

Hyperbranched Polyglycerols: From the Controlled Synthesis of Biocompatible Polyether Polyols to Multipurpose Applications

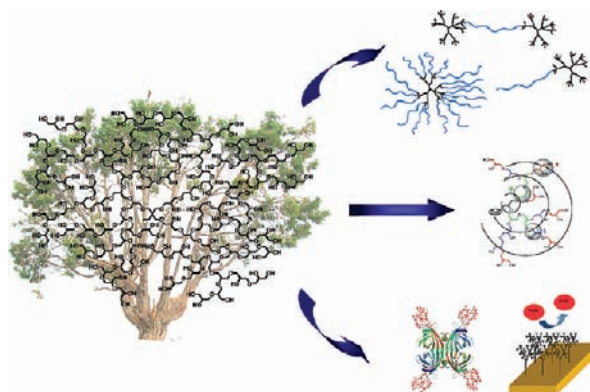
DANIEL WILMS,[†] SALAH-EDDINE STIRIBA,^{*,‡} AND
HOLGER FREY^{*,†}

[†]Institute of Organic Chemistry, Johannes Gutenberg-University Mainz,
Duesbergweg 10-14, D-55099 Mainz, Germany, and [‡]Instituto de Ciencia
Molecular/ICmol, Universidad de Valencia, Polígono La Coma s/n, 46980
Valencia, Spain

RECEIVED ON JUNE 9, 2009

CON SPECTUS

Dendritic macromolecules with random branch-on-branch topology, termed hyperbranched polymers in the late 1980s, have a decided advantage over symmetrical dendrimers by virtue of typically being accessible in a one-step synthesis. Saving this synthetic effort once had an unfortunate consequence, though: hyperbranching polymerization used to result in a broad distribution of molecular weights (that is, very high polydispersities, often $M_w/M_n > 5$). By contrast, a typical dendrimer synthesis yields a single molecule (in other words, $M_w/M_n = 1.0$), albeit by a labor-intensive, multistep process. But 10 years ago, Sunder and colleagues reported the controlled synthesis of well-defined hyperbranched polyglycerol (PG) via ring-opening multibranching polymerization (ROMBP) of glycidol. Since then, hyperbranched and polyfunctional polyethers with controlled molar mass and low polydispersities ($M_w/M_n = 1.2-1.9$) have been prepared, through various monomer addition protocols, by ROMBP. In this Account, we review the progress in the preparation and application of these uniquely versatile polyether polyols over the past decade.



Hyperbranched PGs combine several remarkable features, including a highly flexible aliphatic polyether backbone, multiple hydrophilic groups, and excellent biocompatibility. Within the past decade, intense efforts have been directed at the optimization of synthetic procedures affording PG homo- and copolymers with different molecular weight characteristics and topology. Fundamental parameters of hyperbranched polymers include molar mass, polydispersity, degree of branching, and end-group functionality. Selected approaches for optimizing and tailoring these characteristics are presented and classified with respect to their application potential. Specific functionalization in the core and at the periphery of hyperbranched PG has been pursued to meet the growing demand for novel specialty materials in academia and industry.

A variety of fascinating synthetic approaches now provide access to well-defined, complex macromolecular architectures based on polyether polyols with low polydispersity. For instance, a variety of linear-hyperbranched block copolymers has been reported. The inherent attributes of PG-based materials are useful for a number of individual implementation concepts, such as drug encapsulation or surface modification. The excellent biocompatibility of PG has also led to rapidly growing significance in biomedical applications, for example, bioconjugation with peptides, as well as surface attachment for the creation of protein-resistant surfaces.

1. Introduction

In the late 1980s, Kim and Webster introduced the term “hyperbranched polymers” to define den-

dritic macromolecules with random branch-on-branch topology, prepared by polycondensation of AB_m -type monomers.¹ Flory developed the theo-

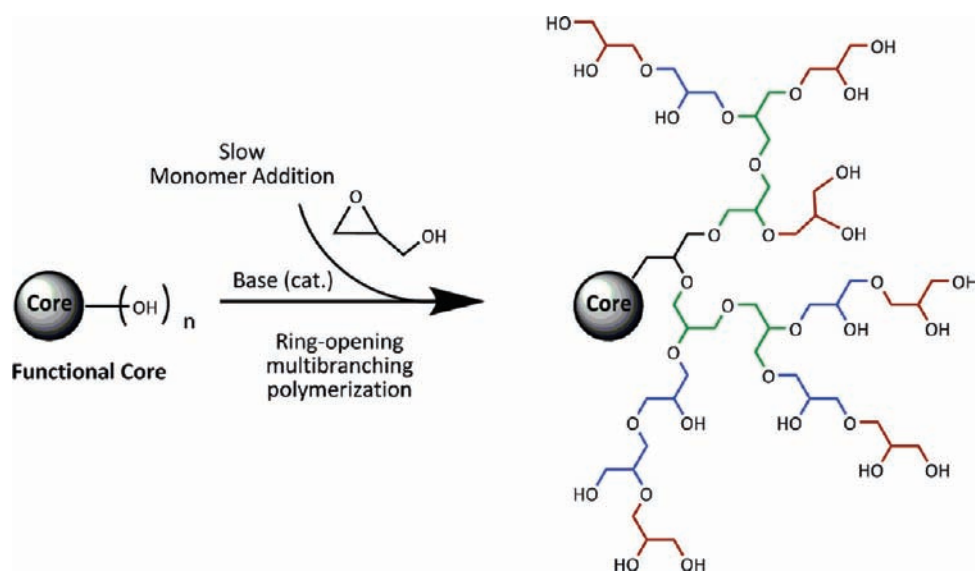


FIGURE 1. Synthesis of hyperbranched polyglycerols by anionic ring-opening multibranching polymerization.

retical fundamentals for “random” $A-R-B_{(f-1)}$ polycondensates, that is, the step-growth polycondensation of multifunctional AB_m -type monomers, containing one A group and m ($m \geq 2$) complementary B groups.²

Unlike most dendrimers,³ prepared in demanding multi-step syntheses, hyperbranched materials⁴ are usually accessible in one-step processes and are often considered to be ill-defined or “the poor cousins of dendrimers”, because of their commonly very high polydispersity (often $M_w/M_n > 5$). The broad molecular weight distribution was already analyzed by Flory and is a consequence of the polyfunctional step-growth synthesis. In addition, hyperbranched polymers are characterized by a random distribution of functional groups throughout their globular structure.^{5,6} Hyperbranched polymers are considered to show no entanglements, which results in extremely low bulk viscosities in comparison to linear polymers. Increasing academic and industrial interest has been sparked by the potential for advanced nanomaterials, novel biomaterials and rheology modifiers.

Several strategies have been developed to render hyperbranched materials more “dendrimer like”. Almost precisely a decade ago, Sunder et al. described the ring-opening multibranching polymerization (ROMBP) (Figure 1)⁷ of glycidol, a commercially available and highly reactive hydroxy epoxide, carried out under slow monomer addition (SMA) conditions. This permitted them to avoid the broad molecular-weight distributions of random AB_m -type polycondensation. In this Account, we summarize both recent advances in the synthesis of hyperbranched polyglycerol and the preparation of complex, branched polymer architectures. Key applications of the

resulting materials prepared by our group as well as others will be covered.

2. Fundamental Parameters Defining Hyperbranched Polymer Structures

Hyperbranched polymers are characterized by three fundamental parameters: (i) molecular weight, (ii) polydispersity (PDI), and (iii) the degree of branching (DB). Control of these parameters is essential to establish structure–property relationships and for the development of complex macromolecular architectures. Therefore, strategies to this end are reviewed in the following paragraphs.

2.1. Molecular Weight and Polydispersity of Hyperbranched Polyglycerol. A key issue for control of the molecular weight of hyperbranched polymers is to circumvent the intrinsic limitations of multifunctional polycondensation that inevitably lead to high polydispersity. Slow addition of a highly reactive branching monomer to a polyfunctional core represents an unusual polymerization strategy. However, it can be used to obtain chain-growth-like kinetics, as was confirmed by a computer simulation study.⁸ In the ideal case, the slow addition (SMA, slow monomer addition) of suitable AB_m monomers to a core with multiple functionality permits control of the molecular weight via the monomer/core ratio and in addition strongly reduces the polydispersity. In detailed theoretical and experimental studies by our group, it was demonstrated that a polydispersity clearly below 1.5 can be obtained. An elegant theoretical work by Müller et al. led to the same conclusions for the self-condensing vinyl polymerization (SCVP).⁹

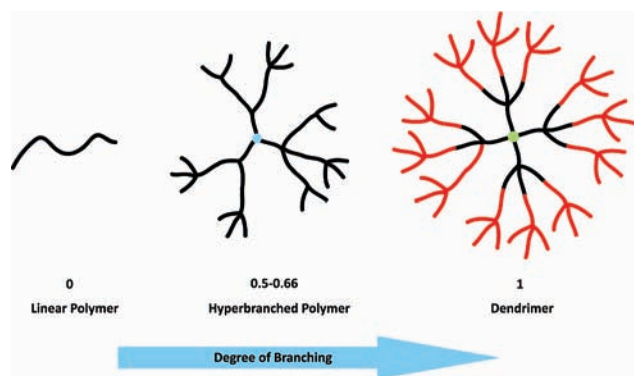


FIGURE 2. Illustration of various polymer architectures and their respective degrees of branching, DB.

2.2. Degree of Branching (DB). In a hyperbranched structure based on a branching multiplicity of 2 (AB_2 monomer), three different building units are present: branched (“dendritic”, D) units, linear units (L), and end groups (“terminal units”, T), as well as precisely one single focal moiety. Perfectly branched dendrimers do not contain any linear units, that is, they consist only of dendritic and terminal units. For such maximum branched structures, the degree of branching has been normalized to 1 (i.e., 100%), whereas for linear polymers, it is obviously 0. Hyperbranched polymers exhibit an intermediate DB between 0 and 1 (Figure 2).

A systematic derivation of the degree of branching was developed in 1997 by Hölter and Frey.¹⁰ The DB for the AB_2 case is given in eq a below:

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

The global parameter DB is determined by NMR spectroscopy, relying on low molecular weight model compounds that possess structures similar to the units present in the respective hyperbranched polymer.

Thus, the DB is a measure of the dendritic character of a structure. It can be enhanced up to values close or equal to 1 by using the concept of postsynthetic modification protocols.^{11,12}

3. Polymerization of Glycidol and Molecular Weights Achievable

The controlled synthesis of well-defined hyperbranched polymers involves various synthetic prerequisites. One major drawback of polycondensation is the necessity to remove the condensation byproduct formed during polymerization in order to achieve high conversion. This can be circumvented in the case of cyclic “inimers”.

Glycidol represents a reactive oxirane monomer with latent AB_2 monomer structure. Polymerization of this compound has

been studied by various groups since the 1960s, focusing on the preparation of functional linear polyethers.¹³ Vandenberg et al. published a seminal paper on the characterization of anionically prepared PGs, including a brief description of the branched structure in 1985.¹⁴ In 1994, Penczek and Dworak reported the cationic ring-opening polymerization of glycidol, leading to hyperbranched polyether polyols, albeit of limited molecular weights ($M_n \leq 6000$ g/mol; PDI = 1.3–1.6).¹⁵

Based on the SMA approach, glycidol was polymerized in a controlled manner via anionic ring-opening multibranching polymerization by Sunder et al. in 1999.^{7,16} In this procedure, glycidol is slowly added to a solution of partially deprotonated (5–10%) trifunctional core-initiator for oxyanionic polymerization. Owing to the fast proton exchange during the polymerization the different chain ends (secondary and primary alcohols) can grow simultaneously, resulting in a branched structure (Figure 3). Chiral hyperbranched polyether polyols have been prepared in a similar manner using enantiomerically pure glycidol monomer.^{16b}

Using ^{13}C NMR spectroscopy, it is possible to distinguish between dendritic (D), two different linear (L_{13} , L_{14}), and terminal (T) glycerol units and, provided the spectra are obtained under inverse-gated conditions (IG), thereby to calculate the DB. As expected from theory, the DB increases with DP_n until it reaches a plateau value. The samples studied exhibited a DB between 0.53 and 0.59 (slightly below the value of 0.66 for ideal slow addition mode), with molar masses ranging from 1200 to 6300 g/mol. Apparent polydispersities of the samples were measured by size-exclusion chromatography (SEC) and generally found to be below 1.5. When MALDI–TOF MS was employed, only a small amount of cyclic products was observed in the low molecular weight range, showing that the slow addition procedure minimized the undesired homopolymerization of glycidol. The versatility of this synthesis protocol has also been successfully applied for the polymerization of glycidol on Si/SiO₂ surfaces by Huck et al.¹⁷

In 2007, our group exploited the intriguing characteristics of microreaction technology to realize an efficient continuous flow approach for the preparation of low-molecular weight hyperbranched PGs ($M_n < 1,500$ g/mol) under significantly reduced experimental effort.¹⁸ A further important improvement in this area was reported in 2006 by Brooks and co-workers, who observed the unexpected formation of very narrowly dispersed, high molecular weight PG when using dioxane as an emulsifying agent of low polarity.¹⁹ Molecular

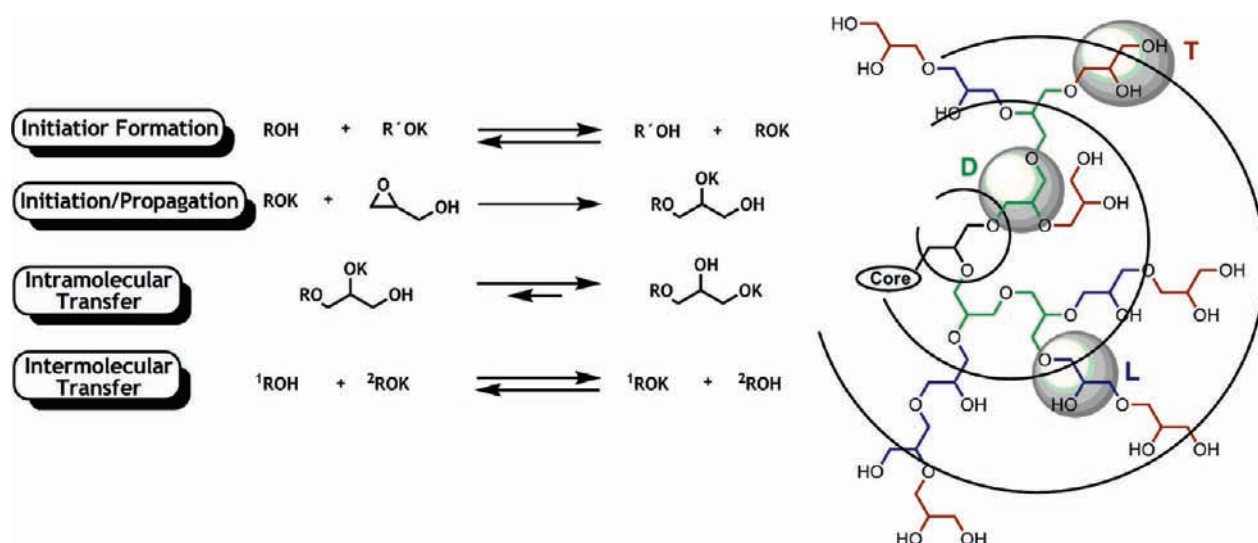


FIGURE 3. Mechanistic pathway of the base-catalyzed ring-opening polymerization of glycidol and structure of the resulting hyperbranched PG (small fragment of the actual polymer structure).

weights of several 100 kDa were reported. The method represents an important step forward, since it gives access to high molecular weight PG samples that are important for a variety of biomedical applications.

Despite these important advances, the *controlled* preparation of polyglycerols with molecular weights exceeding 6000 g/mol has remained a challenge to be overcome until very recently. Since the exponential decrease of active alkoxide site concentration with increasing amount of added glycidol reduces the reaction rate of glycidol with the growing polymer, undesired side reactions such as cyclization become increasingly favored. Accounting for these kinetic prerequisites, a facile two-step approach via low molecular weight polyglycerol macroinitiators was developed. The polyfunctionality of the macroinitiator affords a higher concentration of alkoxide sites even at elevated degrees of polymerization and thus permits the preparation of hyperbranched polyglycerols up to molecular weights of 24 000 g/mol under controlled SMA conditions.²⁰ Analogues of hyperbranched PG nanoparticles with diameters up to 90 nm, obtained via a cross-linking approach in miniemulsion involving click chemistry, have recently been disclosed.²¹ Table 1 summarizes the currently feasible synthetic routes for hyperbranched PG samples of different molecular weights.

A different concept complementing the scope of accessible molecular weights for branched polyglycerol structures, based on the repeated polymerization and deprotection of a protected glycidol monomer, has been developed by Dworak et al.²²

TABLE 1. Methods of Preparing Narrowly Dispersed PG by Ring-Opening Polymerization of Glycidol Employing a Maximum of Two Reaction Steps

molecular weight range	method	reaction steps	molecular weight control	ref
$M_n \leq 1500$ g/mol	anionic (SMA)	1	✓	7,16
	anionic continuous flow	1	✓	18
1500 g/mol $\leq M_n \leq 6000$ g/mol	anionic (SMA)	1	✓	7,16
	cationic	1	×	15
6000 g/mol $\leq M_n \leq 25\,000$ g/mol	anionic (SMA)/macroinitiator	2	✓	20
$M_n \geq 100\,000$ g/mol	anionic (SMA)/emulsion	1	×	19

4. Polyglycerol-Based Complex Polymer Architectures

Until recently, it was believed that hyperbranched structures are too ill-defined to offer potential as well-defined building blocks for complex polymer architectures. Motivated by the preparation of well-defined hyperbranched PGs, various types of core-initiators and latent AB₂ epoxide monomers have been introduced, giving access to a variety of unprecedented polymer architectures.

4.1. Linear–Dendritic Block Copolymers. In 2003, a new type of linear–hyperbranched surfactant was prepared by anionic ring-opening multibranching polymerization of glycidol onto an amino-functional poly(propylene oxide) (PPO) macroinitiator.²³ A strongly hydrophilic hyperbranched PG block was obtained as the polar segment of the structure. The linear–branched surfactants have been shown to influence the transport of doxorubicin through biomembranes

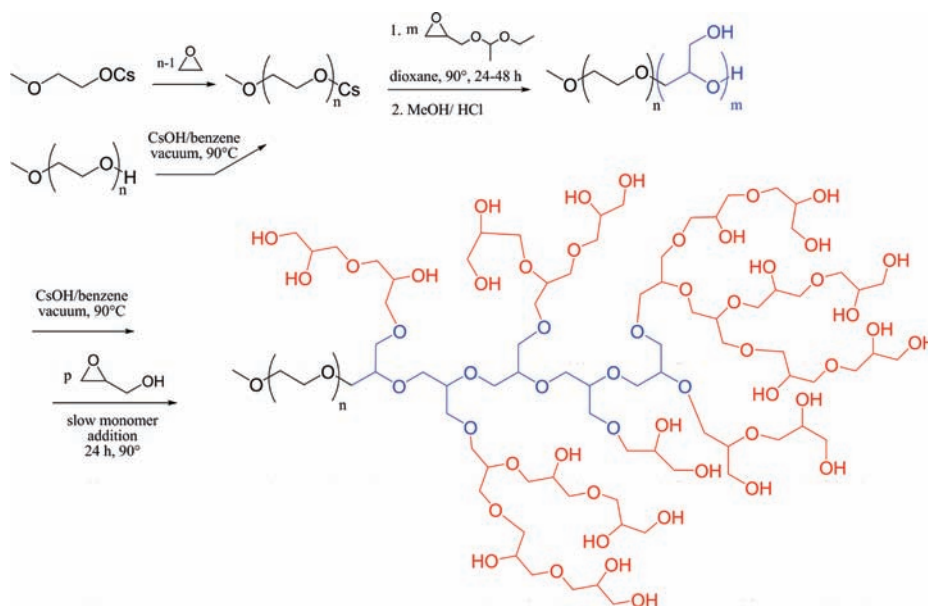


FIGURE 4. Reaction sequence for the synthesis of linear–hyperbranched PEO–PG diblock copolymers.

and into cells, offering interesting possibilities for the chemotherapy of cancer.²⁴

More recently, a convenient four-step (two-pot) approach for the synthesis of biocompatible, double hydrophilic linear–hyperbranched block copolymers based on poly(ethylene oxide) (PEO) and PG with low polydispersities (M_w/M_n in the range of 1.09–1.25) was described.²⁵ The polymers consisting exclusively of an aliphatic polyether structure were prepared from linear PEO-*b*-(*l*-PG) precursor block copolymers, obtained via anionic polymerization of ethylene oxide and subsequently ethoxyethyl glycidyl ether (EEGE) (Figure 4).

It is an intriguing question, whether linear–hyperbranched block copolymers can form ordered structures in solution and in the solid state despite the structural polydispersity of the hyperbranched block. A three-step approach has been developed to prepare well-defined amphiphilic linear–hyperbranched block copolymers by slow addition of glycidol onto a polystyrene-*block*-poly(2-hydroxyethyl)ethylene (PS₅₀₈-*b*-(PB-OH)₅₆) macroinitiator²⁶ obtained by classical anionic polymerization procedures (Figure 5a). In solution, uniform micelles were formed in different solvents, as demonstrated by static and dynamic light scattering as well as AFM after surface deposition (Figure 5b).

Recently our group also introduced two alternative synthetic procedures for the preparation of poly(glyceryl glycerol) block copolymers via (a) polymerization of allyl glycidyl ether (AGE) onto a linear PEO block and subsequent bishydroxylation with catalytic amounts osmium tetroxide and (b) direct synthesis of the double hydrophilic block copolymer by reac-

tion of a deprotonated PEO with DL-1,2-isopropylidene glyceryl glycidyl ether.²⁷

4.2. Random Copolymerization. For the preparation of well-defined hyperbranched random copolymers, mixtures of glycidol with various amounts of glycidyl ethers, that is, AGE and phenyl glycidyl ether (PGE) have been successfully polymerized under the same conditions as glycidol.²⁸ The obtained hyperbranched random copolymers exhibited a controlled degree of polymerization ($DP_n = 42–72$) and fairly low polydispersity ($M_w/M_n < 1.7$). The DB was controlled by the comonomer ratio (DB = 9%–58%). As expected, the solubility behavior of the random copolymers depends strongly on their composition. While the polyglycerol homopolymer is only soluble in very polar solvents, the homopoly(glycidyl ethers) are soluble in a broad variety of organic solvents (e.g., methanol, THF, toluene) with the exception of aliphatic hydrocarbons.

4.3. Functional Core Variation. The development of synthetic strategies allowing the covalent incorporation of functional core units with specific chemical and photophysical properties within hyperbranched structures is important because of the anticipated effect of the hyperbranched backbone on the encapsulated functional core moiety. The number of suitable core molecules is limited due to the stringent oxyanionic polymerization conditions of polyether synthesis. Controlled bisglycidolization followed by further glycidol polymerization (Figure 6) is a straightforward strategy to achieve complete incorporation of the core moieties, as systematically studied by MALDI–TOF mass spectrometry. This strategy has been employed for the syntheses of a large variety of core-functionalized hyperbranched PGs, using

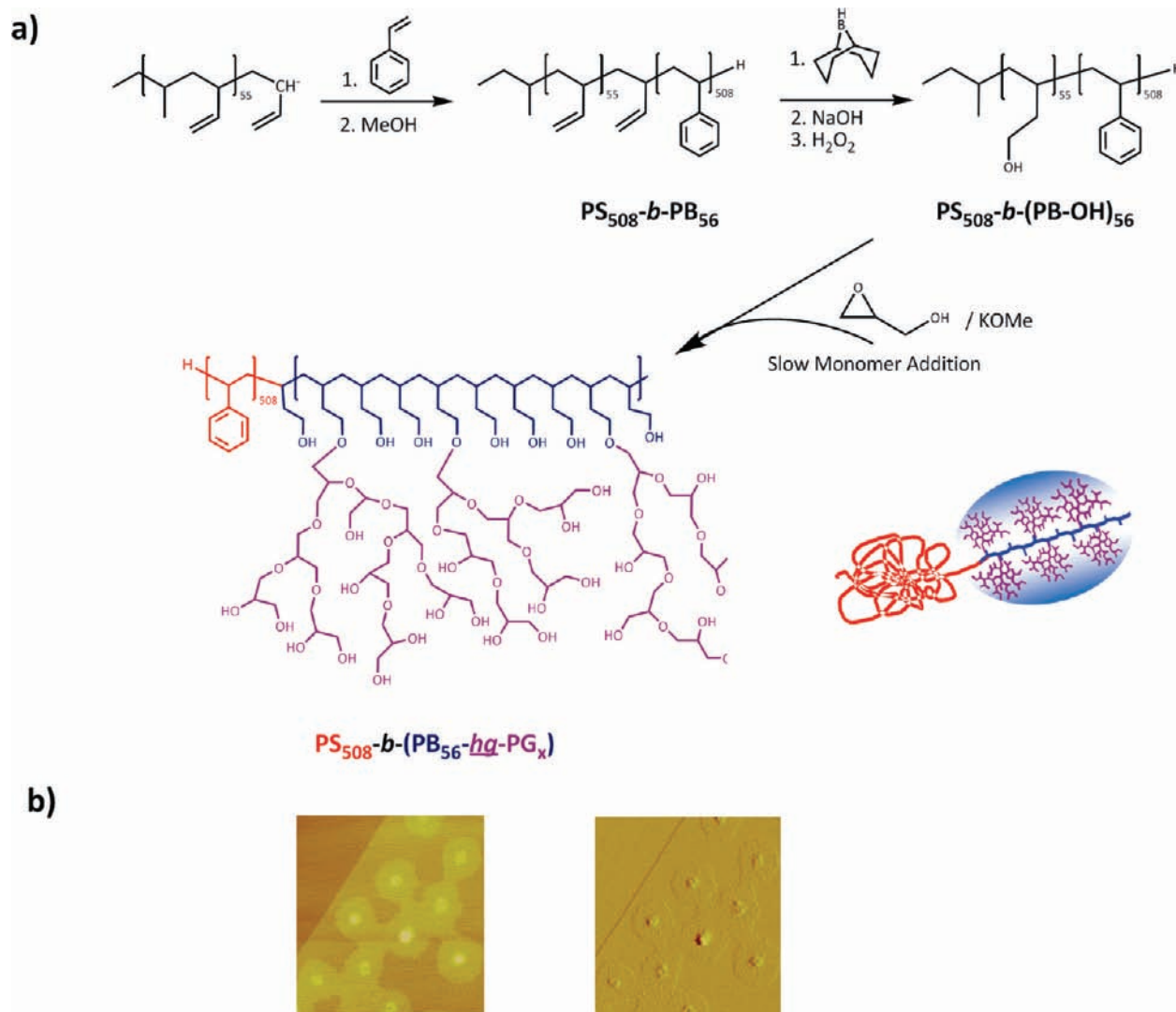


FIGURE 5. (a) Preparation of PS₅₀₈-*b*-(PB₅₆-hg-PG_x) and (b) AFM images of PS₅₀₈-*hb*-PG₂₈₀ from PS₅₀₈-*b*-PB₅₆ macroinitiator in toluene on a graphite substrate, showing the formation of ordered micelles with a PG core.

bisglycidolized *n*-alkyl amines as well as photoactive cores.²⁹ The resulting quantitatively core-functionalized biocompatible structures represent promising compounds for biosensors and labels. In a closely related approach, a photosensitizer (2,2',4,4'-tetrahydroxybenzophenone) has been used as initiating core moiety for the ring-opening polymerization of glycidol.³⁰

4.4. Multiarm Star Polymers. Two major strategies have been employed for the preparation of increasingly popular multiarm star polymer architectures: (i) the *core-first* approach, living polymerization on the basis of a multifunctional initiator-core, resulting in polymers with predetermined numbers of arms; (ii) the *arm-first* approach, which relies on quenching of living polymers by a multifunctional coupling agent. Several materials have been obtained from hyperbranched PG by a *core-first* strategy.

Owing to the high density of hydroxyl groups, PG is insoluble in most common organic solvents. The few exceptions besides water are typically lower alcohols and dipolar aprotic media, such as pyridine, DMF, DMSO, or NMP. However, due to their high boiling points or toxicity, these solvents are often limited in preparative use. In order to reduce the high polarity of the PG, propylene oxide (PO) was directly polymerized onto the living PG chain ends without altering the total number of hydroxyl end groups.^{31a} The resulting multiarm block copolymers with average number of arms in the range of 26–55 exhibited up to five propylene oxide units per end group and showed narrow molecular weight distributions ($M_w/M_n < 1.7$). The flexibility of the hyperbranched scaffold can be tuned by varying the block length from one to five to result in glass transition temperatures (T_g) between those of PG and linear PPO.

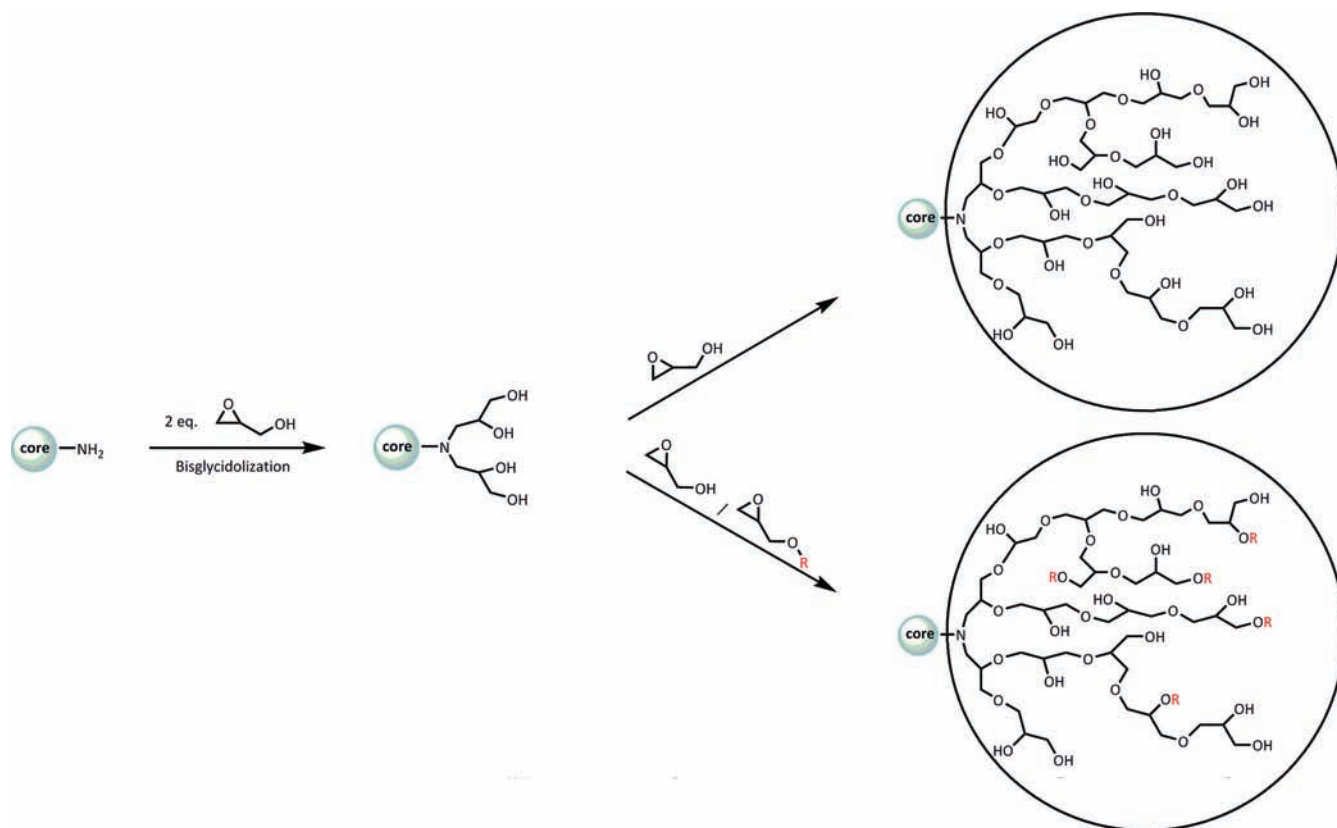


FIGURE 6. Synthesis of initiator bis(2,3-dihydroxypropyl)octadecylamine and base-catalyzed random copolymerization of glycidol and AGE or PGE.

The synthesis of PEO-based multiarm star polymers with M_n values in the range of 34 000–180 000 g/mol (between 26 and 55 arms) with moderate molecular weight distributions ($M_w/M_n < 2.2$) has been accomplished on the basis of the PPO-terminated polyglycerols (Figure 7).^{31b} These novel multiarm star architectures consist of polyether structures exclusively and therefore possess interesting potential for biomedical applications, for example, in hydrogels or amphiphilic networks. Besides PO and EO, AGE has also been directly polymerized onto the living PG or PPO-terminated PG chain ends, resulting in well-defined multiarm star polymers.²⁸ Another established pathway to well-defined star polymers is the polymerization of ϵ -caprolactone by tin catalysts. Copolymerization of ϵ -caprolactone with hyperbranched PG as an initiator proceeded smoothly without additional solvent and yielded multiarm stars with biodegradable poly(ϵ -CL) arms.^{31c}

Suitability of hyperbranched polyglycerols as macroinitiators for atom transfer radical polymerization (ATRP) was demonstrated by attaching an initiator moiety to the hydroxyl end groups (Figure 8). These dendritic macroinitiators initiated methyl acrylate (MA) polymerization in the presence of CuBr/pentamethyldiethylenetriamine (PMDETA), affording multiarm block copolymers with polyether core and 45–55 PMA arms.^{31d} The

ATRP of 2-hydroxyethyl methacrylate (HEMA), initiated by a PG-based macroinitiator has led to a series of multiarm star block copolymers, PG-*b*-PHEMA, with a tunable number of PHEMA arms and low polydispersity ($M_w/M_n = 1.1–1.8$).³²

Based on the well-defined multiarm star block copolymers PG-*b*-PHEMA, inverted and aqueous unimolecular micelle-type nanocapsules have been prepared. By the same methodology as that for HEMA and MA, well-defined star-shaped multiarm PG-*b*-poly(tert-butyl acrylate) (PG-*b*-poly(*t*BAA)) and PG-*b*-poly(dimethylaminoethyl methacrylate) (PG-*b*-poly(DMAEMA)) with 36 arms and M_w/M_n in the range of 1.2–1.4 and 1.4–1.7, respectively, were obtained with hyperbranched PG as core macroinitiator.³³ The PG-*b*-poly(*t*BAA) can be easily converted to multiarm poly(acrylic acid) (PAA), an unusual ionic multiarm star polyelectrolyte. A related functionalization approach afforded liquid crystalline hyperbranched polymers with narrow polydispersities, in which the LC phase is induced by mesogenic end groups.³⁴

5. Specific Topologies and Their Application Potential

5.1. Hyperbranched Nanocapsules. In contrast to the perfect dendrimer structure, the end groups of PG are not alto-

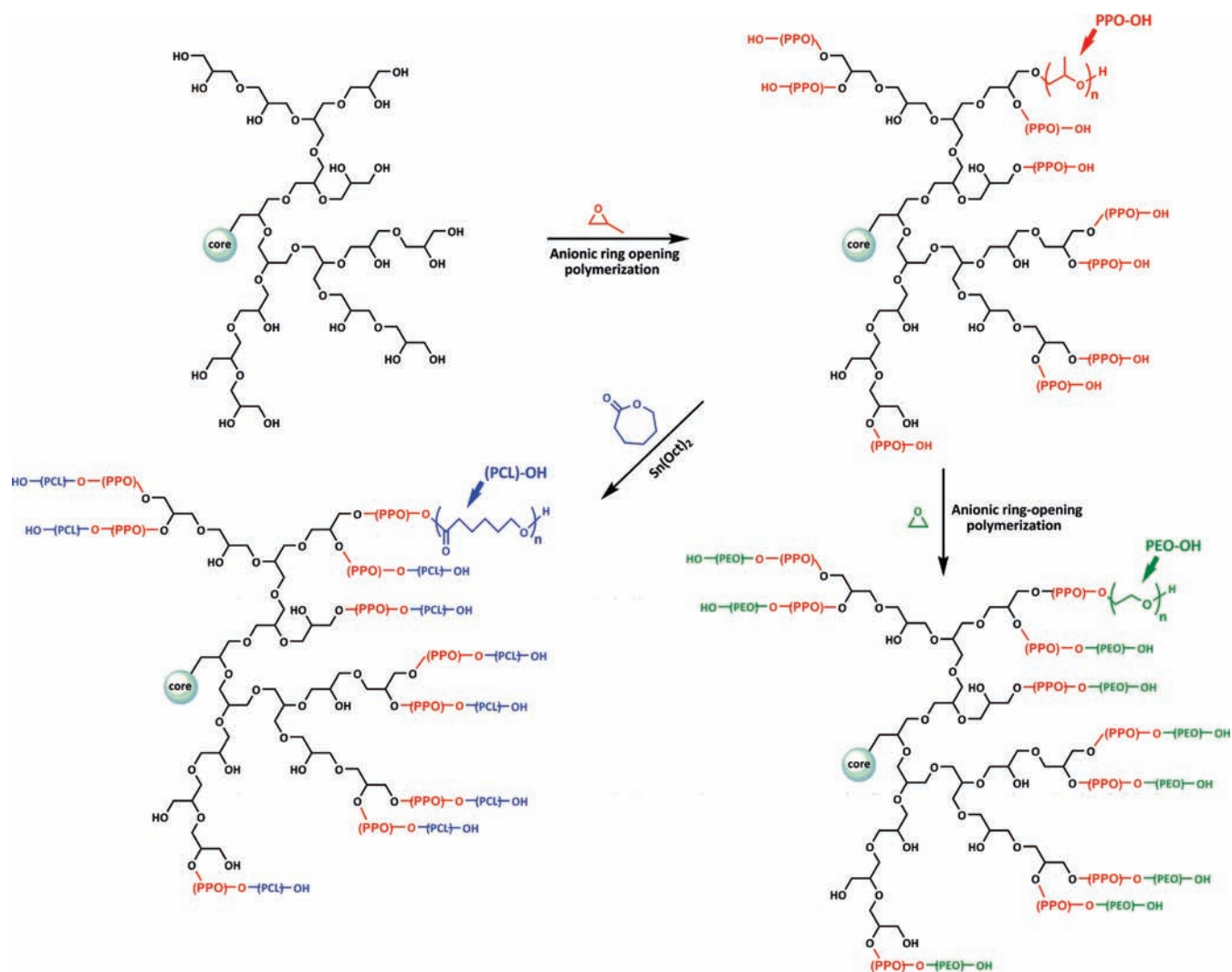


FIGURE 7. Schematic illustration of the core-first synthesis of multiarm star PG-*b*-PPO, PG-*b*-PPO-*b*-PEO, and PG-*b*-PPO-*b*-PCL with the same polyether polyol (polyglycerol) as core.

gether located at the same distance from the core. Partial modification of PG with apolar groups, for example, esterification, etherification, or transketalization, offers promising options for the preparation of amphiphilic core-shell structures. In the case of long alkyl chains, highly organo-soluble amphiphilic macromolecules with a hydrophobic shell and a hydrophilic interior due to remaining unreacted hydroxyl groups were obtained, which can encapsulate hydrophilic guests, just like inverted micelles.^{32,35,36} No aggregates are formed in dilute solution, as demonstrated by dynamic light scattering. Based on their globular core-shell architecture such macromolecules represent inverted-micelle type unimolecular nanocapsules. The selective and modular functionalization of PG with aldehydes and ketones by transketalization processes generated molecular nanocarriers with core-shell structure, exhibiting a pH-responsive shell.^{35a} pH-responsive molecular nanocarriers based on biocompatible hyper-

branched polymers are promising with respect to the use of these compounds as selective drug delivery vehicles in infected or tumor tissues with lower pH values.^{35b} The intriguing phase transfer properties of hyperbranched polyglycerol nanocapsules were demonstrated in a comparative study investigating the encapsulation and viscosity behavior of partially esterified linear and hyperbranched PGs in apolar media. It became evident that a conformational collapse is only possible in the case of the hyperbranched core-shell architecture.³⁶

Further research in the area of guest encapsulation by hyperbranched PG has been carried out through a functionalization sequence using unsubstituted biphenyl groups in the core to obtain an amphiphilic core-shell PG capable of complexing hydrophobic drugs like nimodipine, forming long-term stable drug-loaded polymeric aggregates.³⁷ Cross-linked nanoparticles based on hyperbranched PG as well as the related

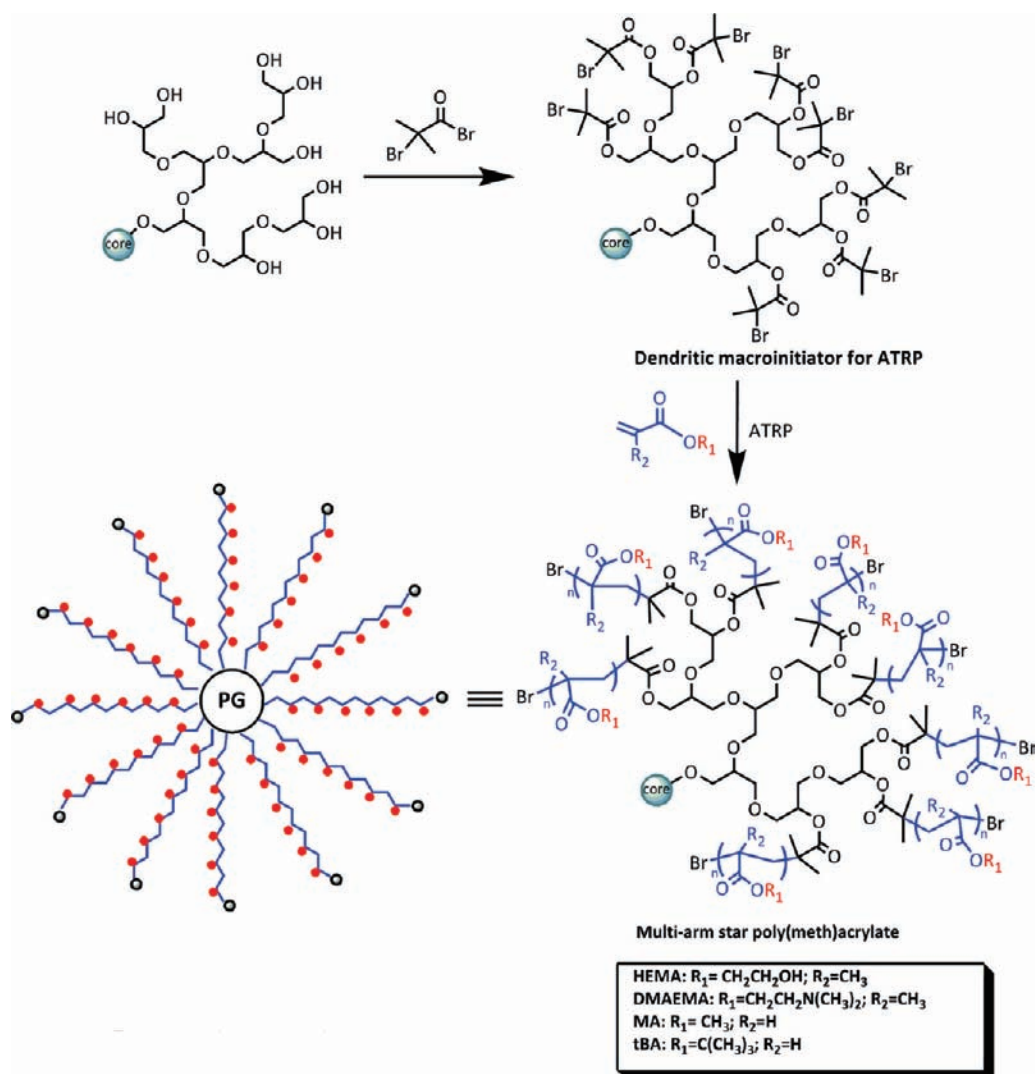


FIGURE 8. Schematic illustration of the synthesis of multiarm star poly(meth)acrylates based on polyglycerol polymer core under ATRP conditions.

glycerol dendrimers were obtained by polyallylation of the hydroxyl groups, subsequent treatment with a suitable metathesis catalyst (Figure 9), and further selective modification. These compounds were shown to exhibit crown-ether-like binding of metal ions, which is particularly interesting for applications in complexation and catalysis.³⁸

5.2. Hyperbranched Polyglycerol as Soluble Support for Catalysts and Organic Synthesis. Both dendrimers and hyperbranched polymers covalently or noncovalently functionalized with catalytically active transition-metal complexes are promising scaffolds with respect to catalyst recovery.^{39–41} The design of catalytically active dendritic materials has been achieved either by fixation of catalytically active complexes at structurally perfect dendrimer surfaces, within the interior “core” of the dendrimer or by the encapsulation of metal nanoparticles. The creation of special environments in the core of amphiphilic hyperbranched polyglycerols for guest encapsulation

has been successfully employed to template palladium nanoparticles with an average size between 2 and 5 nm (Figure 10a). The resulting encapsulated nanosize particles were applied in a model catalytic hydrogenation reaction of cyclohexene.⁴¹

Furthermore, we described the encapsulation of hydrophilic pincer platinum(II) complexes with sulfonate groups in amphiphilic hyperbranched polyglycerols with core–shell structure (Figure 10b). The noncovalently encapsulated Pt(II) complexes showed catalytic activity in double Michael additions without leaching.

The activation of racemic or optically active hyperbranched PG through tosylation was found to be an efficient method to produce suitable starting materials for further functionalization. Nucleophilic displacement of the tosyl groups by NCN-pincer platinum(II) carboxylate gave access to PG with discrete platinum(II) sites.^{39,40} Further reactions that have been

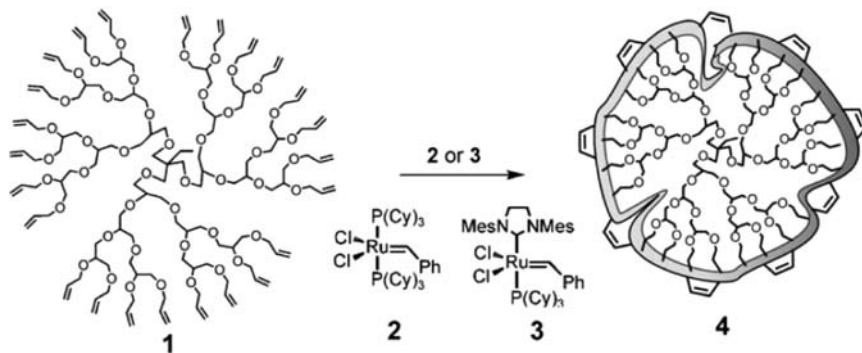


FIGURE 9. Ring-closing metathesis procedure applied for allylated glycerol dendrimers **1** and hyperbranched PG by using Grubbs catalysts **2** or **3** to obtain cross-linked PG **4**.

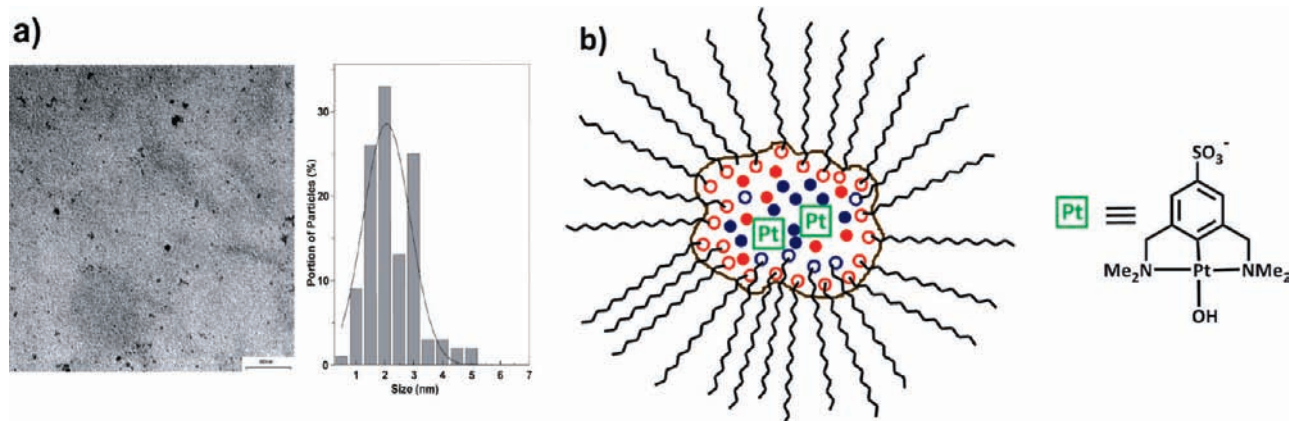


FIGURE 10. (a) TEM image and histogram of amphoteric hyperbranched polyglycerol encapsulating catalytically active palladium nanoparticles and (b) illustration of the encapsulation of polar NCN-pincer platinum(II) catalysts in partially esterified hyperbranched polyglycerol with core-shell structure.

explored with respect to the use of PG as catalyst support include Suzuki cross couplings, Mitsunobu reactions, and ATRP.⁴² The suitability of a support/catalyst system has to be individually evaluated for each possible application because solubility and product separation represent limiting factors. Both racemic and chiral hyperbranched PG show the same properties as molecular capsules for guest encapsulation and catalyst support.^{39b}

5.3. Application in Biomineralization. Many living organisms are able to precisely control the crystallization of inorganic minerals by a small fraction of biomacromolecules at the interface with the inorganic component. The intriguing effect on the biomineralization of calcium carbonate was shown by a study of Frey, Tremel et al.⁴³ A self-assembled, apolar monolayer (SAM) was used for the adsorption of hyperbranched PG and slow crystallization of CaCO₃ was induced in the medium. The morphology (calcite, aragonite, vaterite) of the crystals formed was subsequently investigated by scanning electron microscopy (SEM). PGs of different molecular weight were adsorbed on nonpolar surfaces due to their intrinsic amphiphilic character. For alkyl-terminated SAMs, the crystallization was fully controlled and only aragonite crystals

were observed (Figure 11). As expected, the thermodynamically most stable polymorph calcite was formed in solution. The latter observation shows that the cooperative interaction between the surface and the highly branched macromolecules plays a key role during the biomineralization process.

5.4. Biomedical Application. Probably the most striking motivation for the increasing interest in PG chemistry is the inherent biocompatibility of the polymer and a variety of its derivatives. This fascinating peculiarity can be intuitively presumed from the structural similarity of PG to the well-studied poly(ethylene glycol) (PEG), which is widely employed in the biomedical and pharmaceutical industry for drug conjugation (PEGylation)⁴⁴ and for the suppression of protein adsorption to blood-contacting surfaces.⁴⁵ In pioneering work, a comparative study exploring the biocompatibility of both linear and hyperbranched PG was presented by Brooks et al. in 2006.⁴⁶ In vivo, as well as in vitro, assays resulted in similar or better biocompatibility characteristics compared with PEG or hetastarch. Figure 12 exemplarily depicts the remarkably low cytotoxicity of PG against fibroblast and endothelial cells.

These important fundamental investigations were later expanded to high molecular weight PGs, which have recently

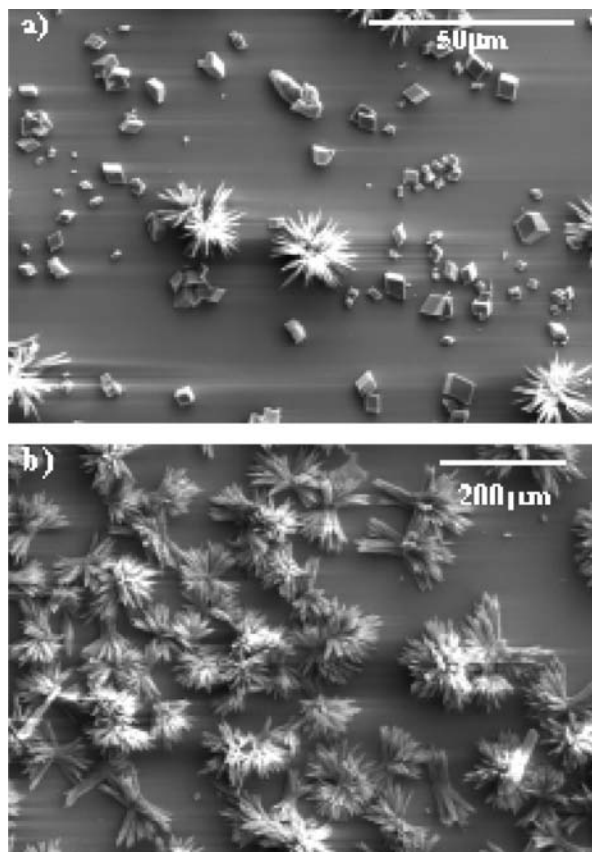


FIGURE 11. SEM images of (a) CaCO_3 crystals on a CH_3 -terminated SAM surface and (b) aragonite on a CH_3 -terminated SAM with adsorbed *hb*-PG ($c = 0.33 \text{ mg/mL}$; $M_n = 5000 \text{ g/mol}$).

become available.¹⁹ Both *in vitro*^{47a} and *in vivo*^{47b} evaluations further substantiated the vast potential of PG for biomedical applications. A recent example pointing out the tremendous practical capabilities of specifically derivatized hyperbranched PG for possible replacement of currently employed biomaterials is based on the sequential attachment of hydrophobic C18 alkyl chains as well as MPEG-350 chains to a certain fraction of the polyether polyol OH groups.⁴⁸ Since the resulting materials exhibited low intrinsic viscosities coupled with high water solubility and facile synthetic accessibility, they are considered extremely promising candidates for use as human serum albumin (HSA) substitutes. Plasma half-lives as high as 34 h clearly hint at the suitability for application as synthetic plasma expanders, avoiding the risk of disease transmission, which is inherent to native HSA. Very recently, our group presented the attachment of singularly amino-functionalized α,ω_n -linear–hyperbranched heterotelechelic to biotin and explored these materials with respect to noncovalent bioconjugation.⁴⁹ This approach offers intriguing possibilities for the introduction of functional groups and bioconjugation with a variety of proteins and peptides.

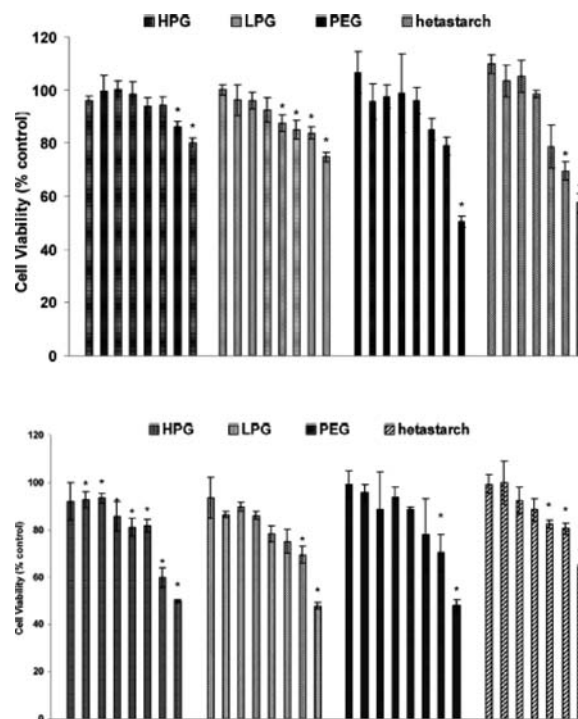


FIGURE 12. Cytotoxicity of hyperbranched (HPG) and linear (LPG) polyglycerol, as well as PEG and hetastarch, against L-929 cells (top) and human umbilical vein endothelial cells (HUVEC) (bottom) at increasing concentrations from left to right.

A further area of major potential regarding biomedical application of PG can be found in protein-resistant surfaces in medical devices or biosensors, since protein adsorption marks a severe problem for polymer objects implanted into the human body such as artificial joints or catheters. Readily available PG has been modified with a surface-active disulfide linker, and subsequently self-assembled monolayers (SAMs) of these polymers on gold as a model surface were prepared.^{50a,c} The respective PG SAMs proved similarly protein resistant as their linear PEG analogues. In a similar manner, protein adsorption onto monoamino oligoglycerol SAMs was systematically investigated to derive a structure–property relationship.^{50b} Further therapeutic potential has been disclosed by Haag et al. who discussed conveniently accessible hyperbranched PG sulfates as alternatives to heparin, a highly sulfated natural glycosaminoglycan that is widely used as an injectable anticoagulant.⁵¹ Figure 13 highlights the intriguing application potential of hyperbranched PG that emerges from a unique combination of chemical and structural prerequisites with preeminent economic viability.

6. Conclusion

Ten years after the publication of the first work on the controlled anionic polymerization of glycidol to hyperbranched

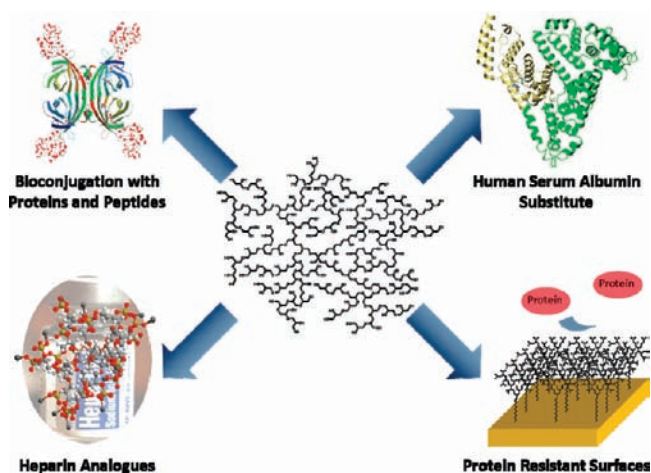


FIGURE 13. Illustration of biomedical application areas disclosed for hyperbranched PG.

polyglycerol in 1999,⁷ many fascinating facets of this material have been explored. As a point of central importance, the synthesis of hyperbranched PG has been developed further, presently giving access to molecular weights in the range of 500 Da to several hundred kilodaltons, keeping polydispersities low ($M_w/M_n < 1.5$). Combining the ring-opening multibranching polymerization of glycidol, carried out in slow monomer addition mode, with the highly versatile epoxide chemistry provides a molecular construction kit for dendritic polyether polyols with controlled functionality. Due to the control over both molecular weights and degree of branching, the resulting structures can be used to prepare well-defined, complex polymer architectures. Due to the excellent biocompatibility of PG, biomedical application offers enormous potential for diagnostics and therapy in the future. In summary, it is a safe bet that the chemistry of hyperbranched polyglycerol will continue to represent an area of exciting polymer research.

We are grateful to Dr. Alexander Sunder and Prof. Rolf Mülhaupt for their encouragement and support in the initial stage of the PG project. Furthermore, we thank the DFG and the Alexander von Humboldt Foundation for financial support. D.W. acknowledges financial support from the VCI and POLYMAT.

BIOGRAPHICAL INFORMATION

Daniel Wilms was born in Mönchengladbach, Germany (1981), and graduated in Chemistry (2007) from the University of Mainz. During his studies, he spent 6 months at the Polymer Science & Engineering Department of the University of Massachusetts in Amherst, MA. He is currently carrying out his Ph.D. research in the group of Prof. Holger Frey at the University of Mainz (Institute of Organic and Macromolecular Chemistry), where he focuses on polyether chemistry and the application of microstructured reaction devices for anionic polymerization.

Salah-E. Stiriba was born in Marrakech, Morocco (1971), graduated (1993) from Université Abdel Malek Essadi in Tetouan and then moved to the Universidad de Valencia where he carried out his Ph.D. thesis (1998). He took various postdoctoral positions, first at the Texas A&M University, then at Université Louis Pasteur, and finally in the Institut für Makromolekulare Chemie at Freiburg University as an Alexander von Humboldt fellow. He joined Universidad de Valencia as senior research scientist in 2002, and then became assistant professor in 2008. His research interests are in the areas of supramolecular organometallic chemistry, asymmetric catalysis, and organic polymer chemistry.

Holger Frey was born in Ellwangen, Germany (1965), and studied Chemistry at the University of Freiburg/Brsg. Following a stay at Carnegie-Mellon University in Pittsburgh, PA, he obtained a Ph. D. from the Universiteit Twente in 1993. From 1994 until 2001, he worked as a senior lecturer and assistant professor at the University of Freiburg. Since 2002, he has held a full professorship at the Johannes-Gutenberg Universität, Mainz, Germany. His research interests are centered on branched and dendritic polymer architectures, block copolymers, and silicon-based polymer chemistry. Recent interests include microreactor-based continuous polymer syntheses as well as novel biomaterials.

FOOTNOTES

*To whom correspondence should be addressed. E-mail addresses: salah.stiriba@uv.es; hfrey@uni-mainz.de.

REFERENCES

- (a) Kim, Y. H.; Webster, O. W. Hyperbranched polyphenylenes. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1988**, *29*, 310–311. (b) Kim, Y. H.; Webster, O. W. Water-soluble hyperbranched polyphenylene: A unimolecular micelle. *J. Am. Chem. Soc.* **1990**, *112*, 4592–4593.
- Flory, P. J. Molecular size-distribution in three dimensional polymers.VI. Branched polymers containing A-R-BF-1 type units. *J. Am. Chem. Soc.* **1952**, *74*, 2718–2723.
- Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons*; WILEY-VCH: Weinheim, Germany, 2001.
- Yan, D.; Gao, C. Hyperbranched polymers: From synthesis to applications. *Prog. Polym. Sci.* **2004**, *29*, 183–275.
- Voit, B. I. New developments in hyperbranched polymers. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 2505–2525.
- Frey, H.; Haag, R. Dendritic polyglycerol: A new versatile biocompatible material. *Mol. Biotechnol.* **2002**, *90*, 257–267.
- Sunder, A.; Hanselmann, R.; Frey, H.; Mülhaupt, R. Controlled synthesis of hyperbranched polyglycerols by ring-opening multibranching polymerization. *Macromolecules* **1999**, *32*, 4240–4246.
- Hanselmann, R.; Höfner, D.; Frey, H. Hyperbranched polymers prepared via the core-dilution/slow monomer addition technique: Computer simulation of molecular weight distribution and degree of branching. *Macromolecules* **1998**, *31*, 3790–3801.
- Radke, W.; Litvinenko, G.; Müller, A. H. E. Effect of core-forming molecules on molecular weight distribution and degree of branching in the synthesis of hyperbranched polymers. *Macromolecules* **1998**, *31*, 239–248.
- (a) Höfner, D.; Burgath, A.; Frey, H. Degree of branching in hyperbranched polymers. *Acta Polym.* **1997**, *48*, 30–35. (b) Höfner, D.; Frey, H. Degree of branching in hyperbranched polymers. 2. Enhancement of the DB: Scope and limitations. *Acta Polym.* **1997**, *48*, 298–309.
- Lach, C.; Frey, H. Enhancing the degree of branching of hyperbranched polymers by postsynthetic modification. *Macromolecules* **1998**, *31*, 2381–2383.
- (a) Haag, R.; Sunder, A.; Stumbé, J.-F. An approach to glycerol dendrimers and pseudo-dendritic polyglycerols. *J. Am. Chem. Soc.* **2000**, *122*, 2954–2955. (b) Wyszogrodzka, M.; Haag, R. A convergent approach to biocompatible polyglycerol "click" dendrons for the synthesis of modular core-shell architectures and their transport behavior. *Chem.—Eur. J.* **2008**, *14*, 9202–9214.
- Sandler, S. R.; Berg, F. R. Room temperature polymerization of glycidol. *J. Polym. Sci., Part A: Polym. Chem.* **1966**, *4*, 1253–1259.

- 14 Vandenberg, E. J. Polymerization of glycidol and its derivatives: A new rearrangement polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **1985**, *23*, 915–949.
- 15 (a) Tokar, R.; Kubisa, P.; Penczek, S. Cationic polymerization of glycidol: Coexistence of the activated monomer and active chain end mechanism. *Macromolecules* **1994**, *27*, 320–322. (b) Dworak, A.; Walach, W.; Trzebicka, B. Cationic polymerization of glycidol. Polymer structure and polymerization mechanism. *Macromol. Chem. Phys.* **1995**, *196*, 1963–1970.
- 16 (a) Sunder, A.; Mülhaupt, R.; Haag, R.; Frey, H. Hyperbranched polyether polyols: A modular approach to complex polymer architectures. *Adv. Mater.* **2000**, *12*, 235–239. (b) Sunder, A.; Mülhaupt, R.; Haag, R.; Frey, H. Chiral hyperbranched dendron analogues. *Macromolecules* **2000**, *33*, 253–254.
- 17 Khan, M.; Huck, T. S. Hyperbranched polyglycidol on Si/SiO₂ surfaces via surface-initiated polymerization. *Macromolecules* **2003**, *36*, 5088–5093.
- 18 Wilms, D.; Nieberle, J.; Klos, J.; Löwe, H.; Frey, H. Synthesis of hyperbranched polyglycerol in a continuous flow microreactor. *Chem. Eng. Technol.* **2007**, *30*, 1519–1524.
- 19 Kainthan, R. K.; Muliawan, E. B.; Hatzikiakos, S. G.; Brooks, D. E. Synthesis, characterization, and viscoelastic properties of high molecular weight hyperbranched polyglycerols. *Macromolecules* **2006**, *39*, 7708–7717.
- 20 Wilms, D.; Wurm, F.; Nieberle, J.; Böhm, P.; Kemmer-Jonas, U.; Frey, H. Hyperbranched polyglycerols with elevated molecular weights: A facile two-step synthesis protocol based on polyglycerol macroinitiators. *Macromolecules* **2009**, *42*, 3230–3236.
- 21 Sisson, A. L.; Papp, I.; Landfester, K.; Haag, R. Functional nanoparticles from dendritic precursors: Hierarchical assembly in miniemulsion. *Macromolecules* **2009**, *42*, 556–559.
- 22 Walach, W.; Kowalczyk, A.; Trzebicka, B.; Dworak, A. Synthesis of high-molar mass absorbent-branched polyglycidol via sequential grafting. *Macromol. Rapid Commun.* **2001**, *22*, 1272–1277.
- 23 Istratov, V.; Kautz, H.; Kim, Y.-K.; Schubert, R.; Frey, H. Linear-dendritic non-ionic poly(propylene oxide)-polyglycerol surfactants. *Tetrahedron* **2003**, *59*, 4017–4024.
- 24 Demina, T.; Grozdova, I.; Krylova, O.; Zhimov, V.; Istratov, H.; Frey, H.; Kautz, H.; Melnik-Nubarov, N. Relationship between the structure of amphiphilic copolymers and their ability to disturb lipid bilayers. *Biochemistry* **2005**, *44*, 4042–4054.
- 25 Wurm, F.; Nieberle, J.; Frey, H. Double hydrophilic linear hyperbranched block copolymers based on poly(ethylene oxide) and poly(glycerol). *Macromolecules* **2008**, *41*, 1184–1188.
- 26 Barriau, E.; Garcia Marcos, A.; Kautz, H.; Frey, H. Linear-hyperbranched amphiphilic AB diblock copolymers based on polystyrene and hyperbranched polyglycerol. *Macromol. Rapid Commun.* **2005**, *26*, 862–867.
- 27 Wurm, F.; Nieberle, J.; Frey, H. Synthesis and characterization of poly(glyceryl glycerol) block copolymers. *Macromolecules* **2008**, *41*, 1909–1911.
- 28 Sunder, A.; Türk, H.; Haag, R.; Frey, H. Copolymers of glycidol and glycidyl ethers: Design of branched polyether polyols by combination of latent cyclic AB₂ and ABR monomers. *Macromolecules* **2000**, *33*, 7682–7692.
- 29 Barriau, E.; Pastor-Pérez, L.; Berger-Nicoletti, E.; Kilbinger, A. F. M.; Pérez-Prieto, J.; Frey, H.; Stiriba, S.-E. Systematic investigation of functional core variation within hyperbranched polyglycerols. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2049–2061.
- 30 Pastor-Pérez, L.; Barriau, E.; Berger-Nicoletti, E.; Kilbinger, A. F. M.; Pérez-Prieto, J.; Frey, H.; Stiriba, S.-E. Incorporation of a photosensitizer-core within hyperbranched polyether polyols: Effect of the branched shell on the core properties. *Macromolecules* **2008**, *41*, 1189–1195.
- 31 (a) Sunder, A.; Mülhaupt, R.; Frey, H. Hyperbranched polyether-polyols based on polyglycerol: Polarity design by block copolymerization with propylene oxide. *Macromolecules* **2000**, *33*, 309–314. (b) Knischka, R.; Lutz, P. J.; Sunder, A.; Mülhaupt, R.; Frey, H. Functional poly(ethylene oxide) multiarm star polymers: Core-first synthesis using hyperbranched polyglycerol initiators. *Macromolecules* **2000**, *33*, 315–320. (c) Burgath, A.; Sunder, A.; Neuner, I.; Mülhaupt, R.; Frey, H. Multi-arm star block copolymers based on ϵ -caprolactone with hyperbranched polyglycerol core. *Macromol. Chem. Phys.* **2000**, *201*, 792–797. (d) Maier, S.; Sunder, A.; Frey, H.; Mülhaupt, R. Synthesis of poly(glycerol)-block-poly(methyl acrylate) multi-arm star polymers. *Macromol. Rapid Commun.* **2000**, *21*, 226–230.
- 32 (a) Sunder, A.; Krämer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. Molecular nanocapsules based on amphiphilic hyperbranched polyglycerols. *Angew. Chem., Int. Ed.* **1999**, *38*, 3552–3555. (b) Haag, R.; Stumbé, J. F.; Sunder, A.; Frey, H.; Hebel, A. An approach to core-shell-type architectures in hyperbranched polyglycerols by selective chemical differentiation. *Macromolecules* **2000**, *33*, 8158–8166.
- 33 Shen, Z.; Chen, Y.; Barriau, E.; Frey, H. Multi-arm star polyglycerol-b-poly(tert-butyl acrylate) and the respective multi-arm poly(acrylic acid) stars. *Macromol. Chem. Phys.* **2006**, *207*, 57–64.
- 34 Sunder, A.; Quincy, M. F.; Mülhaupt, R.; Frey, H. Hyperbranched polyether polyols with liquid crystalline properties. *Angew. Chem., Int. Ed.* **1999**, *38*, 2928–2930.
- 35 (a) Krämer, M.; Stumbé, J.-F.; Türk, H.; Krause, S.; Komp, A.; Delineau, L.; Prokhorova, S.; Kautz, H.; Haag, R. pH-Responsive molecular nanocarriers based on dendritic core-shell architectures. *Angew. Chem., Int. Ed.* **2002**, *41*, 4252–4256. (b) Xu, S.; Luo, Y.; Graeser, R.; Warnecke, A.; Kratz, F.; Hauff, P.; Licha, K.; Haag, R. Development of pH-responsive core-shell nanocarriers for delivery of therapeutic and diagnostic agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1030–1034.
- 36 Stiriba, S.-E.; Kautz, H.; Frey, H. Hyperbranched molecular nanocapsules: Comparison of the hyperbranched architecture with the perfect linear analogue. *J. Am. Chem. Soc.* **2002**, *124*, 9698–9699.
- 37 Türk, H.; Shukla, A.; Rodrigues, P. C. A.; Rehage, H.; Haag, R. Water-soluble dendritic core-shell type architectures based on polyglycerol for solubilization of hydrophobic drugs. *Chem.—Eur. J.* **2007**, *13*, 4187–4196.
- 38 Zimmerman, S. C.; Quinn, J. R.; Burakowska, E.; Haag, R. Cross-linked glycerol dendrimers and hyperbranched polymers as ionophoric, organic nanoparticles soluble in water and organic solvents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8164–8167.
- 39 (a) Slagt, M. Q.; Stiriba, S.-E.; Gebbink, R. J. M. K.; Kautz, H.; Frey, H.; van Koten, G. Encapsulation of hydrophilic pincer-platinum(II) complexes in amphiphilic hyperbranched polyglycerol nanocapsules. *Macromolecules* **2002**, *35*, 5734–5737. (b) Slagt, M. Q.; Stiriba, S.-E.; Kautz, H.; Gebbink, R. J. M. K.; Frey, H.; van Koten, G. Optically active hyperbranched polyglycerol as scaffold for covalent and noncovalent immobilization of platinum(II) NCN-pincer complexes. Catalytic application and recovery. *Organometallics* **2004**, *23*, 1525–1532.
- 40 Stiriba, S.-E.; Slagt, M. Q.; Kautz, H.; Gebbink, R. J. M. K.; Thomann, R.; Frey, H.; van Koten, G. Synthesis and supramolecular association of immobilized ncn-pincer platinum(II) complexes on hyperbranched polyglycerol supports. *Chem.—Eur. J.* **2004**, *10*, 1267–1273.
- 41 Mecking, S.; Thomann, R.; Frey, H.; Sunder, A. Preparation of catalytically active palladium nanoclusters in compartments of amphiphilic hyperbranched polyglycerols. *Macromolecules* **2000**, *33*, 3958–3960.
- 42 (a) Hebel, A.; Haag, R. Polyglycerol as high-loading support for boronic acids with application in solution-phase Suzuki cross-couplings. *J. Org. Chem.* **2002**, *67*, 9452–9455. (b) Roller, S.; Türk, H.; Stumbé, J.-F.; Rapp, W.; Haag, R. Polystyrene-graft-polyglycerol resins: A new type of high-loading hybrid support for organic synthesis. *J. Comb. Chem.* **2006**, *8*, 350–354. (c) Kumar, K. R.; Kizhakkedathu, J. N.; Brooks, D. E. Atom transfer radical polymerization using multidentate amine ligands supported on soluble hyperbranched polyglycidol. *Macromol. Chem. Phys.* **2004**, *205*, 567–573.
- 43 Balz, M.; Barriau, E.; Istratov, V.; Frey, H.; Tremel, W. Controlled crystallization of CaCO₃ on hyperbranched polyglycerol adsorbed to self-assembled monolayers. *Langmuir* **2005**, *21*, 3987–3991.
- 44 Kodera, Y.; Matsushima, A.; Hiroto, M.; Nishimura, H.; Ishii, A.; Ueno, T.; Inada, Y. PEGylation of proteins and bioactive substances for medical and technical applications. *Prog. Polym. Sci.* **2007**, *23*, 1233–1271.
- 45 Pale-Grosdemange, C.; Simon, E. S.; Whitesides, G. M. Formation of self-assembled monolayers by chemisorption of derivatives of oligo(ethylene glycol) of structure HS(CH₂)₁₁(OCH₂CH₂)_nOH on gold. *J. Am. Chem. Soc.* **1991**, *113*, 12–20.
- 46 Kainthan, R. K.; Janzen, J.; Levin, E.; Devine, D. V.; Brooks, D. E. Biocompatibility testing of branched and linear polyglycidol. *Biomacromolecules* **2006**, *7*, 703–709.
- 47 (a) Kainthan, R. K.; Hester, S. R.; Levin, E.; Devine, D. V.; Brooks, D. E. In vitro biological evaluation of high molecular weight hyperbranched polyglycerols. *Biomaterials* **2007**, *28*, 4581–4590. (b) Kainthan, R. K.; Brooks, D. E. In vivo biological evaluation of high molecular weight hyperbranched polyglycerols. *Biomaterials* **2007**, *28*, 4779–4787.
- 48 Kainthan, R. K.; Janzen, J.; Kizhakkedathu, J. N.; Devine, D. V.; Brooks, D. E. Hydrophobically derivatized hyperbranched polyglycerol as a human serum albumin substitute. *Biomaterials* **2008**, *29*, 1693–1704.
- 49 Wurm, F.; Klos, J.; Räder, H.-J.; Frey, H. Synthesis and noncovalent protein conjugation of linear-hyperbranched PEG-poly(glycerol)- α,ω -telechelics. *J. Am. Chem. Soc.* **2009**, *131*, 7954–7955.
- 50 (a) Siegers, C.; Biesalski, M.; Haag, R. Self-assembled monolayers of dendritic polyglycerol derivatives on gold that resist the adsorption of proteins. *Chem.—Eur. J.* **2004**, *10*, 2831–2838. (b) Wyszogrodzka, M.; Haag, R. Study of single protein adsorption onto monoamino oligoglycerol derivatives: A structure–activity relationship. *Langmuir* **2009**, *25*, 5703–5712. (c) Wyszogrodzka, M.; Haag, R. Synthesis and characterization of glycerol dendrons, self-assembled monolayers on gold: a detailed study of their protein resistance. *Biomacromolecules* **2009**, *10*, 1043–1054.
- 51 Türk, H.; Haag, R.; Alban, S. Dendritic polyglycerol sulfates as new heparin analogues and potent inhibitors of the complement system. *Bioconjugate Chem.* **2004**, *15*, 162–167.