12 h. THF was continuously distilled off during the reaction. After completion of the reaction, the product was dissolved in methanol and neutralized by filtration over Dowex 50WX8 ion-exchange resin. The polymer was precipitated twice from methanol solution into acetone and subsequently dried for 24 h at 80 °C in vacuo. The products were obtained as transparent, highly viscous liquids at 80−85% yield.

Polymerizations with Macroinitiators. The respective macroinitiator was transferred to a glass reactor equipped with mechanical stirrer and heated to 80 °C in vacuo for several hours to remove

residual solvent and water. The reactor was filled with argon before the macroinitiator was partially deprotonated by addition of potassium *tert*-butylate (solution in THF) via cannula. After the reaction mixture was stirred for 30 min, THF and alcohol were removed in vacuo. The reactor was backfilled with argon and diglyme (10 mL per mL of monomer) was added via cannula. Polymerization and workup was then carried out in analogy to the synthesis of the macroinitiator. Yields ranged between 80 and 85%.

Results and Discussion

Theoretical Considerations and Basic Investigations. Paralleling the synthetic strategy employed for the living polymerization of propylene oxide,[19] the hydroxyl groups of a trifunctional alcohol, usually trimethylol propane (TMP) are typically deprotonated by 10% before the slow addition of glycidol monomer is started. The subsequent polymerization proceeds according to the mechanism shown in Scheme 1. Branching occurs due to a fast proton exchange equilibrium which represents a well-known phenomenon in oxyanionic polymerizations.[11,10,20]

As the polymerization proceeds, the initial concentration of active alkoxide species with respect to the total number of hydroxyl groups present in the system drops rapidly, because the incorporation of each added monomer unit generates an additional OH-group. This new dormant chain end can be potentially deprotonated (inter- and intramolecular proton transfer) and subsequently attack another glycidol monomer, which would result in ring-opening and branching. An increasing concentration of nondeprotonated hydroxyl end groups can furthermore lead to enhanced intermolecular interaction, which may be responsible for the observed strong increase in viscosity of the reaction mixture when attempting to prepare higher molecular weight PG. Elevated reaction temperatures (typically 120 °C) are applied to ensure sufficient emulsification of the deprotonated species and fast monomer diffusion. Figure 1 depicts the relationship between the degree of deprotonation and the degree of polymerization for a trifunctional initiator like TMP and points out the rapid decrease of alkoxide concentration within the first stages of the reaction. When starting from a core alcohol that is deprotonated by 10%, after addition of the respective amounts of glycidol the corresponding hyperbranched polymers with molecular weights of 2000 g/mol and 5000 g/mol bear only 1% and 0.4% of alkoxide groups, respectively. In order to find a more general expression for this behavior, it is assumed that each monomer unit gets attached to the core and no cyclization occurs. Since each glycidol after ring-opening and attachment to the growing PG leads to the formation of one additional end group, the corresponding total number of hydroxyl groups of the polymer n(OH) is equal to the sum of the initiator functionality f and the degree of polymerization DP_n.

$$n(\mathrm{OH}) = \mathrm{DP_n} + f \tag{1}$$

If the occurrence of termination and/or side reactions is negligible, the number of active alkoxide sites $n(O^-)$ remains constant throughout the reaction and is independent of DP_n. It can be adjusted by the core functionality and the initial degree of deprotonation DD_0.

$$n(\mathrm{O^-}) = \mathrm{DD_0} \times f \tag{2}$$

Thus, at each stage of the reaction, the degree of deprotonation (DD) can be calculated from eq 3.

$$\mathrm{DD} = \frac{\mathrm{DD_0} \times f}{\mathrm{DP_n} + f} \tag{3}$$

Apart from increasing viscosity and diminishing solubility in the employed aprotic ether solvents, the loss of active site concentration over the course of the polymerization represents another momentous factor limiting the access to well-defined hyperbranched polyglycerols with elevated molecular weights.

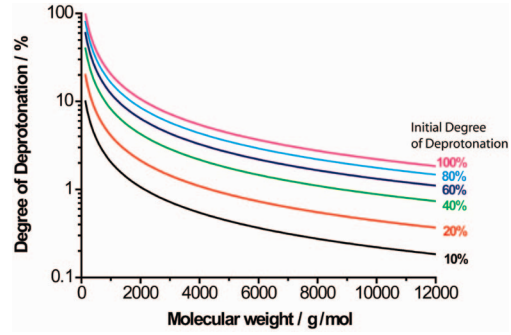


Figure 1. Decrease of the degree of deprotonation calculated for polyglycerol with a trifunctional initiator core.

In an interesting paper, Brooks and co-workers disclosed the synthesis of hyperbranched PG with molecular weights exceeding 350000 g/mol with surprisingly narrow PDIs (1.1−1.4). However, the considerable discrepancy between degrees of polymerization targeted by the monomer/initiator ratio and experimental results was not explained. Within the scope of our investigations, the use of dioxane as an emulsifying agent for the preparation of high molecular weight PG has also led to the formation of at least 10% of low molecular weight oligomers that require separation by dialysis.

A key challenge regarding controlled synthetic approaches in polyglycerol chemistry is based on the inherent kinetic prerequisites. As the rate of monomer addition to the growing polymer chain is reduced due to the lower concentration of alkoxide sites, undesired homopolymerization of glycidol monomer (self-initiation) and subsequent cyclization becomes increasingly favored.

In order to lower the extent of these undesired side-reactions and to fill the obvious gap between currently accessible degrees of polymerization, an increase of the initial degree of deprotonation was studied in detail to maintain a high concentration of active sites, as more monomer becomes incorporated into the polymer. On the other hand it has to be taken into account that the initiator solubility in ether solvents becomes poor with increasing percentage of activated alkoxide groups. For instance, TMP deprotonated with potassium methylate by more than 10% cannot be completely dissolved in diglyme any more, which inherently leads to a deviation from ideal SMA conditions, since a significant fraction of the initiator remains inactive with respect to nucleophilic attack on glycidol monomer. Consequently, molar mass control cannot be achieved and broad polydispersities $M_w/M_n > 3$ commonly result even at low target molecular weights (see Supporting Information). The use of more polar aprotic solvents with better solubility for polyglycerol (e.g., dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO)) has been shown to favor self-initiation of the monomer and leads to a broad and multimodal molecular weight distribution, particularly at target molecular weights exceeding 2000 g/mol.

It is known from theoretical work as well as from simulation studies that multifunctionality of the copolymerized initiator core in combination with slow addition of the monomer is a crucial factor for control over AB_m polymerizations.[21] M_w/M_n is predicted to behave reciprocal to the core functionality, eventually approaching $1 + 1/f$ (for $f > 1$). Thus, it appeared to be promising to avoid the hitherto inevitable loss of molecular weight control at elevated target molar masses by benefiting from the polyfunctionality of conveniently accessible narrowly dispersed low molecular weight oligo- or polyglycerols as macroinitiators for the ring-opening polymerization of glycidol.

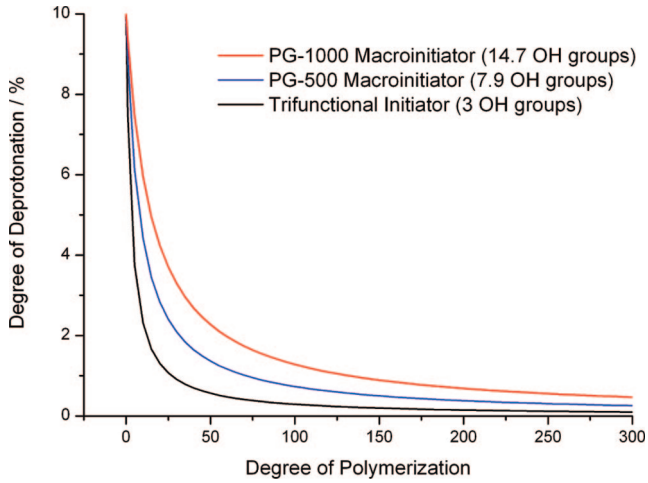


Figure 2. Evolution of the degree of deprotonation with continuous addition of monomer, starting from an initial value of 10%. The concentration of active sites can be kept higher even at elevated degrees of polymerization by employing macroinitiators.

In three different, yet related studies by our group, a comparable synthetic approach has been reported for the preparation of linear-hyperbranched block copolymers, starting from a low polydispersity linear precursor block.[22] Gao et al. polymerized glycidol onto a hyperbranched poly(oxetane), obtaining hyperbranched-hyperbranched structures.[23] Alternatively, continuous addition of a deprotonating agent in order to maintain DD throughout the reaction represents a promising pathway, but requires temporary interruption of monomer addition and, depending on the base employed, leads to the undesired formation of initiating species such as alcohol or water that are difficult to remove from the reaction system. Here we employ a partially deprotonated hyperbranched polyglycerol that should provide a compromise between the requirement for sufficient concentration of active sites at the polymer molecules throughout the reaction and the discussed limitations with respect to initiator solubility and side reactions. Conservation of the desired biological properties is guaranteed by the structural similarity of initiator and growing polymer.

Polyglycerol Macroinitiators. Hyperbranched polyglycerols with target molar masses of 500 g/mol (PG-500) and 1000 g/mol (PG-1000) were prepared according to the established procedure described by Sunder et al. in 1999, using a TMP core.[9a] These two compounds were obtained as well-defined materials in good agreement with theoretical degrees of polymerization with 7.9 and 14.7 OH groups on average per molecule. Molecular weights and polydispersities were determined by size exclusion chromatography (SEC) using linear polystyrene (PS) or poly(ethylene glycol) (PEG) standards. From Figure 2, it can be perceived that 10% deprotonation of the OH-groups of a PG macroinitiator leads to a higher concentration of alkoxide sites even at elevated degrees of polymerization.

For instance, when using a PG-1000 initiator with 10% of initial deprotonation, the concentration of active sites after incorporation of 100 monomer units still ranges above 1% and is more than four times higher than in the case of the conventional TMP initiator. Thus, PG-1000 deprotonated by 10% can be equated to a significantly higher degree of deprotonation of a trifunctional initiator, but in contrast to a TMP core the material still shows fair solubility in the solvent employed. Employing polyfunctional macroinitiators, even at degrees of polymerization corresponding to molar masses above 10 000 g/mol, the active alkoxide concentration exceeds the 0.5% threshold. This is in pronounced contrast to the conventional approach based on a low molecular weight core, where

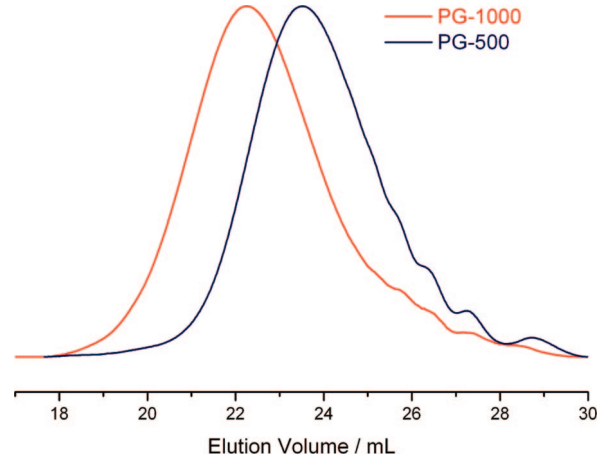


Figure 3. SEC traces of the hyperbranched PG samples used as macroinitiators.

Table 2. Characterization data for PG Macroinitiators PG-500 and PG-1000

no.	core	$M_{n,calc}$ (g/mol)	$M_{n,SEC}$ (g/mol)[a]	M_w/M_n[a]	$M_{n,NMR}$ (g/mol)[b]
PG-500	TMP	500	560	1.32	600
PG-1000	TMP	1000	1000	1.40	1200

[a] Determined via SEC-RI in DMF using linear PEG standards. [b] Calculated from ^{1}H NMR spectra by comparison of repeat unit to core signal intensity.

Table 3. Characterization Data for the Hyperbranched Polyglycerols Based on Macroinitiator PG-500

no.	core	$M_{n,calc}$ (g/mol)	$M_{n,SEC}$ (g/mol)[a]	M_w/M_n[a]	$M_{n,NMR}$ (g/mol)[b]
PG-500−05	PG-500	5000	4600	1.48	6200
PG-500−08	PG-500	8000	7800	1.39	9100
PG-500−10	PG-500	10000	9900	1.38	10200
PG-500−15	PG-500	15000	13400	1.44	14500
PG-500−20	PG-500	20000	1200	17	7800

[a] Determined via SEC-RI in DMF using linear PS standards. [b] Calculated from ^{1}H NMR spectra by comparison of repeat unit signal intensity to core signal intensity.

control over the polymerization becomes critical at this point (corresponding to molecular weights of around 5000 g/mol). Figure 3 shows the SEC traces obtained for the two PG samples employed as macroinitiators. The respective characterization data can be found in Table 2.

Polyglycerols with Macroinitiator Cores. Assuming that an increased number of alkoxide sites is active in the initial stage of the polymerization, when a partially deprotonated macroinitiator is used, control over molar masses and polydispersity should be possible up to higher degrees of polymerization than by use of conventional initiator cores, such as TMP. Besides employing a different initiator, the reactions were carried out in analogy to the pathway established for glycidol polymerization onto a TMP core. Table 3 summarizes the characterization data obtained from hyperbranched PGs based on the macroinitiator PG-500.

It can be observed that up to molar masses of 14 000 g/mol, degrees of polymerization are in good agreement with the calculated values. Starting from a conveniently accessible macroinitiator, structurally analogous to the targeted polymer, samples with narrow and monomodal molecular weight distributions can be obtained under a high degree of molecular weight control. No signals corresponding to unreacted macroinitiator molecules are visible in the SEC elugrams (Figure 4.)

Above the mentioned molecular weight threshold, broad molecular weight distributions and less reproducible results are observed. SEC traces exemplarily for this behavior can be found in the Supporting Information. If this loss of control over the

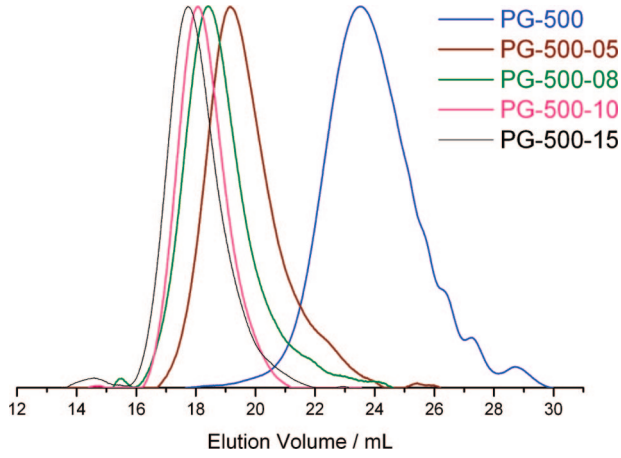


Figure 4. SEC traces (measured in DMF) of the macroinitiator PG-500 and the corresponding hyperbranched PG samples.

reaction is caused by the decrease in alkoxide site concentration, the use of a larger macroinitiator with higher functionality should result in an expansion of the molecular weight range that can be covered without losing control over the polymerization. Hence, we applied the same concept (10% of initiator deprotonation and subsequent slow addition of glycidol onto the activated core) for a polyglycerol with molar mass of 1000 g/mol. The corresponding characterization data is given in Table 4. Degrees of polymerization are in compliance with theoretical expectation and remarkably narrow and monomodal molecular weight distributions can be maintained up to molar masses of M_n = 24 000 g/mol. Obviously, the possibility to maintain reasonably high active site concentrations up to elevated degrees of polymerization, as illustrated in Figure 2, provides the fundament for a significant and fully reproducible expansion of the repertoire of hyperbranched PGs.

Figure 5 shows the respective SEC traces of the PG-samples based on macroinitiator PG-1000. All polymers exhibit monomodal distributions with apparent polydispersities generally lower than 1.8, mostly below 1.6. Residual macroinitiator traces were absent, confirming quantitative conversion of PG-1000 into hyperbranched polymers of elevated molecular weight. In addition, no low molecular weight fraction was observed, in pronounced contrast to the synthetic strategy described by Brooks et al.[16] The attempt to employ PG-1000 as macroinitiator for molar masses exceeding 25 000 g/mol resulted in multimodal molecular weight distributions, most probably as a consequence of the increasing viscosity of the medium and decreasing relative number of active sites on the growing polymers. Due to the unique structural prerequisites, characterization of hyperbranched polymers by SEC involves a systematic error. Owing to the comparably low hydrodynamic radii of hyperbranched polymers, molecular weights are usually underestimated, when linear calibration standards are employed. This effect becomes particularly evident at very high molecular masses, which are not treated here. The use of linear PEG standards for low molar mass hyperbranched PGs (below 5000 g/mol) and linear PS standards for samples with higher degrees of polymerization has proven most adequate and gives reasonable molecular weight data in a standard SEC experiment.

Molar mass determination by ^{1}H NMR spectroscopy provides a useful comparison with SEC results for lower molecular weight samples when the respective integrals of the repeat unit signals and the signals of the TMP core are related to each other. At higher degrees of polymerization (M_n > 15 000), the initiator signals become weaker and can thus hardly be distinguished from noise-induced signals, leading to a less reliable scaling of the integrated peaks and hence requirement for longer measurements. However, molecular weight data obtained from ^{1}H NMR spectra of the PGs is in reasonable agreement. It should also be emphasized that extensive drying of the macroinitiator prior to the reaction is essential for polymerization control, as traces of alcohol or other impurities like water lead to broad and/or multimodal molecular weight distributions. The obtained PGs are transparent and slightly yellowish, very viscous liquids. While the low molar mass PGs (M_n < 3,000 g/mol) are flowable at room temperature, increased temperatures are required for liquid appearance of the samples with higher M_n, indicating a higher degree of intra- and/or intermolecular interaction.

Table 4. Characterization Data for the Hyperbranched Polyglycerols Based on Macroinitiator PG-1000

no.	core	$M_{n,calc}$ (g/mol)	$M_{n,SEC}$ (g/mol)[a]	M_w/M_n[a]	$M_{n,NMR}$ (g/mol)[b]
PG-1000−05	PG-1000	5000	5200	1.59	5400
PG-1000−06	PG-1000	6000	6100	1.55	6300
PG-1000−08	PG-1000	8000	8200	1.46	8400
PG-1000−10	PG-1000	10000	9900	1.41	10200
PG-1000−18	PG-1000	18000	17700	1.41	19400
PG-1000−25	PG-1000	25000	24200	1.77	*c*

[a] Determined via SEC-RI in DMF using linear PS standards. [b] Calculated from ^{1}H NMR spectra by comparison of repeat unit signal intensity to core signal intensity. [c] A reliable calculation of the molar mass for PG-1000−25 was not possible because of the relatively weak initiator signal.

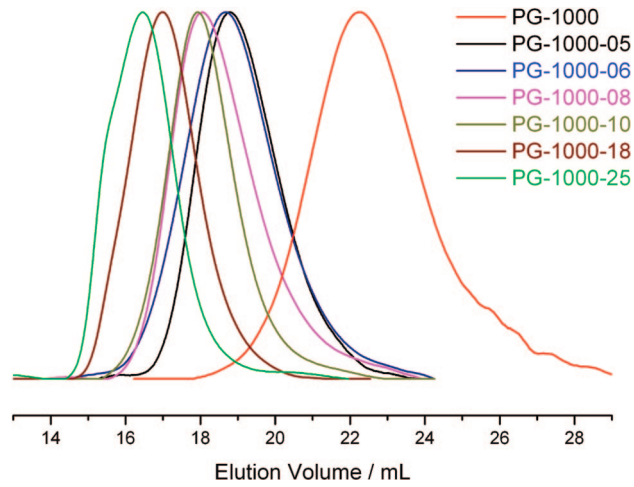


Figure 5. SEC traces (measured in DMF) of the macroinitiator PG-1000 and the corresponding hyperbranched PG samples.

An obvious approach targeting a further expansion of the range of accessible PG molecular weights under controlled conditions involves the use of hyperbranched PGs with higher molar masses as macroinitiators, such as PG-2000 or PG-5000. Due to the increased initial functionality, it should be possible to realize higher concentrations of active alkoxide sites at further elevated degrees of polymerization. However, this approach did not afford reproducible results and frequently led to broad and/or multimodal molecular weight distributions. It can be perceived that additional constricting factors impede controlled initiation and polymerization when these larger macroinitiators are employed. Increased initial viscosity results in an unbalanced dispersion of the growing polymers within the reaction medium under the corresponding conditions and thus interferes with the prerequisites for a controlled SMA approach. The solubility of the deprotonated cores in diglyme is diminished with increasing molar mass and, in combination with higher viscosities, impedes stirring and fast monomer diffusion to the active sites. Complications may also arise from association phenomena that become apparent, when a higher number of anionic sites is present within one macroinitiator molecule. We have thus observed

Table 5. IG ^{13}C NMR Spectroscopy Characterization Data Obtained from Polyglycerols Based on PG-1000 as Macroinitiator

no.	L_{13} (%)	L_{14} (%)	D (%)	T (%)	DB (%)	$DB_{Fréchet}$ (%)
PG-1000	11.8	23.4	21.2	43.6	54.7	64.8
PG-1000−05	11.7	25.0	29.2	34.1	61.4	63.3
PG-1000−06	11.1	25.5	29.2	34.2	61.5	63.4
PG-1000−08	10.3	25.8	29.1	34.8	61.7	63.9
PG-1000−18	10.5	25.3	30.4	33.7	62.9	64.1
PG-1000−25	10.0	27.4	28.7	33.9	60.5	62.6

that optimal polymerization control can be achieved using macroinitiators with molar masses up to 1000 g/mol while results have not yet been sufficiently reproducible above this threshold. While the macroinitiator PG-500 afforded a high degree of polymerization control up to molar masses of 13 000 g/mol, the molecular weight range was further expanded to about 24000 g/mol by using a PG-1000 core with almost doubled functionality.

Degree of Branching of the hyperbranched PG samples. Besides molecular weight and polydispersity, the degree of branching (DB) is a fundamental property of hyperbranched polymers. The DB was first introduced by Kim[24] and later Fréchet et al.[25] (eq 4). Hölter and Frey used an alternative concept to develop a general definition of DB for AB_2 polymerizations (eq 5).[8b]

$$DB_{Fréchet} = \frac{D + T}{D + L + T} \quad (4)$$

$$DB = \frac{2D}{2D + L} \quad (5)$$

D, L, and T refer to the relative amounts of dendritic (D), linear (L), and terminal (T) units within the hyperbranched structure. Theoretical works have demonstrated that under ideal SMA conditions, a maximum DB of 0.67 can be achieved, which means that at high degrees of polymerization, the number of dendritic (branching) units equals the number of linear units.[21] As the well-defined PGs with systematically varied molecular weights (M_n between 6000 and 24 000 g/mol), prepared by the described two-step approach, represent a novelty in the field of hyperbranched polymers, it is intriguing to analyze them with respect to their DB. Inverse gated (IG) ^{13}C NMR spectroscopy permits the integration of carbon core signal intensities and thus allows for a determination of the relative amounts of different dendritic, linear and terminal units. A detailed assignment of the ^{13}C NMR signals to the respective structural units of hyberbranched polyglycerol can be found in the literature.[9a] Table 5 summarizes the results obtained from IG ^{13}C NMR spectra and application of eq 4 (DB) and the expression introduced by Fréchet et al. ($DB_{Fréchet}$). Both equations applied neglect the formation of cyclic structures without core, which can occur to a certain extent in the early stages of the polymerization reaction and decrease the DB.

The data listed in Table 4 confirms the remarkable degree of reaction control achieved via the SMA technique. All polymers prepared by using PG-1000 as macroinitiator possess DBs between 0.60 and 0.65, which range noticeably above the previously published values of 0.52−0.59.[9a] This indicates a reduction of cycle formation achieved by application of the newly developed two-step synthesis pathway. It is noticeable that the DBs calculated by Fréchet's formula are higher, particularly for lower molecular weight polymers, which can be explained by the more pronounced effect of terminal units at low degrees of polymerization. This is also in agreement with expectation, since it is known that the respective definition of the DB leads to an overestimation at low molecular weights.[8b] It is further interesting to note that the ratio between L_{13} and L_{14} units is found to be approximately 1:2.25 in all cases. This confirms the significance of intramolecular transfer in favor of the more reactive primary alkoxides.

Conclusion and Perspectives

In summary, we have presented the first example of a controlled hyperbranching polymerization method that provides access to a broad range of molar masses for PG up to 24 000 g/mol (DP_n > 300). The degree of deprotonation of hydroxyl end groups has been established as a key parameter of the ring-opening multibranching polymerization of glycidol. Polymerization control in experiments targeting molar masses exceeding 6000 g/mol was achieved by applying a low molecular weight polyglycerol that chemically resembles the final polymer as a macroinitiator. This synthetic strategy does not require previously inevitable purification steps limiting yields and feasible scales. The discovery of novel terrain in terms of the size, shape and thus the properties of hyperbranched PG with narrow molecular weight distributions and high degrees of branching will open new possibilities to benefit from the intriguing potential of this polymer class, particularly with respect to biomedical application. Future research on these polymers will involve detailed investigations of physical properties, such as rheological studies and correlation with molecular weights, encapsulation studies and the exploration of alternative initiator/solvent systems in order to further expand the range of accessible molar masses.

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Supporting Information Available: Figures showing additional SEC traces and NMR spectra. ^{13}C NMR assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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