

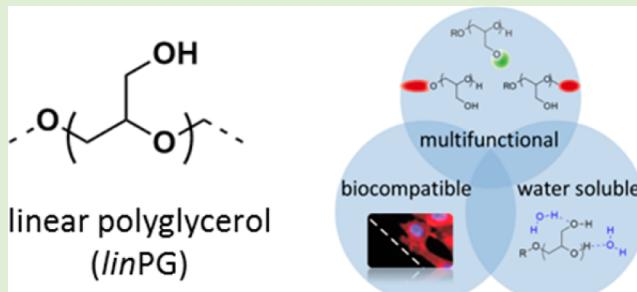
Beyond Poly(ethylene glycol): Linear Polyglycerol as a Multifunctional Polyether for Biomedical and Pharmaceutical Applications

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ABSTRACT: Polyglycerols (sometimes also called “polyglycidols”) represent a class of highly biocompatible and multihydroxy-functional polymers that may be considered as a multifunctional analogue of poly(ethylene glycol) (PEG). Various architectures based on a polyglycerol scaffold are feasible depending on the monomer employed. While polymerization of glycidol leads to hyperbranched polyglycerols, the precisely defined linear analogue is obtained by using suitably protected glycidol as a monomer, followed by removal of the protective group in a postpolymerization step. This review summarizes the properties and synthetic approaches toward linear polyglycerols (*linPG*), which are at present mainly based on the application of ethoxyethyl glycidyl ether (EEGE) as an acetal-protected glycidol derivative. Particular emphasis is placed on the manifold functionalization strategies including, e.g., the synthesis of end-functional *linPGs* or multiheterofunctional modifications at the polyether backbone. Potential applications like bioconjugation and utilization as a component in degradable biomaterials or for diagnostics, in which polyglycerol acts as a promising PEG substitute are discussed. In the last section, the important role of linear polyglycerol as a macroinitiator or as a highly hydrophilic segment in block co- or terpolymers is highlighted.



In recent years, polyglycerols (also known as “polyglycidols”) are increasingly recognized as a structurally similar, albeit multihydroxy-functional alternative to conventional PEG (Figure 1).

It is a remarkable feature of the chemistry of glycidol and its protected derivatives that a plethora of different architectures

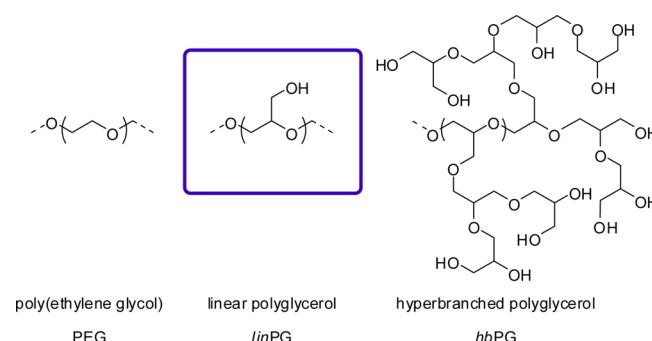


Figure 1. Chemical structures of poly(ethylene glycol) (PEG), linear polyglycerol (*linPG*) and hyperbranched polyglycerol (*hbPG*). This review focuses on synthetic procedures, functionalization possibilities and potential applications of *linPG* (middle).

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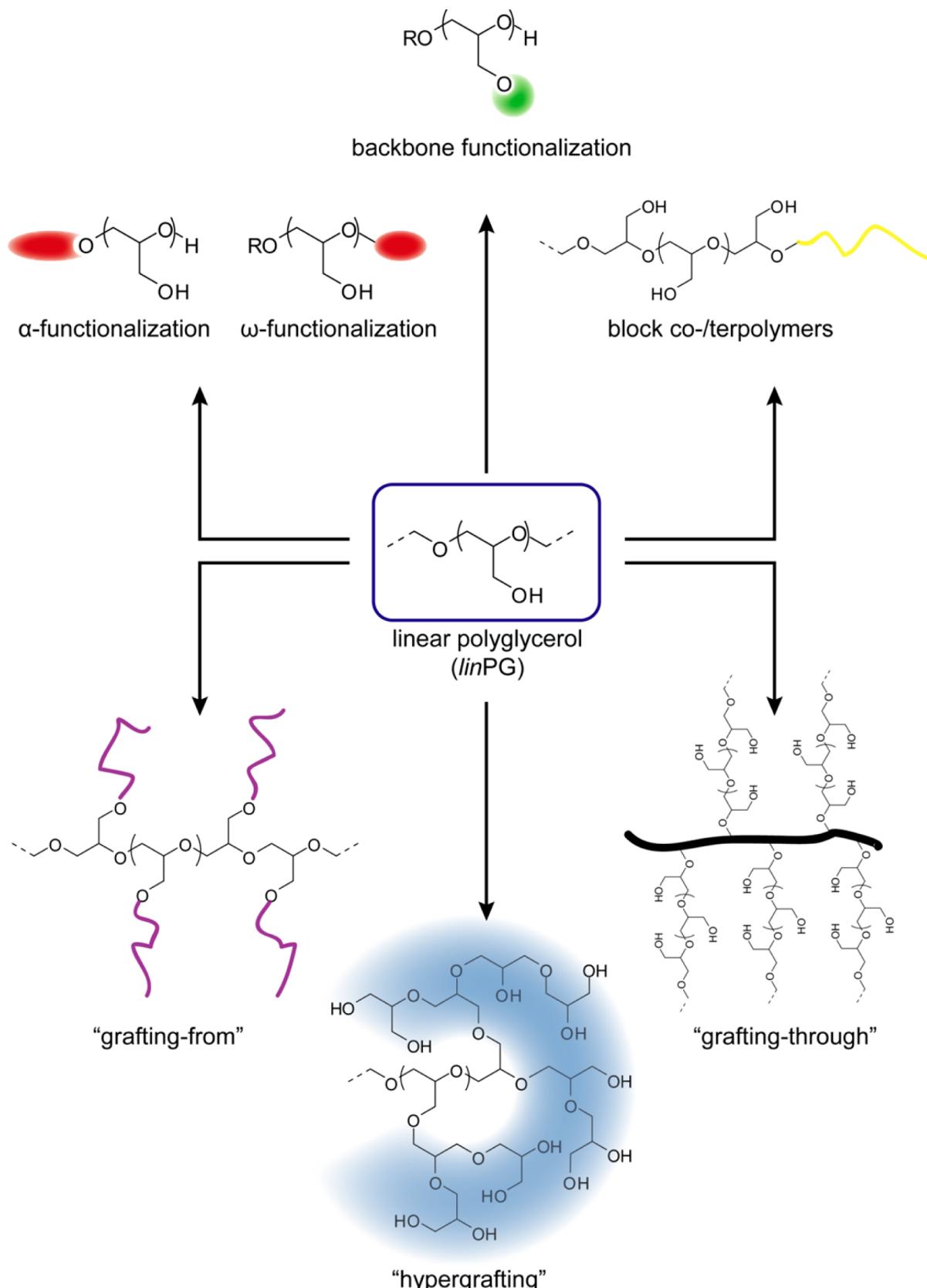


Figure 2. Overview of the vast topological variety available based on *linPG* building blocks.

ranging from linear to hyperbranched or even more complex structures are accessible, depending on the monomer and synthetic strategy applied. By using glycidol as a latent AB₂

monomer, hyperbranched polyglycerol scaffolds can be obtained via cationic or anionic polymerization. The synthetic pathways and properties of hyperbranched polyether polyols

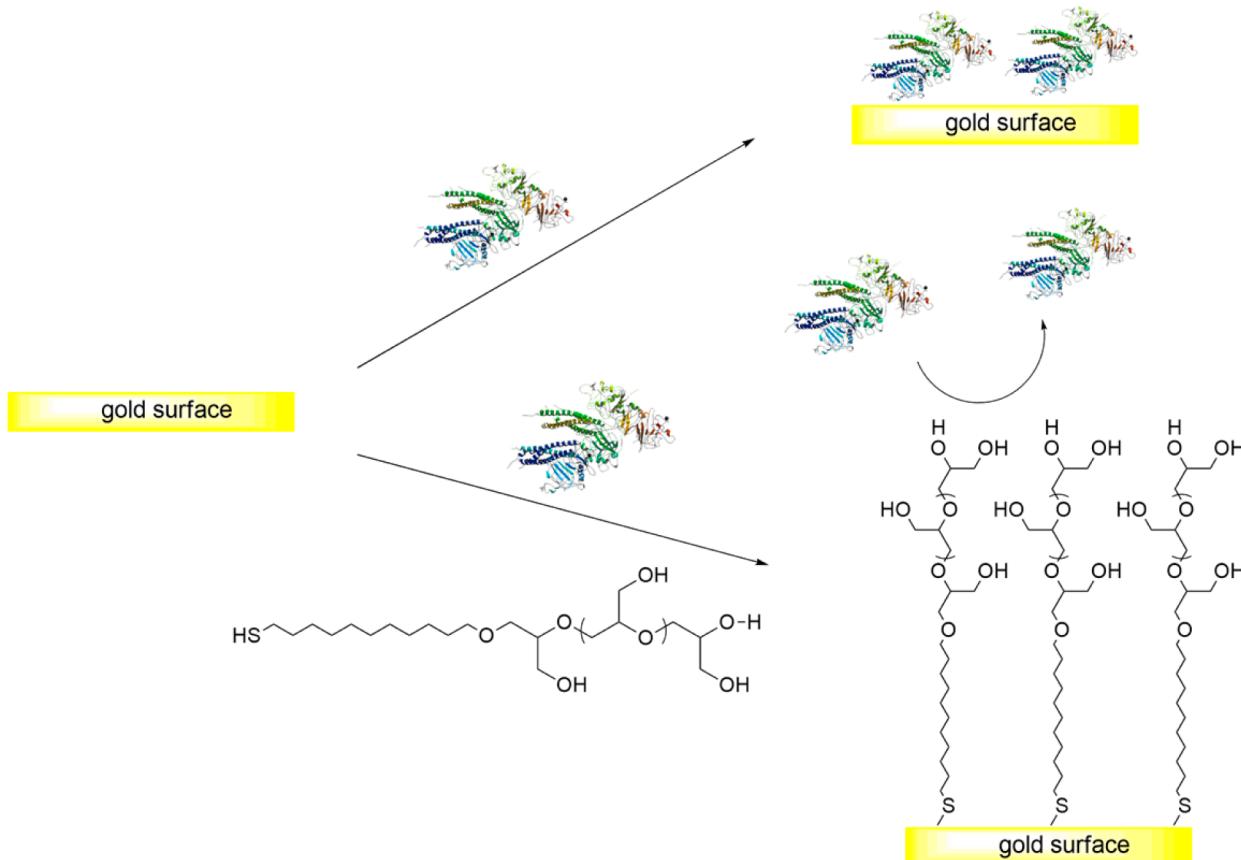


Figure 3. Protein adhesion and antifouling properties of linear polyglycerol on a PG-model surface.

like polyglycerol (*hbPG*) have recently been reviewed in depth.^{8–10} The branching reaction of glycidol during the polymerization process can be effectively prevented by protecting the hydroxyl function. This strategy gives access to versatile and precisely defined architectures from linear structures to comb-like or even more complex structural designs (Figure 2).

In contrast to *hbPG*, the application of protected glycidol monomers allows the incorporation of exactly one discrete end-functionality, while for *hbPG* the number of *in-chain* functional groups usually only averages the targeted value. In this context, some peculiar aspects concerning linear polyglycerol (*linPG*) have recently been highlighted.^{3,4,11,12} In this review article, we aim at a comprehensive summary of the state of the art in this area.

Compared to PEG, the resulting water-soluble *linPG* exhibits a similar or even slightly superior biocompatibility profile.^{13–15} No significant effects on coagulation, complement activation, or cell viability have been observed to date. In fact, esters of oligoglycerols with a degree of polymerization up to 10 and considerable polydispersity both in molecular weight and structure were approved by the American Food and Drug Administration (FDA) as food and pharmaceutical additives and have been used for these purposes for several decades.^{3,16}

Antifouling properties of *linPGs* employed for surface modification were intensively studied by Haag and co-workers and were found to be similar to PEG. The authors demonstrate that the adsorption of proteins, cells, or bacterial strains (compare Figure 3) significantly decreases with increasing degree of polymerization of *linPGs* (DP_n = 10 or 16) or poly(glycidyl methyl ether) (P(GME)) (DP_n = 6, 10, or 16) as

the fully methylated analogue attached to a model surface.^{17–19} A minimum molecular weight of around 1000 g·mol^{−1} of the polyglycerol derivatives is described to provide efficient biorepellent properties.¹⁸ Computational entropy estimations for PEG, *linPG*, and P(GME) were suggested by the authors to give insight into the underlying protein repellent mechanism.²⁰ The studies revealed a slightly higher flexibility of PEG chains compared to *linPG* or P(GME). Unfortunately, no significant conclusion could be drawn, as to whether an interfacial water layer or chain flexibility of the polymers attached determines the degree of protein resistance.

Although the chemical structures of PEG and *linPG* are quite similar (Figure 1), the thermal properties of the linear polyethers differ drastically. PEG is a highly crystalline material with melting points up to about 63 °C for elevated molecular weights >20.000 g·mol^{−1}.^{1,21} In contrast, the dense packing of the polyether chains is disturbed for *linPG* due to the additional hydroxyl group per monomer unit, and the atactic nature of the polymer resulting in (highly) viscous and amorphous structures. It is interesting to note that studies on the synthesis of *linPGs* with controlled stereochemistry and tacticity have only been sparsely reported in the literature,^{22,23} rendering this an almost neglected field at present. Glass transition temperatures (T_g) ranging from −8 °C to −27 °C for varying molecular weights have been mentioned occasionally,^{23–26} however, it is surprising to note that no systematic investigation of the influence of molecular weight and initiator on the thermal properties of *linPG* has been published to date. A slightly higher thermal and oxidative stability has been claimed for hyperbranched polyglycerols in comparison to PEG.²⁷ For *linPG*, studies on the thermal degradation are rare, with the

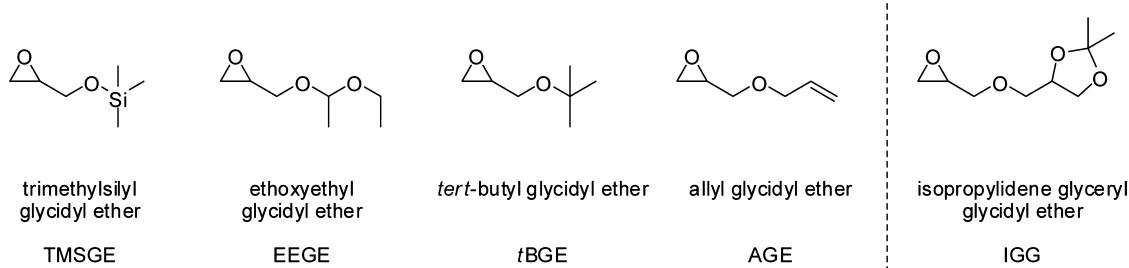
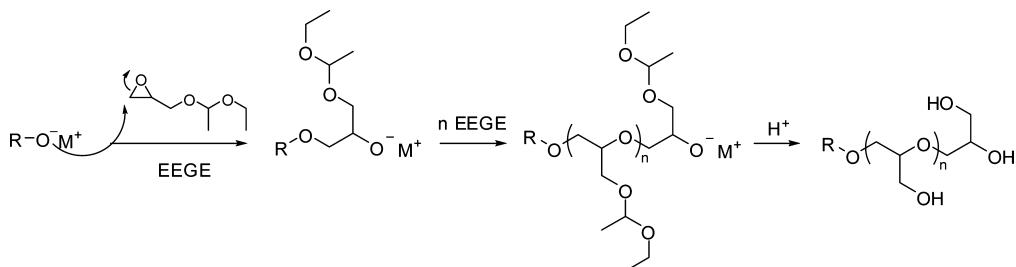


Figure 4. Typical monomers for the synthesis of linear polyglycerol (*linPG*) structures.

Scheme 1. Anionic Ring-Opening Polymerization of EEGE Followed by Acidic Deprotection of the Acetal Protecting Group



degradation of a single sample being reported to start at temperatures exceeding 250 °C.²⁵

Although PEG is water-soluble in a broad temperature range, thermoresponsive behavior is observed at elevated temperatures, depending on molecular weight and concentration.²⁸ In the case of *linPGs*, a lower critical solution temperature (LCST) can be induced by hydrophobic modification of the hydroxyl groups. Examples for this kind of derivatization are given in section 3.3.1.

2. SYNTHETIC STRATEGIES FOR *linPG*

Ethylene oxide (EO) as the monomer of choice for the synthesis of PEG is industrially prepared on a large scale by epoxidation of ethene. Therefore, one major advantage of PEG is its commercial availability in a broad range of molecular weights that permits to tailor properties such as solubility and melting point for a specific application. For *linPGs*, at present only the low molecular weight oligomers diglycerol and triglycerol can be purchased, however, usually containing cyclic or branched components. *LinPGs* can be prepared from protected glycidol derivatives (glycidyl ethers) via oxyanionic ring-opening polymerization. The commonly applied glycidyl ethers are liquids, which renders the experimental procedure more facile compared to the use of the gaseous and highly toxic EO. The most commonly used monomers for the synthesis of *linPG* are illustrated in Figure 4.

While the monomers trimethylsilyl glycidyl ether (TMSGE), ethoxyethyl glycidyl ether (EEGE), *tert*-butyl glycidyl ether (*t*BGE), and allyl glycidyl ether (AGE) lead to linear polyglycerols after deprotection, isopropylidene glyceryl glycidyl ether (IGG)³⁰ (Figure 4, right) provides linear polyglycerols with additional pendant glycerols in each repeating unit, poly(glyceryl glycerol), offering additional options for functionalization.

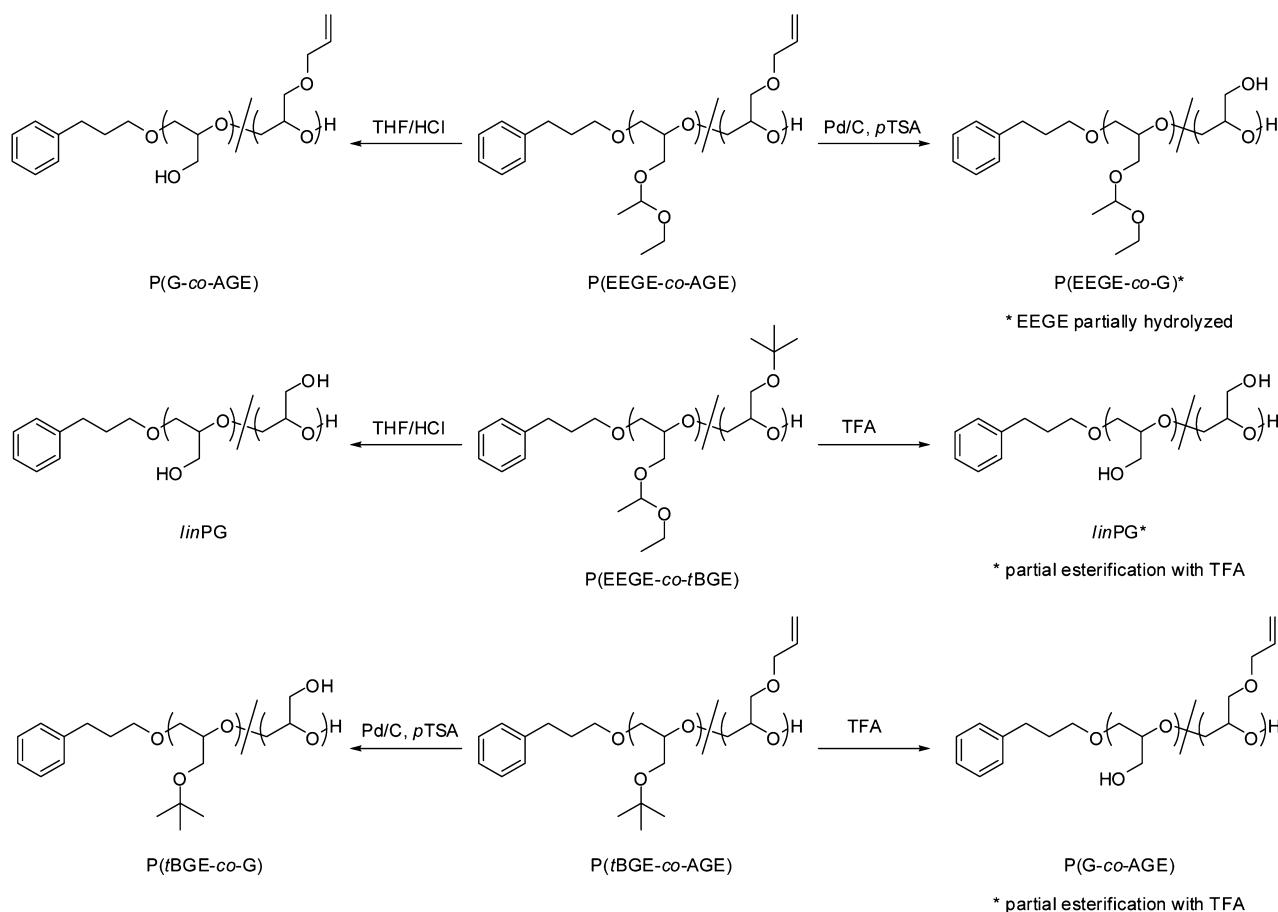
Although *t*BGE and AGE are commercially available, EEGE is most frequently used for the preparation of linear PG due to the facile removal of the acetal protecting group under mild acidic conditions. EEGE can be prepared as described by Fitton et al.²⁹ by the reaction of glycidol and ethyl vinyl ether. IGG,³⁰

recently introduced by our group, gives access to interesting linear polyglycerol structures with pendant glycerol units providing vicinal 1,2-diols after removal of the acetonide protecting group. Typical polymerization procedures and general mechanisms for epoxide polymerization have recently been summarized in an excellent review by Carlotti et al.³¹ Therefore, only synthetic strategies applicable to the synthesis of *linPG* will be discussed in this Review.

First attempts to obtain *linPG* were reported already in 1968, using mainly TMSGE or *t*BGE as monomers.^{22,23,32–34} In particular, the polymerization of TMSGE has been studied to a large extent. While under base catalysis only low molecular weight oligomers were obtained due to the instability of the TMS protecting group, coordination polymerization led to higher molecular weight polymers. However, control of the molecular weight was not possible using coordination-type initiators. In groundbreaking work, Taton et al. reported the first successful anionic ring-opening polymerization of EEGE with molecular weights up to $\approx 30\,000 \text{ g}\cdot\text{mol}^{-1}$ ($M_w/M_n = 1.38–1.89$ for CsOH as initiator).³⁵ Using potassium or cesium alkoxides as initiators for the polymerization of EEGE, Dworak et al. synthesized a series of well-defined *linPGs* with narrow polydispersities ($M_w/M_n < 1.20$).^{36,37} Starting from the as-synthesized *linPG*, they were also able to prepare advanced high molecular weight ($M_n > 1,800,000 \text{ g}\cdot\text{mol}^{-1}$) graft on graft structures by repeating sequential grafting cycles consisting of deprotection, polymerization of EEGE and removal of protecting groups.³⁸ Expanding this work, Möller and co-workers described the synthesis of star-shaped *linPGs* by using di(trimethylol propane) as a multifunctional initiator for the polymerization of EEGE.³⁹ These increasingly complex architectures will be further discussed in section 4.

To date, several low molecular weight initiators including potassium *tert*-butoxide (*t*-BuOK),^{36,37,40,41} potassium 3-phenyl propanolate (PPOK),^{39,41,42} alkoxy ethanolates,^{43,44} potassium methoxide (MeOK)^{43,45} or BuLi/phosphazene base ($\text{Li}^+/\text{t-BuP}_4$)⁴¹ have been successfully applied to polymerize EEGE in a controlled manner (Scheme 1).

Scheme 2. Removal of Orthogonal Protecting Groups in Glycidyl Ether Copolymers,⁴² Leading to Partially Functionalized Linear Polyglycerols

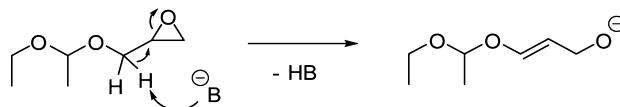


In an interesting work by Möller, Keul et al. homo- and random copolymers of EEGE, *t*BGE and AGE have been prepared by anionic ring-opening polymerization, and the authors studied selective removal of the protecting groups.⁴² In this work, the authors developed an elegant synthetic strategy for the introduction of orthogonal protecting groups at the polyglycerol backbone. A schematic overview of the deprotection of the respective copolymers is given in Scheme 2. While exclusive deprotection of the acetal protecting group in P(EEGE-*co*-AGE) was successful, complete cleavage of protecting groups was observed for P(EEGE-*co*-*t*BGE) upon treatment with HCl. Deprotection of the *tert*-butyl protecting groups with trifluoroacetic acid (TFA) was selective for P(*t*BGE-*co*-AGE), but resulted also in *linPG* for P(EEGE-*co*-*t*BGE) copolymers. During deprotection, a few hydroxyl groups were esterified by TFA. Allyl protecting groups were selectively cleaved by treatment with Pd/C and *para*-toluenesulfonic acid (*p*TSA); however, partial hydrolysis of the acetal moieties in P(EEGE-*co*-AGE) was observed.

Complete deprotection of both P(AGE), P(EEGE), and P(*t*BGE) homopolymers renders all of the protected glycidyl ethers suitable as precursor polymers for *linPG*. Unexpectedly, in case of the homopolymers removal of the *tert*-butoxy group was not possible under the conditions used for the deprotection of P(EEGE). In a follow-up work, the same group described the selective deprotection of block copolymers of EEGE and *t*BGE, claiming a strong influence of the polymer microstructure on the stability of the protecting groups.^{11,46}

Despite the narrow molecular weight distribution obtained for the low to moderate molecular weight *linPGs*, a limitation in molecular weight to $\approx 30\,000\text{ g}\cdot\text{mol}^{-1}$ for protected P(EEGE) was observed, which translates to a degree of polymerization (DP_n) of ≈ 200 .^{35,41,47} This limitation is explained by a chain transfer reaction between either the propagating chain or the initiator oxanion and EEGE. During this chain transfer reaction (Scheme 3), a proton is abstracted from the methylene

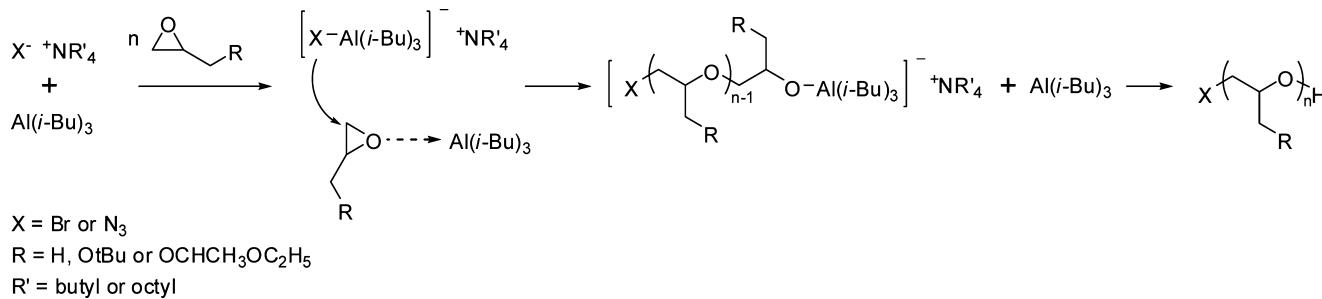
Scheme 3. Proton Abstraction from an EEGE Monomer by a Strong Base^a Leading to Chain Transfer Reactions⁴¹



^aB = propagating polymer chain or initiator.

group adjacent to the oxirane ring, leading to the formation of an allyl alkoxide. This side reaction is also known in an analogous manner for other monosubstituted epoxides, e.g., propylene oxide or phenyl glycidyl ether.³¹

The influence of the reaction temperature, initiator, and counterion on the EEGE polymerization has also been investigated by Keul, Möller, and co-workers.⁴¹ The side reaction was described to become more pronounced for higher monomer to initiator ratios and for higher temperatures. A significant decrease of the transfer reaction was observed by

Scheme 4. Polymerization of Oxiranes by X-Al(*i*-Bu)₃/NR₄⁺ Catalysts

lowering the temperature from 120 to 60 °C in polymerizations initiated with PPOK. However, for Li⁺/*t*-BuP₄ as an initiating system, side reactions could not be prevented even in polymerizations performed at 20 °C. The high basicity of *sec*-BuLi and the phosphazene base itself are most likely responsible for this side reaction.⁴¹ Consequently, it is generally assumed that in order to achieve high molecular weight polyethers, the active chain end has to exhibit high nucleophilicity to exert efficient ring-opening of the epoxide, but also low basicity to avoid proton abstraction and chain transfer.

As a first concept on the way to high molecular weight *lin*PGs, the application of partially hydrolyzed diethylzinc (ZnEt₂/H₂O) as a catalyst was introduced. Scientists in the 1960s and 1980s already made use of this system to obtain the first high molecular weight *lin*PGs by polymerization of TMSGE, as confirmed by high intrinsic viscosity.^{22,33} This was later adopted by Dworak and co-workers for the polymerization of EEEGE. After deprotection, high molecular weight *lin*PGs were obtained with *M*_n up to 1 000 000 g·mol⁻¹, however, accompanied by a loss of control over molecular weight and broader molecular weight distributions (*M*_w/*M*_n = 1.46–1.80),^{48–50} owing to the little controlled catalytic process.

Utilization of a calcium amide-alkoxide catalyst in heptane resulted in P(EEGE)s with high molecular weights up to 180,000 g·mol⁻¹, however, polydispersities were even higher (*M*_w/*M*_n = 3.4–4.5) and only a maximum conversion of 52% was achieved.⁵¹

Important progress was achieved by Deffieux, Carlotti, and co-workers. Their strategy involves the activation of the monomer toward nucleophiles as well as a reduction of the basicity of the growing chain end by coordination of triisobutyl aluminum (*i*-Bu₃Al) (Scheme 4).^{52–54} Both alkali metal alkoxides and ammonium salts (R₄N⁺X⁻) have been used as initiators. Ammonium salts lead to improved control of molecular weights and polydispersity. Within the range of ammonium salts, longer alkylene chains were found to increase monomer reactivity and polymerization rate.⁵⁵ Since especially a combination of *i*-Bu₃Al and ammonium salts was shown to significantly suppress the transfer reaction of protons adjacent to the oxirane ring, this concept was also transferred to the polymerization of EEEGE and *t*BGE to yield well-defined high molecular weight *lin*PGs with impressive molecular weights up to 85 000 g·mol⁻¹.^{56–58} For more details, see section 3.1.1.

In contrast to the aforementioned chain growth mechanisms, low molecular weight linear oligoglycerols have been prepared as perfectly monodisperse oligomers by various multistep syntheses.^{59,60}

3. HETEROFUNCTIONAL LINEAR POLYGLYCEROL

This section deals with versatile modification reactions leading to heterofunctional *lin*PG. Polyglycerol bearing a variety of different functionalities can be obtained by a multitude of synthetic strategies comprising initiation by a functional molecule, end-capping with an appropriate reagent or postpolymerization modifications, transforming either the hydroxyl groups at the polymer backbone or the α - and/or ω -positions. In the ensuing paragraph, approaches leading to α - and/or ω -functional *lin*PGs are discussed. As a special type of end-functional polymers, polyglycerol-based macromonomers are considered as precursors for highly functional graft copolymer structures and polymer brushes in the second paragraph. The third paragraph describes polymer modifications by reacting pendant hydroxyl groups at the backbone of *lin*PG. Random copolymerization of functional glycidyl ethers with EO will not be part of this Review, as such strategies have been highlighted recently by our group.^{61,62}

3.1. End-Functional *lin*PGs. End-functional polymers can either be prepared by using a suitable functional initiator or by efficient termination reactions.

3.1.1. Functional Initiators for the Synthesis of *lin*PG. The introduction of functionalities via specifically designed initiators presents an elegant synthetic pathway toward completely end-functionalized polymers. However, for the anionic ring-opening polymerization as the most common method for the preparation of *lin*PG, the applied initiator has to tolerate the harsh, basic conditions at elevated temperature without being subject to side reactions. A large number of heterottelechelic polyethers containing, e.g., –OH, –NH₂, –COOH, –CHO or –SH moieties has been developed in the last decades. For PEG oligomers, various synthetic strategies have been highlighted by Thompson et al.,⁶³ and a general overview was given recently by Carlotti and co-workers.³¹ We will focus on functional groups introduced in *lin*PG structures. The introduction of single amino groups in polymer chains has attracted enormous interest in the past, since amino groups are versatile functionalities for the attachment of biomolecules or conjugation chemistry in general. For a highly functional polymer like polyglycerol, the introduction of selectively reacting moieties is crucial to avoid side reactions during the conjugation step. In recent years, some approaches have been developed to attach one single amino group at the chain end of both linear and hyperbranched polyglycerol.^{18,19,64} Most of them rely on the utilization of protected amine-containing initiators for the anionic ring-opening polymerization of glycidyl ethers. Protecting groups are usually cleaved by catalytic hydrogenation, thereby offering an orthogonal modification to the acid-labile acetal in EEEGE. In an elegant work published by Klok et al., amine-initiated polyglycerols of

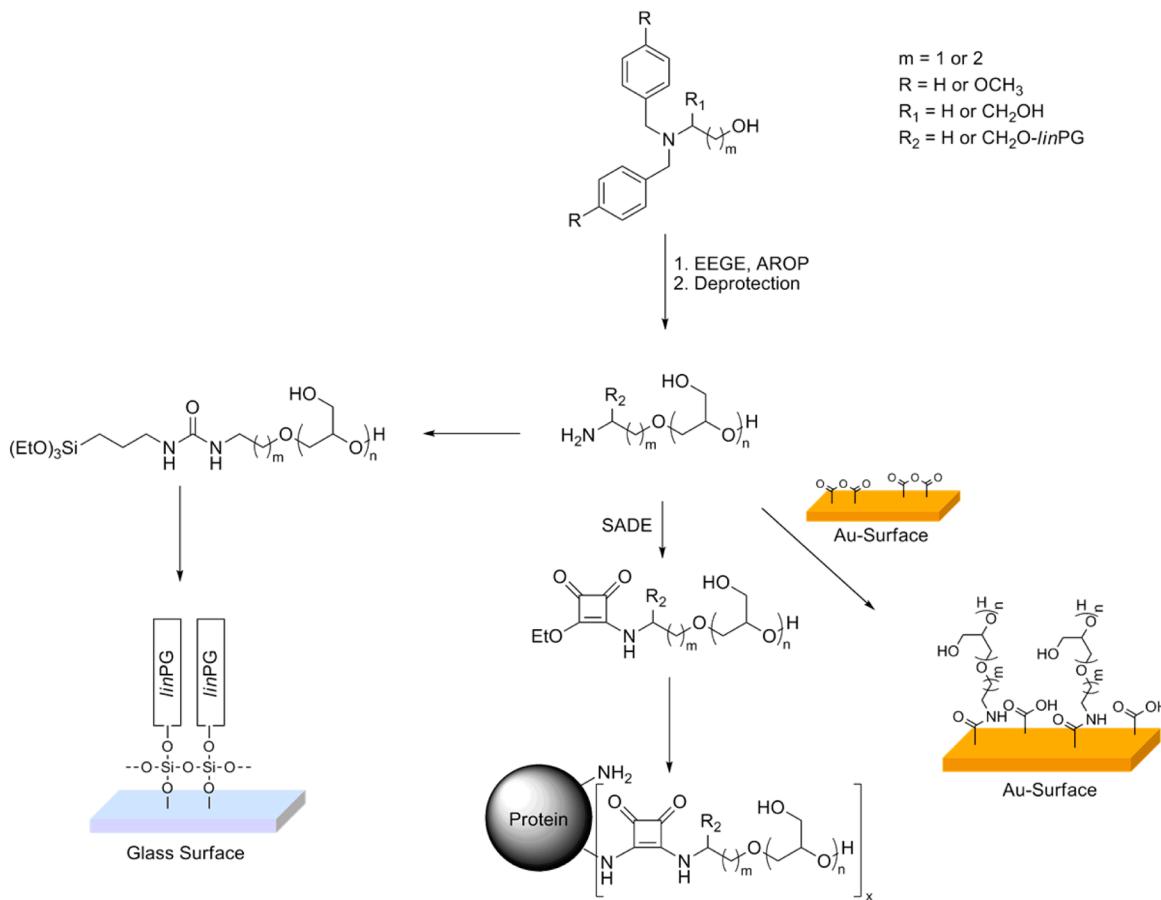


Figure 5. Summary of anionic ring-opening approaches targeting amino-functional linear polyglycerols for surface modification and bioconjugation developed by Haag et al. and Klok et al., respectively^{18,19,64} (SADE = squaric acid diethyl ester). Adapted in part from ref 19. Copyright 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. With permission from John Wiley and Sons.

varying architectures were prepared via anionic ring-opening polymerization of EEGE. By using a methoxybenzyl-protected aminoethanol or serinol initiator, linear polyglycerols containing an end- or midchain amino functionality were obtained. After removal of both the methoxybenzyl and acetal protecting groups, the monoamino- and multihydroxy-functional polyglycerols were conjugated to various proteins (bovine serum albumin and lysozyme) via selective squaric acid coupling (see Figure 5).⁶⁴ This renders a “PGylation” with *lin*PG feasible, in analogy to the widely employed PEGylation strategy that is currently used for a wide range of proteins to prolong circulatory time by reducing renal clearance. PGylation is a promising strategy with respect to therapeutic proteins and can permit to combine the well-known “stealth” effects of polyether chains with additional functional groups for targeting.

Similar to PEG, polyglycerol layers have been found to prevent undesired protein adsorption on surfaces. Haag and co-workers applied amino-functional *lin*PGs for the modification of several surfaces (gold and glass), thereby providing highly biorepellent coatings. The polymers were prepared utilizing an *N,N*-dibenzyl-protected aminopropanol initiator to synthesize well-defined α -amino *lin*PGs or P(GME)s via anionic ring-opening polymerization of EEGE or glycidyl methyl ether (GME). After subsequent palladium-catalyzed hydrogenation of the benzyl protecting groups, the monoamino-functional polyethers ($M_n = 600–1500 \text{ g}\cdot\text{mol}^{-1}$) were used as hydrophilic coatings for anhydride-functionalized gold surfaces.¹⁸

In a follow-up work, these amino-functional precursor polymers were reacted with 3-(triethoxysilyl)propyl isocyanate forming a stable urea bond. The triethoxysilyl moiety served as a strong anchoring unit for the covalent attachment to glass surfaces.¹⁹ Pronounced biorepellent behavior similar or even superior to PEG was described for both gold and glass surfaces coated with these linear polyethers. An overview of amino-functional *lin*PGs synthesized via anionic ring-opening polymerization (AROP) and their use for surface modification and bioconjugation is given in Figure 5. In contrast to the above-mentioned straightforward approaches using an amine-functional initiator, amine-containing and truly monodisperse oligoglycerols (up to trimers) were also prepared via a multistep synthesis and their antifouling properties on gold surfaces were compared to different polyglycerol or P(GME) architectures.¹⁷

Besides amines, other functional groups have proven to be beneficial for the immobilization of polymers on various surfaces. Thiols show high affinity towards gold surfaces and have therefore been used as popular linkers in surface chemistry.⁶⁵ However, they have only very sparsely been reported for the end-functionalization of *lin*PGs. Weinhart et al. described the synthesis of thiol-functional *lin*PG by applying 11-benzylthio-undecanol as an initiator for the anionic ring-opening polymerization of EEGE or GME.¹⁸ Deprotection of the thiol was carried out under careful exclusion of oxygen by using sodium in liquid ammonia/THF. The final thiol-

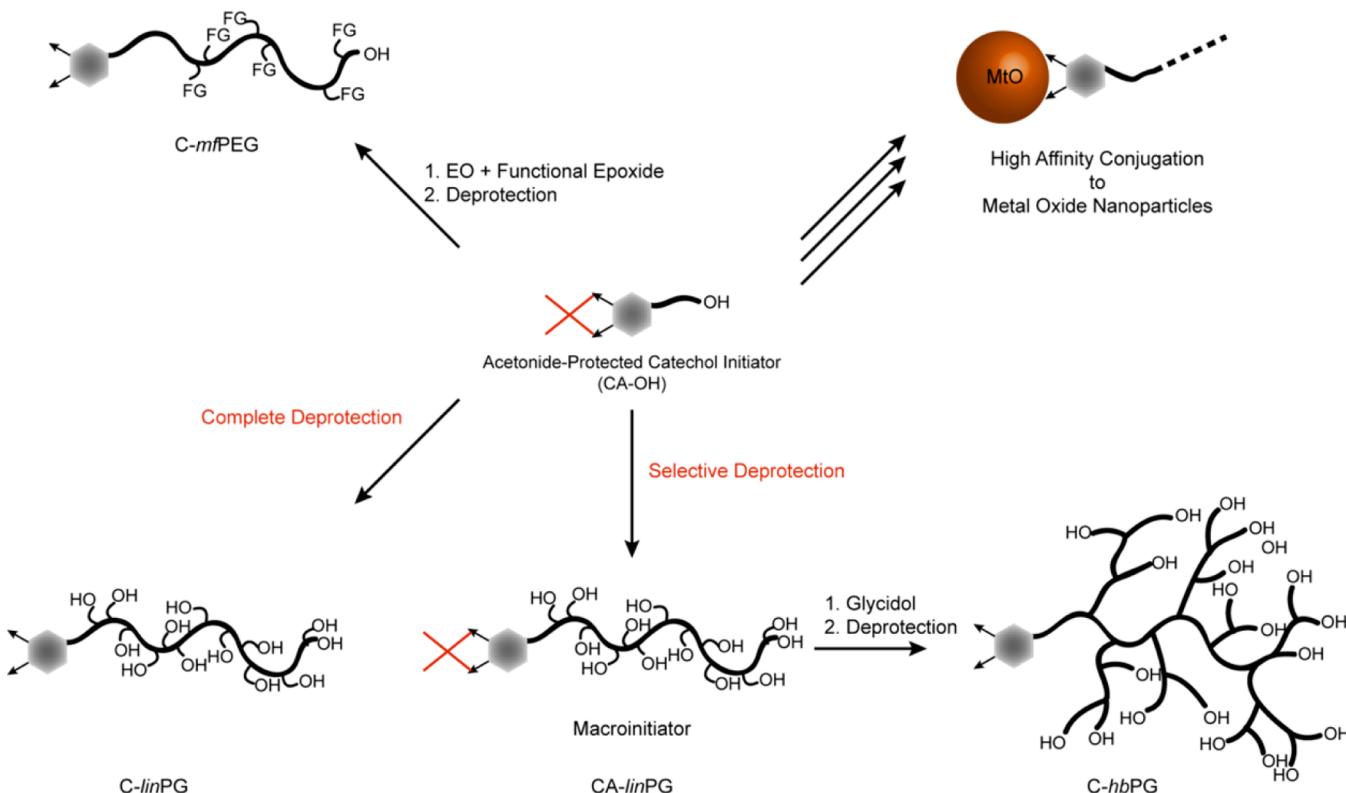


Figure 6. Overview of catechol initiated polyether structures including a selective deprotection step for EEGE under maintenance of the catechol acetonide protecting group. The catechol-bearing polyethers present suitable candidates for the hydrophilic coating of metal oxide nanoparticles.⁶⁸

functional PGs were deposited on gold surfaces to obtain biorepellent coatings (Figure 3).

Almost universal adhesion can be induced by the incorporation of catechol units into polymer structures.^{66,67} Catechols are a widespread constituent in naturally occurring molecules like neurotransmitters, polyphenols or amino acids. Especially, the nonessential amino acid L-DOPA has been found to be a major component in marine mussels and to be responsible for their intriguing adhesion properties.⁶⁶ Intense effort has been taken to make use of these properties in a variety of polymer architectures in biomimetic approaches.⁶⁷

Very recently, our group developed a catechol-based initiator (Figure 7) allowing for the synthesis of a large variety of catechol-functional polyether structures by anionic ring-opening polymerization.⁶⁹ This initiator has also been used for the synthesis of well-defined linear and hyperbranched polyglycerols with a single catechol moiety (Figure 6).⁶⁸ Selective binding of the catechol moiety to manganese oxide (MnO) nanoparticles despite the presence of a large number of hydroxyl groups derived from the polyglycerol backbone has been demonstrated for both linear and hyperbranched catechol-initiated polyglycerols. Efficient dispersion of MnO nanoparticles in aqueous solution was observed for different types of hydrophilic polyethers, rendering them suitable as contrast agents for magnetic resonance imaging.^{68,69} Toxicity studies revealed high biocompatibility for all polyether-coated MnO nanoparticles up to a concentration of $50 \mu\text{g}\cdot\text{mL}^{-1}$.⁷⁰ The concept relies on the “grafting-to” strategy of prefabricated PG blocks and can be applied to a broad range of nanoparticles and surfaces to impart water solubility and also antibiofouling properties.

Only few examples of functional initiators have been described that can be applied in oxyanionic ring-opening polymerizations without further protection steps. Among them, cholesterol as an essential structural component of the lipid bilayer in cell membranes is a valuable building block for the synthesis of amphiphilic architectures. Due to its inherent hydroxyl group, the readily available cholesterol can be used without further modification (Figure 7).⁷¹ Anionic ring-opening

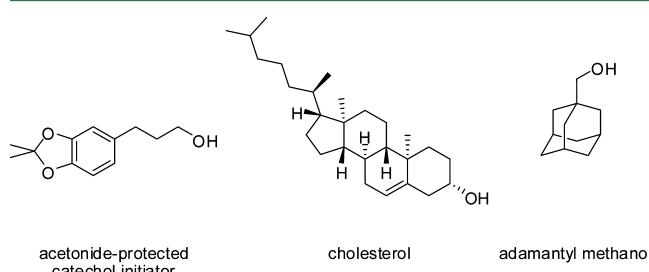


Figure 7. Nonconventional initiators used for the synthesis of linPG.

approaches making use of cholesterol as an initiator have been studied intensively by our group. As a rather simple structure, cholesterol-initiated linear polyglycerol has been prepared by polymerizing EEGE and subsequent acidic cleavage of the acetal-protecting groups.⁷² For a series of molecular weights, liquid crystalline order was observed in a broad temperature range up to 260°C . Remarkably, the incorporation of a single cholesterol led to ordering of the usually amorphous linPG chains with up to 26 glycerol units.⁷³ More complex linear–hyperbranched architectures using cholesterol as an initiator have also been realized via so-called “hypergrafting” strategies

and will be discussed in section 3.3.3 together with potential applications.

Besides functional initiators that are capable of undergoing derivatization reactions, supramolecular, complex polymer structures assembled by host–guest interactions are of great interest. For this purpose, adamantyl methanol-initiated polyglycerols have been recently developed by our group (Figure 7).⁷⁴ Induced by the hydrophobic adamantyl residue, these slightly amphiphilic linear, hyperbranched, or linear–hyperbranched polyether polyols can form an inclusion complex with the hydrophobic cavity of cyclodextrin. Complex supramolecular graft copolymer structures comprising a cyclodextrin-functional poly(methacrylate) backbone and supramolecularly linked polyglycerol side chains have been prepared and analyzed by isothermal titration calorimetry, demonstrating the effect of a PEG-spacer on the assembly.⁷⁴

The synthetic strategy developed by Deffieux and co-workers including the monomer-activated anionic polymerization of EEEGE or tBGE (see section 2) also leads to highly end-functional linPGs. The employed tetraoctylammonium bromide and *i*-Bu₃Al initiator–catalyst system provides well-defined polyethers bearing a single bromine atom in their α -position.^{57,58} In another work, the authors showed that ammonium salts containing pseudo halogens can also efficiently be used as initiators in combination with *i*-Bu₃Al. α -Azido-functional polyethers including poly(alkylene oxide)s, poly(epichlorohydrin), and poly(EEGE) were prepared by using tetrabutylammonium azide/*i*-Bu₃Al as the catalyst in a one-step approach. A high degree of α -functionalization was indicated by matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF) measurements,^{56,58} and the azide functionalities were successfully reacted with alkyne-containing compounds in a copper-catalyzed azide–alkyne cycloaddition (CuAAC).

3.1.2. End-Functional linPGs via End-Capping. Due to the living character of anionic polymerizations, oxyanionic ring-opening polymerization is a well-established method for the synthesis of well-defined end-functional polyethers via the end-capping technique.¹⁶⁶

Möller et al. described the synthesis of vinylsulfonate-functional linear and star-shaped polyglycerols by reacting ω -hydroxy-functional protected polyglycerols with 2-chloroethylsulfonyl chloride. The attached vinyl sulfonate was found to react efficiently with various amines or alcohols, but not with thiols.^{75,76} In an approach by our group, linPGs or poly(glyceryl glycerol) bearing one single alkyne moiety in the ω -position have been synthesized by end-capping living polymer chains with propargyl bromide.⁴⁴ Similar to the aforementioned azide-functional polyethers prepared by Carlotti and co-workers,^{56,58} the structures present promising precursors for complex architectures via click-reaction. Another approach by Kuckling et al. includes esterification of the ω -hydroxyl group by 2-halogenopropionyl halides, offering linPG macroinitiators for the formation of block copolymers by atom transfer radical polymerization (ATRP).⁴⁷ End-capping reactions of polyglycerols have also been applied to introduce polymerizable styrene or methacrylate residues. The synthesis of these macromonomers will be discussed in the next paragraph.

3.2. Macromonomers Based on Linear Polyglycerol. Polyglycerol-based macromonomers have been prepared via strategies described in the following. Common preparation techniques for macromonomers include the “end-capping method” and the “initiator method”. In the end-capping approach, an activated chain end is reacted with a polymer-

izable end-group, while in the “initiator method”, the polymerization is initiated by the polymerizable unit of the macromonomer. In one of the pioneering works, Dworak and co-workers described end-capping of living P(EEGE) chains with *p*-chloromethylstyrene to obtain ω -vinylbenzyl-functional macromonomers.^{36,37} The resulting acetal-protected macromonomers were copolymerized with styrene in a free radical polymerization and deprotected to afford polystyrene-*graft*-linPG copolymers. However, a maximum conversion of only 65% of the macromonomer was observed. Higher conversions (up to 85%) were achieved when the deprotected macromonomers (ω -vinylbenzyl-polyglycerol) were used as “surfmers” (surfactant and monomer) in an emulsifier free emulsion polymerization with styrene to obtain hydrophobic styrene microspheres with a hydrophilic polyglycerol corona (Figure 8).

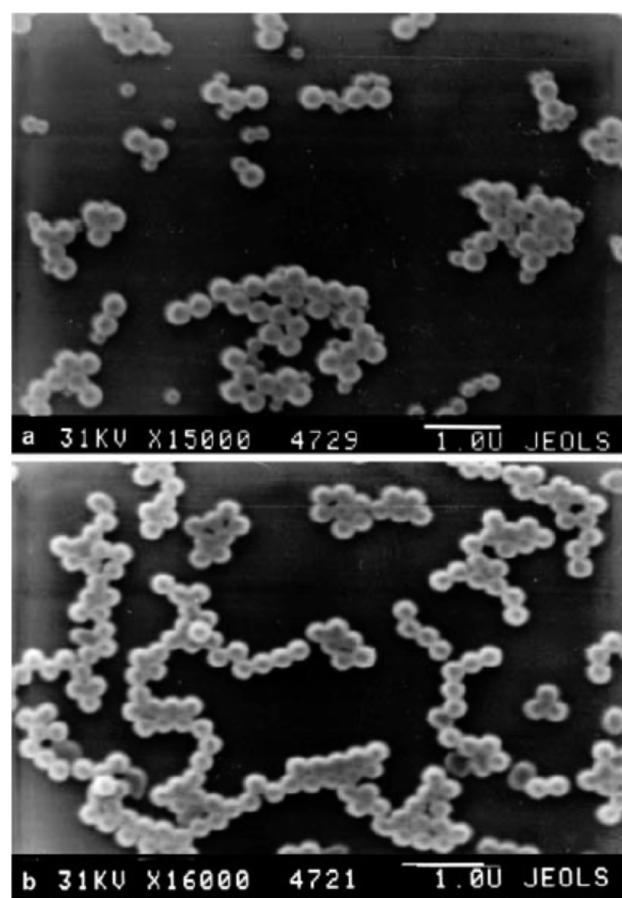


Figure 8. Scanning electron microscope microphotograph of poly(styrene/ω-vinylbenzyl-polyglycerol) microspheres.⁷⁷ Reproduced from ref 77. Copyright 2001 Springer-Verlag. With kind permission from Springer Science and Business Media.

These microspheres were later intensively investigated by Basinska and Slomkowski et al. Results on the composition and properties of the polyglycerol surface^{77–83} as well as studies on protein adsorption^{77,84} and potential biomedical applications^{85–88} of the microspheres have been discussed at full length in a recent publication.⁸⁹ As a cleavable alternative to the ether-bound styrene functionality, the end-capping technique can also be applied to prepare polyglycerol-based macromonomers bearing one terminal methacrylate function covalently linked via an ester bond. This was accomplished

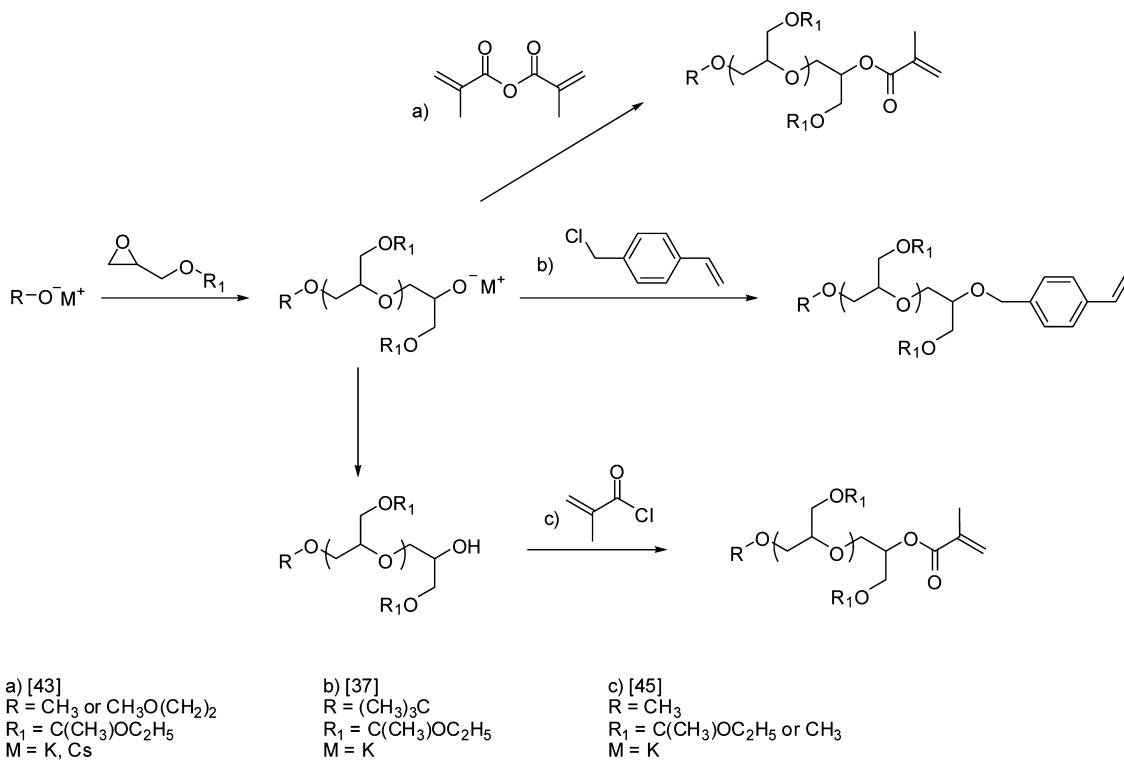


Figure 9. Summary of the synthetic protocols developed for the preparation of macromonomers based on linear polyglycerol via the end-capping technique.^{37,43,45}

both by our group and Haag et al.^{43,45} In our work, a straightforward one-pot approach is described.⁴³ EGE was polymerized from alkoxide initiators (Figure 9) to obtain well-defined precursor oligomers. The living chain ends were directly end-capped by the sequential addition of excess triethylamine and methacrylic anhydride to the reaction mixture. Homopolymerization of the narrowly distributed macromonomers ($M_w/M_n < 1.30$) by ATRP and subsequent deprotection resulted in water-soluble and well-defined graft copolymers ($M_w/M_n < 1.31$) containing a methacrylate backbone and densely grafted oligoglycerol side chains. Due to steric crowding, the conversion in homopolymerization was limited to 65% but could be increased by the addition of different amounts of the sterically less demanding hydroxy ethyl methacrylate (HEMA) as a comonomer.

In various multistep protocols, Haag and co-workers synthesized a variety of oligoglycerol (meth-)acrylates, ranging from linear oligoglycerol methacrylate or oligo(GME) methacrylates to dendronized oligoglycerol acrylates.⁴⁵ Linear oligoglycerol methacrylates or oligo(GME) methacrylates were also prepared via anionic ring-opening polymerization of EGE or GME. However, the precursor polymers were purified before, in a second reaction step, the terminal hydroxyl group was reacted with methacryloyl chloride. After deprotection, both linear and dendronized macromonomers were polymerized by ATRP from initiators attached to gold surfaces. Antifouling properties of the oligoglycerol brushes were determined and compared to brushes prepared of low molecular weight glycerol methacrylate. An overview of the end-capping approaches reported to date is given in Figure 9.

The incorporation of a radically polymerizable group into the multihydroxy-functional polyglycerol structure also gives access to highly functional surface coatings. In a recent work by Carbonnier, Basinska, and Chehimi et al., the aforementioned

ω -vinylbenzyl-polyglycerol macromonomers were grafted from modified gold or stainless steel surfaces, leading to a strong increase in the wettability of the surfaces. Protein adsorption was investigated and found to be reduced for surfaces grafted with ω -vinylbenzyl-polyglycerol macromonomers compared to surfaces bearing only the initiator or for poly(hydroxyethyl methacrylate)-grafted surfaces.⁹⁰

A different synthetic strategy was published by Keul and Möller et al., who described the anionic ring-opening polymerization of EGE and glycidol, respectively, initiated by vinylic initiators.⁹¹ A variety of initiators including vinyl benzyl alcohol (VBA), N-(2-hydroxyethyl)-methacrylamide (HEAM), N-(2-hydroxyethyl)-acrylamide (HEAAm), HEMA, and allyl glycol were deprotonated by the addition of potassium *tert*-butoxide, and the oxirane monomers were polymerized in the presence of hydroquinone as a radical stabilizer. As expected, for HEMA and HEAAm as initiators no controlled polymerization of epoxides was observed due to backbiting and the high reactivity of the acrylate double bond. Unexpectedly, no initiation by the hydroquinone stabilizer was observed by the authors. The resulting macromonomers prepared with VBA and HEAM were utilized in copolymerizations with low molecular weight comonomers. However, only rather low molecular weights for the resulting graft copolymers ranging from 1700 g·mol⁻¹ to a maximum of 15 800 g·mol⁻¹ were detected by SEC measurements.

Similar to the works by Basinska, Slomkowski et al., these VBA-initiated oligoglycerols (either branched (*b*) or linear (*lin*)) were also used as “surfmers” in the emulsion polymerization of styrene to form polystyrene particles with a hydrophilic polyglycerol periphery.⁹² Amphiphilicity of the macromonomers was found to be a key parameter concerning polymerization rates. This is in analogy to other reports describing an improved and accelerated polymerization for

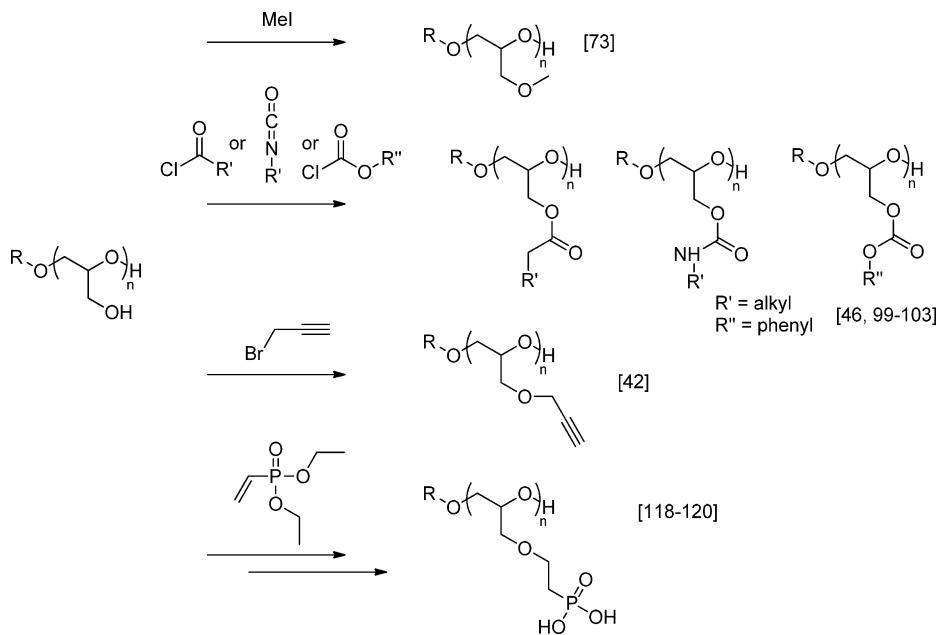


Figure 10. Typical examples of backbone-modified linear polyglycerols.

PEG-based amphiphilic macromonomers due to micellar preorganization in water.^{93–95} A similar micellar polymerization process was described for amphiphilic polyglycerol-based macromonomers by Kuckling and Dworak et al.^{96,97} The respective macromonomers were prepared via the end-capping technique using block copolymers of hydrophilic glycidol (acetal-protected precursor) and hydrophobic glycidyl phenyl ether.

A different, more general concept for the preparation of amphiphilic polyether polyol-based macromonomers via anionic ring-opening polymerization and click-chemistry was recently introduced by our group.^{44,98} In a copper-catalyzed azide–alkyne cycloaddition, well-defined, monoalkyne-functional *linPG* and P(GG) hydrophilic precursors were reacted with azido alkyl methacrylates of variable spacer lengths. By varying both the block length of ω -alkyne-functional polyether polyols and the hydrophobic alkyne spacer, a set of macromonomers with tunable amphiphilicity was obtained. Polymerization of the amphiphilic macromonomers resulted in high molecular weight graft copolymers. For polyglycerol-based macromonomers conversion decreased for longer polyglycerol chains, whereas increasing the length of the alkyne spacer from propylene to more flexible hexylene or undecanoyleylene resulted in a significant increase to near quantitative conversion.^{44,98}

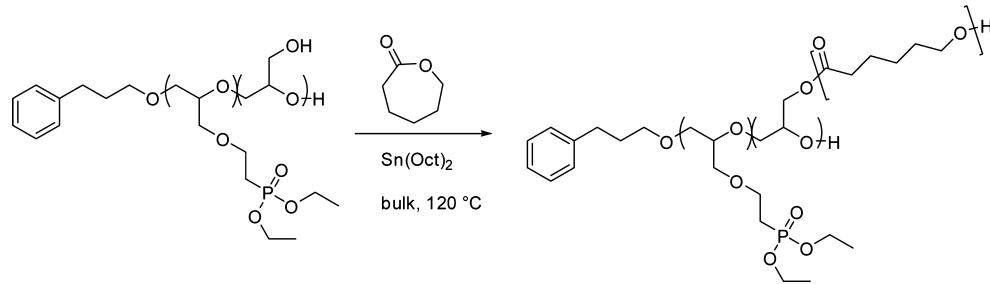
3.3. Backbone Functionalization of Linear Polyglycerol. This section presents the synthetic routes for the functionalization of the multiple hydroxyl groups at the *linPG* backbone. The pendant hydroxyl groups can either be addressed in postpolymerization reactions using low molecular weight reactants or serve as a macroinitiator in “grafting-from” approaches aiming at different architectures, such as brush-like or grafted hyperbranched structures.

3.3.1. Hydrophobic and Hydrophilic Functionalized Linear Polyglycerol. The hydroxyl moieties of linear polyglycerol can be converted into various functional groups like ethers,^{42,73} esters,^{99,100} urethanes,^{46,101,102} or carbonates¹⁰³ (see Figure 10), which are described in more detail below. Chau and co-workers presented a library of homofunctional and heterofunc-

tional derivatives of linear polyether polyols including allyl, alkynyl, acyl and azide groups as orthogonal precursors for the attachment of, e.g., drugs and biomolecules.¹⁰⁴

The simplest method to functionalize *linPG* and thereby tune the polarity is the methylation of the pendant hydroxyl groups of the polyether backbone. By using methyl iodide, for example, the interaction of the hydroxyl groups can be “switched off”, which is useful for studying the importance of hydrophilic interactions on the thermal and rheological properties of *linPG*.⁷³ A clearly more convenient strategy is the direct polymerization of GME (glycidyl methyl ether), where the hydroxyl group of glycidol is already methylated. GME is commercially available and can be used for anionic ring-opening polymerizations resulting in quantitatively methylated and thermoresponsive *linPG* derivatives.^{105–107} Furthermore, end-functionalized P(GME) (M_n between 600 and 1500 g·mol^{−1}) and its copolymer with ethyl glycidyl ether (EGE) can be used in surface modification reactions and as a potent protein repellent material.^{18,108,109} Poly(ether imide) membranes functionalized with side chain-methylated oligoglycerols (O(GME)) showed good stability under oxidative conditions, which is also relevant in biomedical applications.^{110–112}

Modification of the hydroxyl groups of *linPG* can also be achieved through (partial) esterification with aliphatic acyl chlorides, e.g., palmitoyl chloride. Such systems were investigated in comparison to their hyperbranched analogues as “nanocapsules” or “nanoreactors”, but showed no or low encapsulation efficiency.^{99,113} In the respective publication, the fundamental difference between linear and hyperbranched polyglycerols derivatized with fatty acid esters has been established with respect to guest encapsulation, establishing the core–shell topology of the hyperbranched polymer. Furthermore, acetic acid^{36,48} and acetic anhydride¹⁰⁰ were used as reactants for the hydrophobic modification of *linPG* resulting in poly(glycerol-*co*-glycerol acetate)s with a varying degree of functionalization and LCST behavior (LCST = 4 to 100 °C). In another approach by Dworak and co-workers, LCST behavior was induced in *linPG* by synthesizing ABA or BAB poly(ethylene glycol) (A)/poly(ethyl glycidyl carbamate)

Scheme 5. Heterografted Linear Polyglycerol with Poly(ϵ -caprolactone) as Degradable Side-Arms

(B) amphiphilic block copolymers, in which the hydroxyl groups were modified with ethyl isocyanate.¹⁰¹ For ABA copolymers, the cloud point was determined to be around 80 °C, and for BAB 46 °C was detected, whereas, remarkably, the AB diblock did not exhibit thermoresponsive behavior. Esterification with glutaric aldehyde,¹¹⁴ poly(ethylene glycol)-bis-(carboxymethyl ether chloride)¹¹⁵ or 3,3-dithiodipropionic acid¹¹⁶ led to *linPG*-based hydrogels with different swelling properties. Figure 10 gives an overview of the main chemical transformations of the polyglycerol backbone.

CuAAC is widely used as an orthogonal method in postpolymerization modifications. Erberich, Keul and Möller were able to convert the partially protected linear polyglycerol backbone into an alkyne-functionalized polymer by using propargyl bromide. In a proof-of-principle concept they showed the cycloaddition of an azido-functional sugar moiety to the glycidyl propargyl ether repeating units, aiming at heteromultifunctional polyethers.⁴²

The introduction of functional groups, which are commonly hydrophilic, is interesting in biomedical applications, where the attachment of biomolecules is necessary or the attachment onto surfaces is desired. Penczek et al. successfully introduced both phosphonic and carboxylic acid groups along the polyglycerol backbone.¹¹⁷ Phosphoethylated polyglycerols have been obtained by Michael addition of the hydroxyl groups of *linPG* to diethyl vinylphosphonate. After hydrolysis, a tunable amount of phosphonic acid side groups is available for applications in biorelated fields.^{118–120}

3.3.2. "Grafting-From" Strategies Based on *linPG*. Transformations of *linPG* comprise small molecule chemistry addressing the hydroxyl groups as well as "grafting-from" approaches, in which *linPG* is used as a macroinitiator. As an example, *linPG* has been used as a suitable macroinitiator for the ring-opening grafting polymerization of cyclic esters. Various works have been published describing the synthesis of, e.g., branched poly(lactide)s^{121,122} or poly(glycerol-*graft*- ϵ -caprolactone)^{39,123,124} with a combination of anionic and coordinative ring-opening polymerization. Chemoenzymatic approaches, i.e., the combination of chemical and enzyme-catalyzed reactions, have led to densely or loosely grafted poly(ether-*graft*-polyester)s, respectively.^{125–127} Heterografted polyether brushes via chemical and enzymatic reactions, mainly developed by Möller and co-workers, were highlighted in 2009.¹¹

Interesting degradable polyether-*graft*-polyesters with pendant diethylphosphonatoethyl groups (DEPE) were prepared by enzymatic grafting of ϵ -caprolactone from *linPG*. Via different reaction parameters, such as the ratio of lipase to monomer concentration, grafting densities could be varied from 31% to 81%.¹¹⁹ The hydrolytically degradable materials contain only biocompatible (polyglycerol) and biodegradable (polyester/

phosphonate groups) segments. In a recent follow-up work, the group of Möller showed that poly((glycerol ethylphosphonatoethyl)-*co*-(glycerol-*graft*- ϵ -caprolactone)) copolymers can degrade within 7 d (in vitro study in phosphate-buffered solution at 55 °C), whereas poly((glycerol diethylphosphonatoethyl)-*co*-(glycerol-*graft*- ϵ -caprolactone)) was stable for prolonged periods of up to 63 d. The reaction route is shown in Scheme 5. This demonstrates the significant influence of ethylphosphonate groups or diethylphosphonate groups on the degradation behavior of such biomaterials.¹²⁰

Sequential grafting can also be used to synthesize remarkably high molecular weight (82 000–1 800 000 g·mol^{−1}) polyglycerol-*graft*-polyglycerol polymers. Due to the fast proton exchange between the alkoxide and hydroxyl groups, this multiple anionic "grafting-from" process yielded densely packed (grafting density ~70%–90%) arborescent-branched macromolecules.³⁸ In this context, "pom-pom like" structures based on polyethers have also been investigated.¹²⁸

ABA type block-*graft* copolymers via a combination of CuAAC and atom transfer nitroxide radical coupling (ATNRC) reaction were also reported. Copolymerization of 4-glycidyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl (GTEMPO) and EEGE provided a backbone with pendant TEMPO and hydroxyl groups. The hydroxyl groups were esterified with 2-bromoisoctyl bromide, and ATRP was performed to generate graft copolymers.¹²⁹

3.3.3. Linear Polyglycerol as a Macroinitiator for "Hypergrafting" of Glycidol. This section focuses on the use of linear polyglycerol segments as an excellent polyfunctional macroinitiator for the "hypergrafting" of glycidol, i.e., the grafting of AB₂ or latent AB₂-type monomers onto a linear chain to form hyperbranched polyethers that can be analogous to dendronized polymers. The number of initiating hydroxyl groups is a critical issue for the control over molecular weight and the polydispersity (usually <2) of the branched block. In simulation studies it could be shown that for the slow monomer addition of an AB_n monomer, such as glycidol, the monomer/core functionality ratio is important. Furthermore, it was found that the polydispersity is in reciprocal relation to the number of functional groups (*f*, eq 1).¹³⁰

$$\frac{M_w}{M_n} = 1 + \frac{1}{f} \quad (1)$$

Equation 1 translates to decreasing polydispersity (*M_w/M_n*) with increasing core functionality *f*. Thus, rather monodisperse, multihydroxy-functional initiators are required for the controlled formation of hyperbranched polyglycerol. In addition, the probability for homopolymerization of glycidol is decreased in this case. This renders linear polyglycerol derivatives ideal candidates for the initiation of hyperbranched polyethers

Scheme 6. “Hypergrafting” Process of Glycidol onto a Functional *lin*PG as the Macroinitiator^{130b}

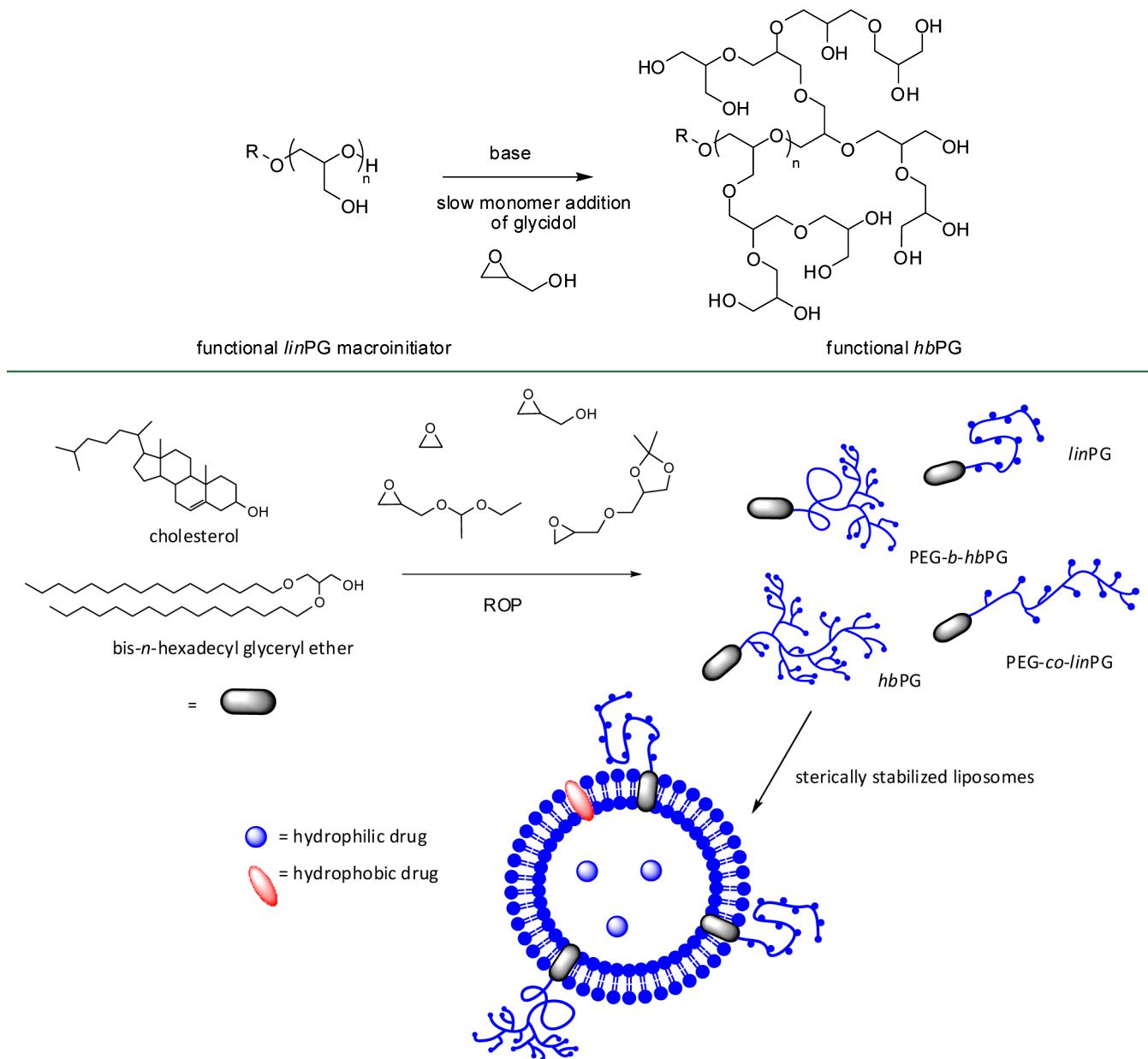


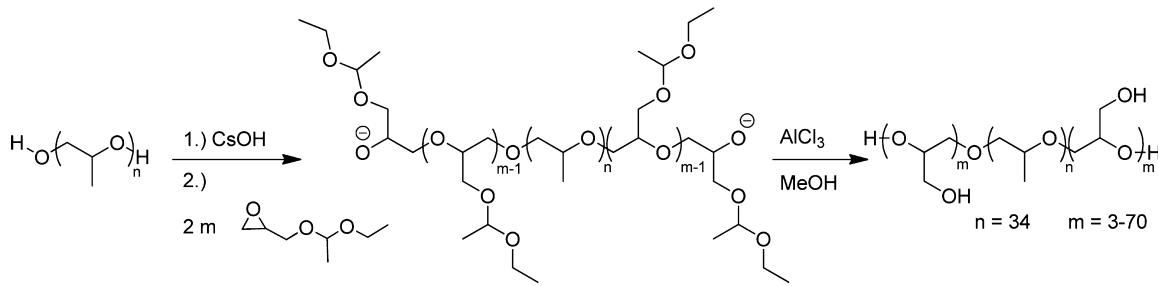
Figure 11. Epoxide construction kit for the synthesis of linear and branched polyether-lipids in novel sterically stabilized “stealth”-type liposomes.^{72,136,137} Reproduced from refs 72 and 137. Copyright 2011 and 2013 American Chemical Society.

(Scheme 6) to generate a wide range of linear–hyperbranched polyglycerol hybrid structures.

Our group introduced double-hydrophilic linear–hyperbranched block copolymers with PEG and polyglycerol segments.²⁴ To this end, a PEG-*lin*P(EEGE) block copolymer was deprotected under acidic conditions, providing PEG-*b-lin*PG copolymers with 13–40 hydroxyl groups. Partial deprotonation of the *lin*PG block and slow monomer addition of glycidol (“hypergrafting” process) afforded linear–hyperbranched PEG-*b-hb*PG copolymers. ABA-type block copolymers (*hb*PG-*b*-PEG-*b-hb*PG) were synthesized in a similar manner with low polydispersities (see section 4.2).¹³¹ The obtained branched polyether structures have unique properties, i.e., high terminal functionality and excellent biocompatibility.^{8,9,13} Both architecture and multifunctionality can be tuned by adjusting the degree of polymerization of polyglycerol,

leading to polyether polyols with a predefined number of hydroxyl groups. The aforementioned advantages of the hyperbranched systems based on *lin*PG as a building block have been used for a variety of biomedical purposes. Non-covalent protein conjugation of linear-hyperbranched PEG-polyglycerols, i.e., α , ω_n -telechelics with one terminal amino group and multiple hydroxyl groups, have been investigated in the avidin-biotin system for supramolecular bioconjugation and in solubilizing carbon nanotubes.^{132,133} The double-hydrophilic linear-hyperbranched structure (PEG-*b*-*hb*PG) was also applied in a drug-delivery system based on micellar structures. In this case, doxorubicin was attached to the multiple hydroxyl groups via an acid-labile hydrazone bond, thereby rendering the polymer pH-sensitive. Increased drug loading efficiency, high biocompatibility, and water solubility of the polyether

Scheme 7. Synthesis of “Pluronic-like” Linear Triblock Copolymers *linPG-b-PPO-b-linPG*.¹⁵⁰



structures are proposed to be beneficial in anti-cancer treatment.¹³⁴

“Stealth” liposomes, polymer-coated vesicles commonly based on PEGylated lipids, are being exploited in clinical use with excellent results.¹³⁵ One of the drawbacks of methoxy poly(ethylene glycol) (mPEG) that is preferentially incorporated as a biorepellent shell, is its lack of functional groups. As mentioned in section 3.1.1, our group has used cholesterol directly as an initiator for the oxyanionic polymerization of various epoxides including EO, EEEG, IGG, and glycidol (see Figure 11).^{72,136}

In contrast to cholesterol, phospholipids as initiators are not stable under the acidic and basic reaction conditions in the deprotection and “hypergrafting” step of glycidol. Cholesterol, as a natural membrane component, forms the hydrophobic segment in these polyether-based lipid mimetics. Cholesterol represents an excellent anchor in the phospholipid bilayer of the liposome.^{138–141} The cholesterol-based multivalent structures, with tunable architectures and number of hydroxyl groups, offer further possibilities for derivatization, e.g., via click-chemistry,^{72,141} which is important for active targeting. The concept of incorporating branched cholesterol-polyether polyols, was recently highlighted and remains promising to impart improved “stealth” properties in combination with functional groups to liposomes.^{137a}

4. BLOCK COPOLYMERS BASED ON LINEAR POLYGLYCEROL

Linear polyglycerol is an interesting component in block copolymers as a hydrophilic segment. Due to its multiple hydroxyl groups at the polyether backbone, it is highly water-soluble and therefore serves as an excellent, functional building block in amphiphilic block copolymers and nonionic polymer surfactants. In the following section, the incorporation of *linPG* into AB, ABA or even ABC block co- or terpolymers and other architectures will be highlighted.

4.1. Diblock Copolymers Containing Linear Polyglycerol. Möller and co-workers synthesized polystyrene-*b*-polyglycerol (PS-*b*-*linPG*) block copolymers via carbanionic polymerization of styrene initiated with *sec*-butyl lithium and subsequent oxyanionic ring-opening polymerization of EEEG. To achieve sufficient reactivity of the propagating oxyanion, a phosphazene base ($P_4-t\text{-Bu}$) was added for the formation of the second block, resulting in block copolymers with polydispersities between 1.04 and 1.48 ($M_n = 18\,000\text{--}102\,000\text{ g mol}^{-1}$).^{142,143} $P_4-t\text{-Bu}$ functions as a complexing agent for the cation (lithium) and thereby allows to “switch” directly from carbanionic to oxyanionic living chains, without intermediate work-up of the first block. A phosphazene base system was also used in the low-temperature metal-free anionic

ring-opening polymerization of EEEG and AGE, using 3-phenyl-1-propanol as the initiator. Using this method, well-defined EEEG/AGE diblock copolymers were obtained, which are versatile, functionalizable linear aliphatic polyethers.¹⁴⁴

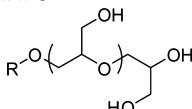
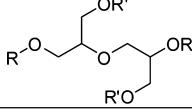
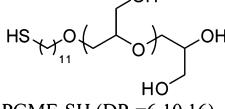
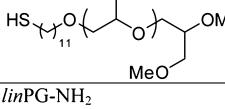
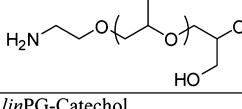
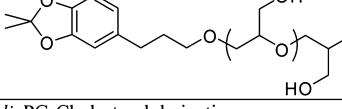
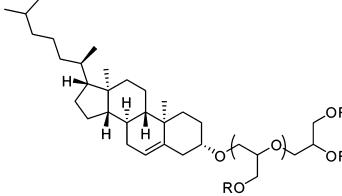
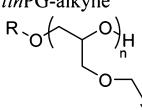
Another mild modification method was presented by Möller and co-workers for the synthesis of random and block copolymers with glycidol and glycidyl amines.¹⁴⁵ They used tetraoctylammonium bromide and *i*-Bu₃Al as a catalyst system for the copolymerization of EEEG and epichlorohydrin, which does not sustain the harsh conditions of a conventional base-initiated oxyanionic polymerization. In a three-step protocol, polyethers with hydroxymethyl and aminomethyl side chains were obtained after polymer modification, albeit with slightly increased polydispersities ($M_w/M_n = 1.35$ for random copolymers; $M_w/M_n = 1.58$ for block copolymers). Intermediate products, azide-functional polyethers, are useful for click-reactions for the functionalization of the copolymers.

The same group also prepared linear multifunctional polyethers via cationic ring-opening polymerization of a protected glycidyl ether (*t*BGE) with THF. Kinetic studies support the incorporation of both monomers into the polymer backbone. Deprotection resulted in linear poly(tetrahydrofuran-*co*-glycerol) with molecular weights up to 16 800 g mol⁻¹ and polydispersities <1.8.¹⁰³

Dendritic block copolymers are a complex class of polymers, and these architectures have also been achieved using polyglycerol building blocks in dendritic stars made from ethylene oxide and glycidol¹⁴⁶ or *t*BGE and glycidol.¹⁴⁷ Furthermore, P(EEEG)-*b*-hyperbranched polyglycerol-*co*-P(EEE) was synthesized.¹⁴⁸ The preparation of all of these systems included EEEG as a hydrophobic comonomer, and the amphiphilic core–shell structures were investigated with respect to their encapsulation behavior.

4.2. Triblock Copolymers Containing Linear Polyglycerol. Pluronics are nonionic surfactants based on an amphiphilic ABA structure of linear triblock copolymers poly(ethylene glycol)-*b*-poly(propylene oxide)-*b*-poly(ethylene glycol) (PEG-*b*-PPO-*b*-PEG). They are produced on a large scale and are commercially available with a variety of molecular weights. These highly established systems show interesting physical properties such as a LCST for short PEG-segments and good water-solubility with increasing molecular weight of the hydrophilic part. Applications range from cosmetic and pharmaceutical purposes to paper and textile modification.¹⁴⁹ As mentioned earlier, the PEG block can be replaced by linear polyglycerol to introduce numerous hydroxymethylene groups into the hydrophilic block. In a pioneering work, Tsvetanov and co-workers published a synthetic pathway toward polyglycerol-based Pluronics (linear glycerol/propylene oxide- LGPs), which is shown in Scheme 7.¹⁵⁰ They used poly(propylene oxide) (PPO) as the macroinitiator for the anionic ring-opening

Table 1. Exploratory Biomedical and Pharmaceutical Applications of *linPG*

Tested Polymer Structure	References	Exploratory test for biomedical and pharmaceutical applications
<i>linPG</i> 	13-15	Hemocompatibility testing, red blood cell aggregation, blood viscosity measurements, cytotoxicity experiments, biocompatibility testing <i>In vivo</i> circulation/ biodistribution/ renal clearance
Esters of oligoglycerol (PG10-ester) R' = ester group 	3,16	FDA approved, pharma additives
Endfunctional <i>linPG</i>		
<i>linPG-SH</i> ($DP_n=10-16$)  <i>PGME-SH</i> ($DP_n=6,10,16$) 	17,18,20 18, 20, 108	Surface modification/ SAM on gold Antifouling properties/ Biorepellent Resistant towards the adsorption of: fibrinogen, pepsin, albumin, and lysozyme protein and cell resistance
<i>linPG-NH₂</i> 	18,19 64 132	Surface modification gold/glass reduced non-specific protein adsorption of fibrinogen and BSA Bioconjugation → "PGylation" Noncovalent conjugation via avidin-biotin
<i>linPG-Catechol</i> 	68 70	MnO Nanoparticle conjugation Biocompatibility studies
<i>linPG-Cholesterol derivatives</i> (R=H; glycerol moieties) 	72,136,137	"Stealth" liposome formation
Oligoglycerol brushes based on methacrylate	45	Antibiofouling properties
Copolymers containing <i>linPG</i>		
PG-based microspheres	82,83,85, 86,87,88 79,84,89,90	Covalent attachment of antigens, proteins and marker (biosensors, diagnostic) → Determination of antibodies against <i>Helicobacter pylori</i> Protein adsorption studies
Backbone-functionalized <i>linPG</i>		
Mono-heterobifunctional	104	Potential bioconjugation platform
<i>linPG-alkyne</i> 	42	Azido-functional sugar conjugation
Poly((glycerol ethylphosphonatoethyl)-co-(glycerol-graft-ε-caprolactone)	119 120	Enzymatic grafting- <i>from</i> <i>In vitro</i> degradation of ester side chains

polymerization of EEGE and subsequent acidic cleavage of the acetal protecting groups. Well-defined copolymers with varying amounts of linear polyglycerol (20–84 wt %) and a PPO block of 2000 g·mol⁻¹ were prepared and characterized in solution. Their critical micelle concentration (CMC) was investigated, and a dependence on the *linPG* content and temperature was found. The decrease of the CMC with decreasing length of the hydrophilic part was not as strong as for conventional Pluronic copolymers. In various follow-up works by the same group, detailed characterization and the influence of the PPO block length (1000 g·mol⁻¹) on the CMC were studied.^{151–153} Additionally, P(EEGE)-*b*-PPO-*b*-P(EEGE) and PPO-*b*-P(EEGE)-*b*-PPO without the deprotected segments and their association behavior have been investigated.¹⁵⁴

These functional surfactants may also bear promise for the sensitization of multidrug resistant cancer cells in analogy to linear–hyperbranched surfactants based on a hyperbranched polyglycerol block.^{154b} Interesting ABA triblock copolymers based on PEG and polyglycerol with an amphiphilic¹⁰¹ or double-hydrophilic structure were prepared by Dworak et al.^{36,114} and by our group.¹³¹ Subsequent to deprotonation of commercially available dihydroxy-functional PEGs and the anionic ring-opening polymerization of EEGE, P(EEGE)-*b*-PEG-*b*-P(EEGE) was obtained, yielding *linPG*-*b*-PEG-*b*-*linPG* after removal of the acetal protecting group. Hyperbranched–linear–hyperbranched ABA-type polyethers were synthesized from a *linPG*-*b*-PEG-*b*-*linPG* polyfunctional macroinitiator with narrow molecular weight distributions ($M_w/M_n = 1.19\text{--}1.45$) and molecular weights between 6300 and 26,000 g·mol⁻¹.¹³¹ Maximum biocompatibility is achieved by using merely polyethers as building blocks for these ABA architectures, and laborious coupling reactions between the blocks can be avoided. Surprisingly, studies of the thermal properties revealed that all samples were still crystalline to some extent, although the large hyperbranched block (high number of terminal functionalities, amorphous segment) was expected to impede crystallization of the PEG block. Dworak et al. reported the synthesis of polyglycerol-*b*-polystyrene-*b*-polyglycerol ABA structures under living reaction conditions with styrene and EEGE initiated with potassium naphthalenide.³⁶

ABC triblock terpolymers consisting of polyglycerol-*b*-poly(ethylene glycol)-*b*-poly(D,L-lactide) were synthesized after deprotonation of 1-methoxy-2-ethanol, followed by the ring-opening polymerization of EEGE, EO and D,L-lactide. The formation of nonspherical micelles was observed.¹⁵⁵ PS-*b*-PEG-*b*-P(EEGE) triblock copolymers were obtained by combining carbanionic and oxyanionic polymerization techniques, capitalizing on a phosphazene base, allowing the one-pot synthesis of narrowly distributed ($M_w/M_n = 1.02\text{--}1.10$) terpolymers.¹⁵⁶

4.3. Star Polymers Containing Linear Polyglycerol Segments.

Multifunctional low molecular weight initiators like trimethylolpropane,¹⁵⁷ di(trimethylolpropane),^{39,126,157} pentaerythritol,^{147,158} dipentaerythritol,^{75,76,147,157,159} and inositol¹⁴⁷ have efficiently been used for the synthesis of multiarm stars based on linear polyglycerol. The chemical composition and properties of the resulting stars can be easily modified by choosing glycidyl ethers that can be selectively deprotected. As an example, fully polyether-based amphiphilic star copolymers were prepared by Walach and co-workers via sequential polymerization of tBGE and EEGE from a multifunctional initiator followed by selective deprotection of the P(EEGE) block.¹⁵⁸ In a follow-up work, “dendritic stars” were prepared

by repeating the aforementioned reaction cycle (tBGE, EEGE, deprotection).¹⁴⁷

Multihydroxy-functional star-shaped polyglycerols serve as unusual macroinitiators for the synthesis of star block copolymers with a core–shell structure. The ring-opening polymerization of *ɛ*-caprolactone^{39,126} and L-lactide from star-shaped PG-macroinitiators has been discussed in detail by Möller et al.¹⁶⁰ Furthermore, they reported the use of multiarm P(EEGE)s blended with poly(*ɛ*-caprolactone) for the fabrication of hydrophilic, yet water-insoluble fibers showing decreased protein adsorption.¹⁵⁹ In another work, Keul et al. investigated 3-, 4-, and 6-arm *linPG*-based stars modified with ATRP initiators with respect to their utility in the controlled radical polymerization of *tert*-butyl acrylate and methyl acrylate.¹⁵⁷

Various approaches have been described for the synthesis of heteroarm star polymers, bearing at least one *linPG* arm.^{161–165} As an example, Huang and co-workers prepared ABC-miktoarm star polymers by carbanionic polymerization of styrene, end-capping with EEGE and successive anionic ring-opening polymerization of EO and EEGE.¹⁶⁴

5. EXPLORATION OF BIOMEDICAL AND PHARMACEUTICAL APPLICATIONS

In comparison to the vast number of established applications of PEG, the development of actual applications of *linPG* is still in its infancy. The excellent biocompatibility in combination with its biorepellent properties on surfaces have motivated various research groups to perform cell tests. In addition, conjugation with proteins (“PGylation”) is likely to lead to further application-oriented concepts with respect to “functional bi conjugation” of therapeutic proteins. Table 1 summarizes all literature that is currently available on biomedical and pharmaceutical applications.

6. CONCLUSION AND OUTLOOK

Although linear polyglycerol has been known for a long time, it appears that this material has been overlooked for a long time with respect to its high potential for biomedical and pharmaceutical application. Seminal reports by Fitton et al. and Taton et al. on the polymerization of EEGE, followed by facile removal of the protecting groups, paved the way for the intense current interest. It should be emphasized that *linPG* is available by three simple synthetic steps only: (i) addition of vinyl ethyl ether to glycidol, (ii) subsequent anionic ring-opening polymerization, and (iii) facile acidic deprotection in the same vessel within several minutes.

Only in the past decade, *linPG* is increasingly considered as a promising biomedical material, mainly due to its high hydroxyl functionality, allowing an immense scope of further modifications and applications. This Review has presented both basic synthetic strategies toward linear and more complex architectures, versatile modification approaches as well as manifold block co- or terpolymer structures. Outstanding properties like high water solubility, excellent biocompatibility and antifouling behavior have been explored, but clearly this field of research is by no means mature. Linear polyglycerol can be expected to show similar properties in biological systems as hyperbranched PG,^{167,168} but so far it has not been applied for biomedical purposes as much as PEG or *hbPG*. On the other hand, molecular encapsulation is different compared to *hbPG*⁹⁹ and rheological properties can be expected to vary as well.

Nevertheless, the low intrinsic viscosity of *linPG* makes it attractive in intravenous applications.¹³

It is obvious that *linPG* is not suitable to replace PEG for large-scale applications, such as for cosmetics and in established pharmaceutical fields; however, it may be considered as a promising highly functional building block in specialty applications. On the other hand, random copolymers comprising both PEG segments and a predefined amount of linear glycerol units can be obtained by random or block copolymerization of EO and EEEGE, permitting one to obtain heteromultifunctional poly(ethylene glycol) copolymers with multiple hydroxyl groups. In this case, only a minor amount of EEEGE is required. Via this approach, the high number of hydroxyl functionalities of *linPG* can be “diluted” and thereby tailored for specific purposes, as is the case for the copolymerization of EO and EEEGE, leading to structures that combine the properties of PEG with the functionality of PG.¹⁶⁹ A wide range of copolymerizations of EEEGE with other glycidyl ethers has recently been studied to include other functional moieties in linear polyglycerols, e.g., (1-adamantyl)methyl glycidyl ether¹⁷⁰ or for biocompatible nano- and microgels.¹⁷¹ Recent publications have also shown strategies to overcome the non-degradability of *linPG* by synthesizing poly(1,2-glycerol carbonate)s.^{172,173} In summary, biomedical applications comprising drug delivery and controlled release, bioinert coatings, or tissue engineering purposes as well as bioconjugation will benefit from the enormous versatility of *linPG* as a highly functional biomaterial.

AUTHOR INFORMATION

Author Contributions

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Notes

The authors declare no competing financial interest.

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