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Acetal-Based Functional Epoxide Monomers: Polymerizations and Applications

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Protecting group chemistry is essential for various organic transformation and polymerization processes. In particular, conventional anionic ring-opening polymerization (AROP) often requires proper protecting group chemistry because it is typically incompatible with most functional groups due to the highly basic and nucleophilic conditions. In this context, many functional epoxide monomers with proper protecting groups are developed, including the acetal group as a representative example. Since the early introduction of ethoxyethyl glycidyl ether, there is significant development of acetal-based monomers in the polyethers. These monomers are now utilized not only as protecting groups for hydroxyl groups under AROP conditions but also as pH-responsive moieties for biomedical applications, further expanding their utility in the use of functionalized polyethers. Recent progress in this field is outlined from their synthesis, polymerization, and biomedical applications.

1. Introduction

Poly(ethylene glycol) (PEG) is drawing considerable attention as one of the most widely used polymers for biological and biomedical applications by virtue of its excellent aqueous solubility, biocompatibility, oxidation stability, and protein resistance.[1–6] However, the lack of reactive functional handles along its backbone often limits its application in broader areas. Alternatively, polyglycerol (PG) offers a promising solution owing to its high functionality and facile access to various topologies, while sharing many of the advantageous features of PEG.[7–11]

While PGs with different architectures are accessible via coordination,[12,13] cationic,[14–16] and anionic ring-opening polymerization (AROP),[8] conventional AROP is typically incompatible with most functional groups, such as hydroxyl, carboxylic acid, primary amine, nitrile, and halide, due to the highly basic and nucleophilic conditions. To alleviate the undesirable side reactions, the use of coordination-type initiators and glycidol with protected hydroxyl group has been suggested.[17] Although there are many ways to protect hydroxyl groups, most of the protecting groups are cleaved during the AROP. Even if the protecting groups are stable during polymerization, it is sometimes difficult to liberate the hydroxyl group afterward.

Acetal bonds are widely used as protecting groups for carbonyl and hydroxyl groups in organic synthesis owing to their high stability against bases, oxidizing and reducing agents.[18] Meanwhile, acetal bonds can be easily hydrolyzed under moderate acidic conditions. By taking advantages of acetal groups in the synthesis of PG derivatives, Fitton et al. first developed a novel method for protecting the hydroxyl group on glycidyl ether with ethyl vinyl ether to produce 1-ethoxyethyl glycidyl ether (EEGE),[19] which was subsequently polymerized to yield the poly(EEGE) using cesium hydroxide as a base.[20] Because of its stability and resistance under harsh polymerization conditions together with its facile cleavage under mild acidic conditions, EEGE has been used in the synthesis of PGs and derivatives with diverse structures.[21,22]

After the successful introduction of the EEGE monomer, various types of acetal-based monomers have been employed in the synthesis of polyethers, including 1,2-isopropylidene glyceryl glycidyl ether (IGG),[23] catechol acetonide glycidyl ether (CAGE),[24] 1-(glycidyloxy)ethyl ethylene glycol ether (GEGE),[25] tetrahydropyranyl glycidyl ether (TPGE),[26] tetrahydrofuranyl glycidyl ether (TFGE),[26,27] and cyclohexyloxy ethyl glycidyl ether (CHGE)[28] (**Figure 1**). These monomers not only utilized as protecting groups for hydroxyl groups under AROP conditions but also used as pH-responsive moieties in biomedical applications, further expanding their utility in the use of functionalized polyethers.

Although there are excellent reviews of functional epoxide monomers from their synthesis and functionalization to their diverse applications,[29,30] there have only been a few studies on summarizing acetal-based functional epoxide monomers.[31] In this review, we aim to outline recent progress in this field with a particular focus on the contribution of our studies. Moreover, the review is structured from the synthesis, polymerization, and applications of acetal-based glycidyl ether monomers.

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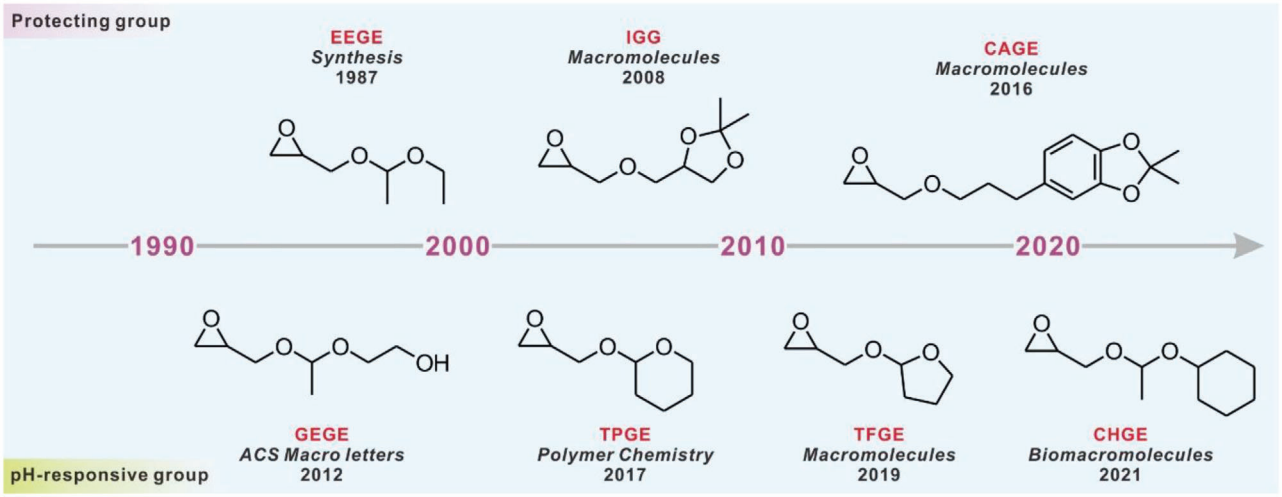

Figure 1. Schematic illustration of the historical development of the acetal-based glycidyl ether monomers.

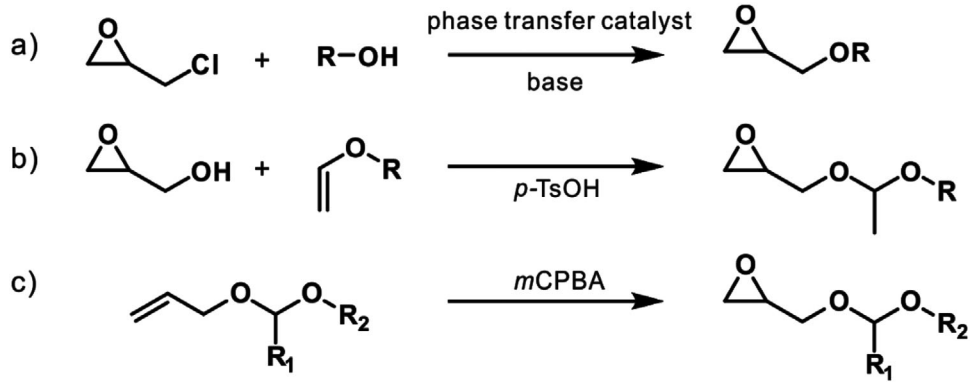

Figure 2. Synthetic protocols for functionalized glycidyl ether monomers. a) Nucleophilic substitution of epichlorohydrin in the presence of a phase transfer catalyst, b) the addition of vinyl ether derivatives with glycidol using *p*-toluenesulfonic acid (*p*-TsOH), and c) epoxidation of a double bond using *meta*-chloroperoxybenzoic acid (*m*CPBA).

2. Overview

2.1. Monomer Synthesis

Functional glycidyl ethers are typically synthesized starting with either epichlorohydrin or glycidol (**Figure 2**). First, epichlorohydrin can be converted into a functionalized epoxide through nucleophilic substitution using various types of nucleophiles, including amines and alkoxides (Figure 2a).[32,33] The reaction for activation of hydroxyl group generally occurs under basic conditions, while the functional groups that are reactive under basic conditions should be properly protected prior to the reaction. For example, IGG is prepared from the reaction between 1,2-isopropylidene glycerol (a protected form of glycerol) and epichlorohydrin in a single step.[23] Protecting two hydroxyl groups with an acetal moiety avoids undesirable side reactions. After successful monomer preparation and subsequent polymerization, the acetal protecting group is removed and two hydroxyl groups are recovered for further modification of the prepared polymer.

While epichlorohydrin is widely employed owing to its flexible transformation, glycidol is particularly used for the synthesis of functional epoxide monomers bearing acetal groups by reacting with vinyl ether (Figure 2b). In the case of EEGE (one of the most widely used glycidyl ether monomers bearing an acetal group as a latent hydroxyl group),[34–36] the vinyl ether group reacts with glycidol under moderate acidic conditions to produce the acetal linkage in a single step with high yield.[19] As various vinyl ethers can be incorporated into glycidol, our group has successfully prepared a series of acetal functionalized epoxide monomers using diverse vinyl ether groups such as cyclic and acyclic vinyl ethers. The resulting acetal groups can undergo different degradation kinetics, which is discussed later on in the following section.

Another method is the epoxidation of double bonds with *meta*-chloroperoxybenzoic acid (*m*CPBA) (Figure 2c). As a representative example, Kizhakkedathu and co-workers prepared acetal-incorporated glycidyl ethers with diverse structural arrays of acetal groups which affected noticeable difference in the hydrolysis rate.[37] Hyperbranched polyglycerols were prepared by random copolymerization of different monomers, after which

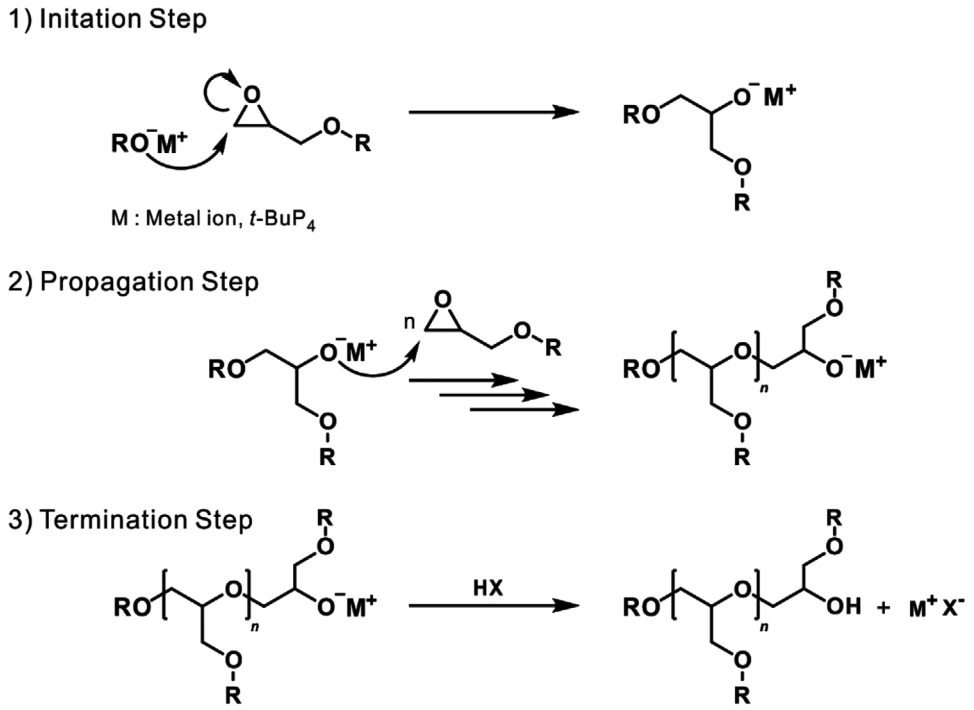

Figure 3. General polymerization processes of AROP of functional glycidyl ether monomers to afford the desired substituted poly(glycidyl ether)s.

the resulting polymer could be degraded gradually under acidic conditions. Because of the orthogonal nature of the acetal group during the process, this method can be further expanded for the preparation of the various functional epoxide monomers starting with the double bond.

2.2. Polymerization via AROP

Functionalized epoxide monomers can be efficiently polymerized via AROP due to their intrinsic high ring strain (≈114 kJ mol^{-1}).[38] Furthermore, because of its controllable and living characteristics, AROP is widely utilized for the polymerization of epoxide monomers (**Figure 3**). Generally, AROP processes are initiated from the hydroxyl group of an alcohol, which can be activated with bases using either metal hydroxides or organic bases such as *t*-BuP_4.

When an AROP system is activated by a metal hydroxide, the type of metal cations critically affects the whole polymerization process.[39] Specifically, the metal cation is required to shield the free alkoxide groups on the growing chain to ensure the living character and, at the same time, needs to be effectively detached from the alkoxide group to reactivate the metal hydroxide. As the alkoxide group is a hard base, the rate of polymerization is enhanced as the softness of the metal cation increases. Often, the initiator is pretreated with a metal hydroxide and, subsequently, dried in salt form for use as an AROP system initiator. One example is the polymerization of IGG with α-methoxypoly(ethylene glycol) (*m*PEG) as a macroinitiator.[23] After activation of *m*PEG with cesium hydroxide (CsOH), polymerization with IGG monomer was initiated with cesium alkoxide of *m*PEG, which resulted in *m*PEG-*b*-poly(IGG) with a narrow molecular weight distribution (*Đ*) of less than 1.15. Although the metal hydroxide ensures narrow dispersity of the polymer, its kinetic behavior is difficult to predict due to diverse forms of the cation complexation during polymerization.[16,40] Moreover, a high temperature during polymerization often limits the high degree of polymerization (DP). In the case of poly(IGG), the upper limit of the DP is 26, which is far from the targeted DP of 80. Side reactions like proton abstraction are another problem that can result in chain transfer during polymerization.

Organic superbase based on phosphazene can also provide an alternative means of synthesizing polyethers.[27,41,42] Due to the significant size and charge separation of the countercation, they can effectively act as bases rather than nucleophiles, thereby preventing other side reactions. However, the relatively lower basicity of the phosphazene family compared to metal hydroxides makes them useful in only limited cases such as polymerization using epoxide as a monomer.[43] Therefore, among them, the strongest phosphazene base, *t*-BuP_4, is widely utilized as a metal-free base. Moreover, unlike metal hydroxide bases, it does not require a high temperature for activation, rapid polymerization kinetics are ensured due to its high basicity (pK_a: 42.7 in acetonitrile),[44] and the additional drying step can be avoided, suggesting that it is easier to handle during the course of the polymerization.

As a representative example, Satoh and co-workers successfully demonstrated several distinct polymers based on various alcohols such as 3-phenyl-1-propanol and 4-phenyl-2-butanol along with epoxide monomers such as propylene oxide and butylene oxide via activation with a phosphazene base.[45] The resulting polymers attained a narrow dispersity of less than 1.13 when targeting DP of around 100. Moreover, our group utilized a phosphazene base as an activator for the polymerization of TFGE

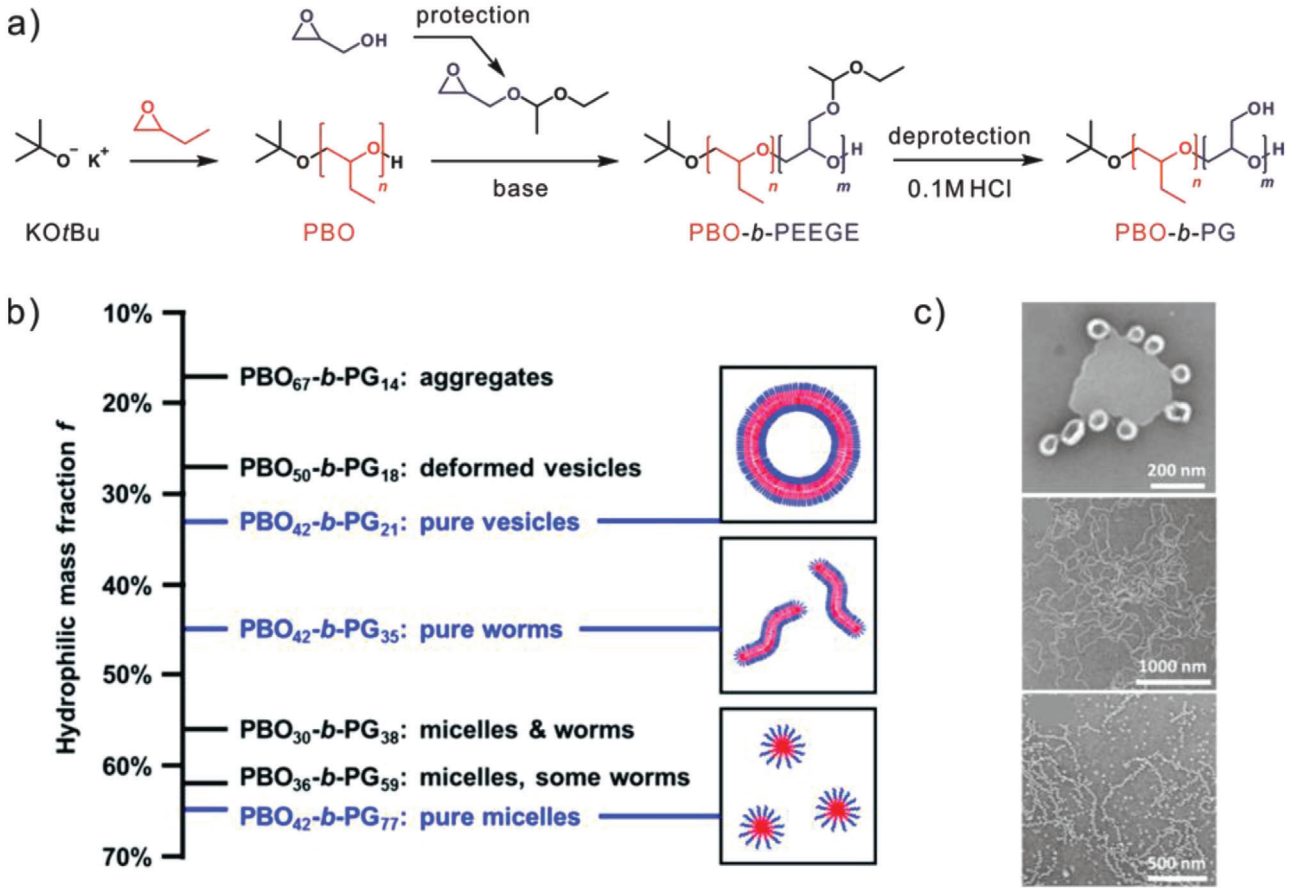

Figure 4. Polymerization of poly(butylene oxide)-*b*-polyglycidol (PBO-*b*-PG) and its amphiphilic characteristics. a) The overall synthetic scheme of PBO-*b*-PG using EEGE. b) Transition of the PBO-*b*-PG micelle structures via composition. c) Corresponding transmission electron microscopy images of the self-assembled PBO-*b*-PG micelles. Reproduced with permission.[49] Copyright 2020, The Royal Society of Chemistry.

using benzyl alcohol as an initiator.[27] The resulting poly(TFGE) possessed controlled molecular weights with a narrow dispersity. While phosphazene bases are highly effective in the control of the molecular weight of the polymers under mild reaction conditions, it has recently been found that only a small amount of residual phosphazene can severely decrease cell viability.[46] Therefore, precise purification steps should be taken before the biological application of these polymers.

3. Glycidyl Ethers with an Acetal Moiety

3.1. The Acetal Bond as a Protecting Group

The hydroxyl groups in a polymer can be further modified with various functional groups, yet during the progress of anionic polymerization, the former can cause undesired chain transfer reactions, thereby limiting the molecular weight of the polymers. To overcome this drawback, various monomers (including acetals) have been developed that can be easily removed by simple acidic treatment. In this section, we outline different types of glycidyl ether monomers bearing the acetal moiety and discuss their utility in a number of different aspects.

3.1.1. EEGE

As one of the most widely used acetal-bearing epoxide monomers, EEGE has long been used as a protecting group for hydroxyl groups in the synthesis of linear polyglycidol (*l*-PG).[22,47,48] Fitton et al. first synthesized EEGE from the reaction between glycidol and ethyl vinyl ether as a latent hydroxyl group in glycidol.[19]

Meier and co-workers reported the synthesis of poly(butylene oxide)-*b*-polyglycidol (PBO-*b*-PG) via an intermediate through the use of poly(butylene oxide)-b-poly(1-ethoxyethyl glycidyl ether) (PBO-*b*-PEEGE) (**Figure 4**a).[49] The high aqueous solubility of PG together with its flexibility and biocompatibility enabled the preparation of a diverse array of self-assembled block copolymer nanostructures. Specifically, the prepared PBO-*b*-PGs demonstrated various self-assembled morphologies (including micelles, worms, and polymersomes) according to the hydrophobic/hydrophilic compositional fraction. As shown in Figure 4b, diverse self-assembled structures of the obtained block copolymer depending on the hydrophobic/hydrophilic mass ratio (*f*) of PBO-*b*-PG were obtained: PBO_{42}-*b*-PG_{77} with the highest *f* value comprised spherical micelles with a hydrodynamic radius of 11.2 ± 0.6 nm, PBO_{42}-*b*-PG_{35} comprised pure wormlike

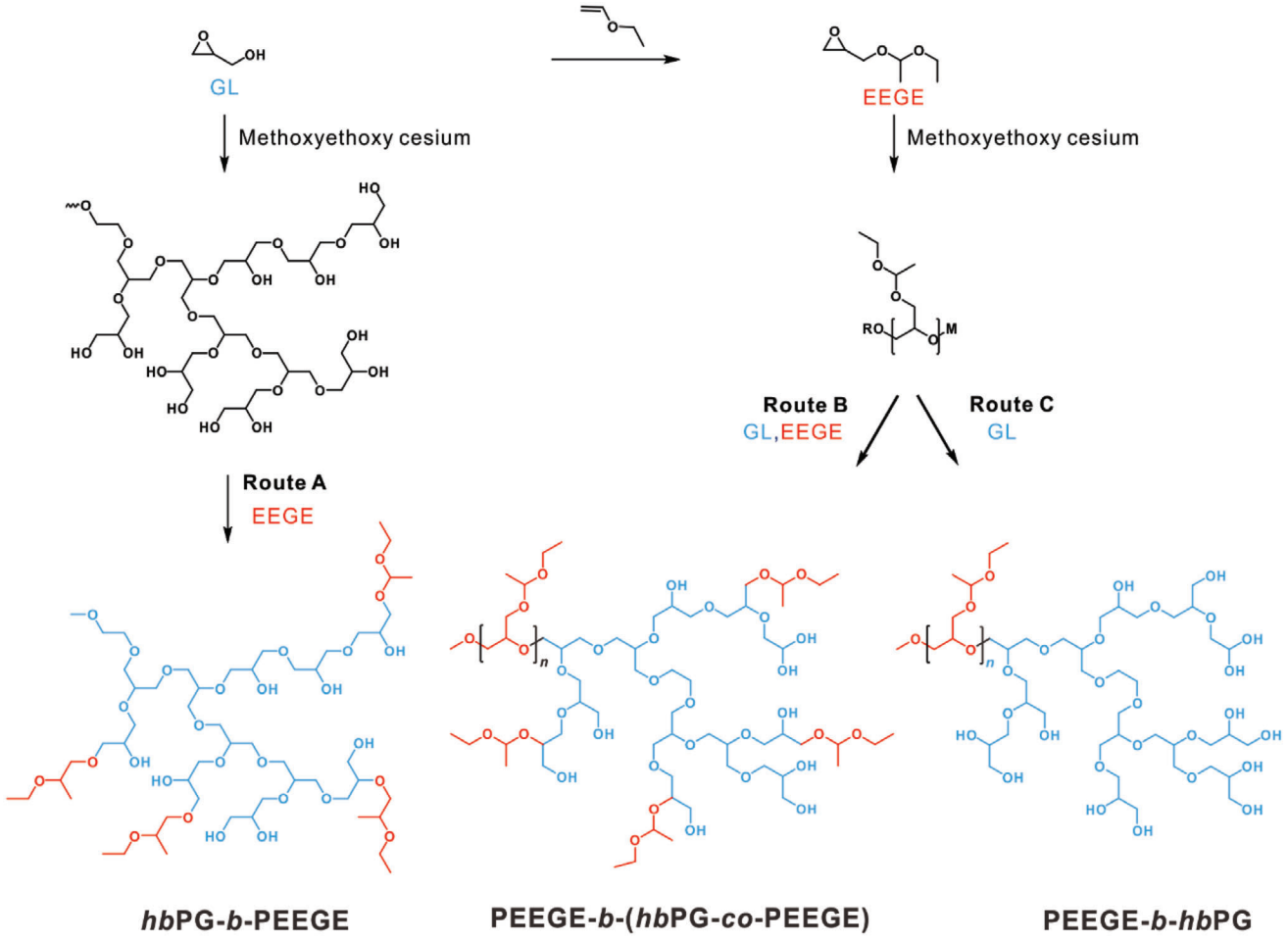

Figure 5. Synthetic pathways of PG-based polymers with different architectures prepared from glycidol (GL) and EEGE via three different synthetic routes. Reproduced with permission.[50] Copyright 2013, American Chemical Society.

structures with a hydrodynamic radius of 26.0 ± 2.0 nm, and when *f* was further decreased to 33%, PBO-$_{42}$-*b*-PG$_{21}$ comprised pure vesicles with a hydrodynamic radius of 127 ± 16 nm.

Unlike previous research, Shibasaki and co-workers utilized the hydrophobicity of PEEGE in the formation of amphiphilic copolymers (**Figure 5**).[50] As shown in Figure 5, three different synthetic routes were employed to prepare the amphiphilic copolymers with glycidol (GL) as the hydrophilic and EEGE as the hydrophobic block. Among the prepared polymers, PEEGE-*b*-(*hb*PG-*co*-PEEGE) displayed a unique self-assembly into a micelle structure, in which the critical micelle concentration value was tunable with respect to the ratio of PEEGE and the PG blocks. The potential of this micelle as a pH-responsive drug carrier was evaluated by taking advantage of the transformation of the acid-labile hydrophobic PEEGE blocks into hydrophilic PG blocks, resulting in the disassembly under acidic conditions.

Similarly, Guégan and co-workers reported the synthesis of amphiphilic block copolymer PEG-*b*-PEEGE as a drug delivery carrier for hydrophobic curcumin.[41] While the PEEGE blocks afford the necessary hydrophobicity for the formation of micelles in water, its degradation into hydrophilic PG blocks in acidic conditions can trigger disintegration of the micelles and the concomitant release of curcumin. Both of these studies show the dual role of EEGE as a glycidol-protecting unit as well as pH-responsive hydrophobic units in the amphiphilic copolymer.

3.1.2. IGG

While the EEGE monomer is widely used for the synthesis of linear polyglycol (*l*-PG), one can also utilize IGG for the synthesis of dendritic and hyperbranched poly(glyceryl glycerol) (PGG) (**Figure 6**). IGG was first prepared using epichlorohydrin and 1,2-isopropylideneglycerol (i.e., solketal) in the presence of a phase transfer catalyst.[23] The acetal group in IGG is stable under anionic polymerization conditions and can be cleaved by treatment in dilute hydrochloric acid. The resulting side-chain glycerol moiety thus enables convenient postpolymerization modification. In this research, obtained *m*PEG-*b*-PGG using allyl glycidyl ether (AGE) and osmium tetroxide (OsO_4) attained a higher yield than the method using IGG and full conversion. Nevertheless, it is noteworthy that the use of IGG is advantageous in that it can avoid the use of toxic OsO_4 and thereby reduce the toxicity of the synthesized polymers.[51]

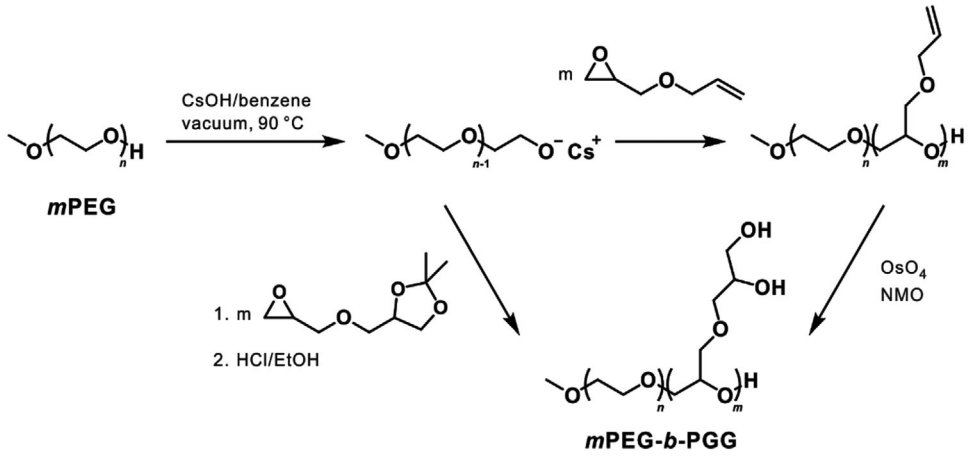

Figure 6. Synthetic schemes of *m*PEG-*b*-poly(glyceryl glycerol) (PGG). While one synthetic route employs the use of allyl glycidyl ether (AGE) followed by catalytic dihydroxylation, the other uses 1,2-isopropylidene glyceryl glycidyl ether (IGG) and subsequent acidic deprotection toward the preparation of *m*PEG-*b*-PGG. Reproduced with permission.[23] Copyright 2008, American Chemical Society.

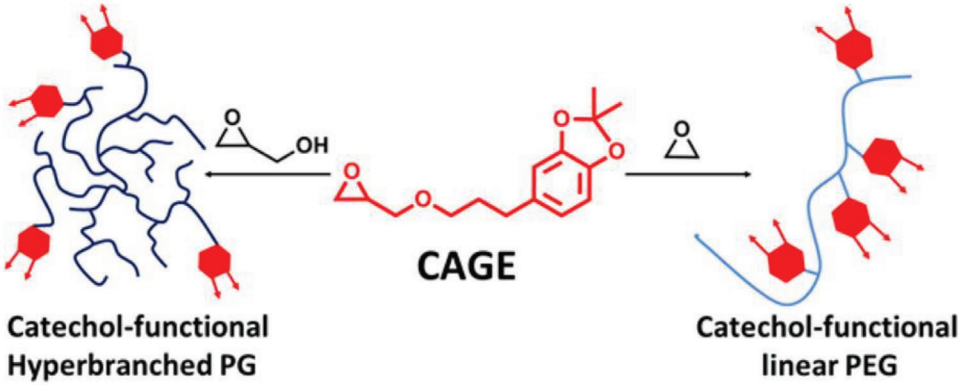

Figure 7. Polymerization of various structures of polyethers using the catechol-modified monomer CAGE. Reproduced with permission.[24] Copyright 2016, American Chemical Society.

3.1.3. CAGE

The widespread interests in mussel-inspired catechol chemistry brought about the corresponding protected form of the glycidyl ether monomer, CAGE (**Figure 7**).[24] Hydroxyl groups in the catechol moiety are protected by the acetonide group, which is an acetal group. It has been demonstrated that CAGE can participate in polymerization at both terminals of PEG to form ABA-type block copolymers and in random copolymerization with ethylene oxide or AB_2-type glycidol. Once the polymerization has proceeded successfully, the acetonide groups of CAGE can be deprotected by acidic treatment to recover the catechol groups. Catechol functionality offers versatile adhesion capability to Fe^{3+} ions as well as the surfaces of titanium(IV) oxide (TiO_2) nanoparticles, poly(tetrafluoro ethylene), and poly(vinyl chloride).[52]

This unique adhesive property of the CAGE moiety was recently translated into the study of the antifouling effect of PEG.[53] A series of poly(ethylene glycol)-*b*-poly(catechol acetonide glycidyl ether) (PEG-*b*-PCAGE) diblock copolymers and PCAGE-*b*-PEG-*b*-PCAGE triblock copolymers were synthesized through AROP using phosphazene base, *t*-Bu-P_4 (**Figure 8**a). While the PEG segment exhibited excellent antifouling behavior, the introduction of this unique property onto the given substrates has been hampered due to the lack of functional handles. By taking advantages of the versatile surface adhesive feature of the catechol moiety, the prepared AB-type diblock copolymers formed brush conformation, whereas the ABA-type triblock copolymers displayed loop conformation on the surface after deprotection of the acetonide protecting group (Figure 8b). Moreover, the deprotected catechol moiety showed a similar static contact angle with the noncoated surfaces. While both the brush and loop polymers offered effective surface coatings due to the presence of the catechol moiety, the latter polymer exhibited superior surface antifouling compared to the former due to its excluded volume and high surface coverage of the loop conformation.

3.2. The Acetal Bond as a pH-Responsive Linker

The acetal bond in functionalized epoxide monomers can be used as a pH-responsive linker, resulting in the polymers often being employed in pH-responsive drug delivery systems because they can target acidic sites in the body where tumor cells and inflammation are present. Due to the well-known biocompatibility of

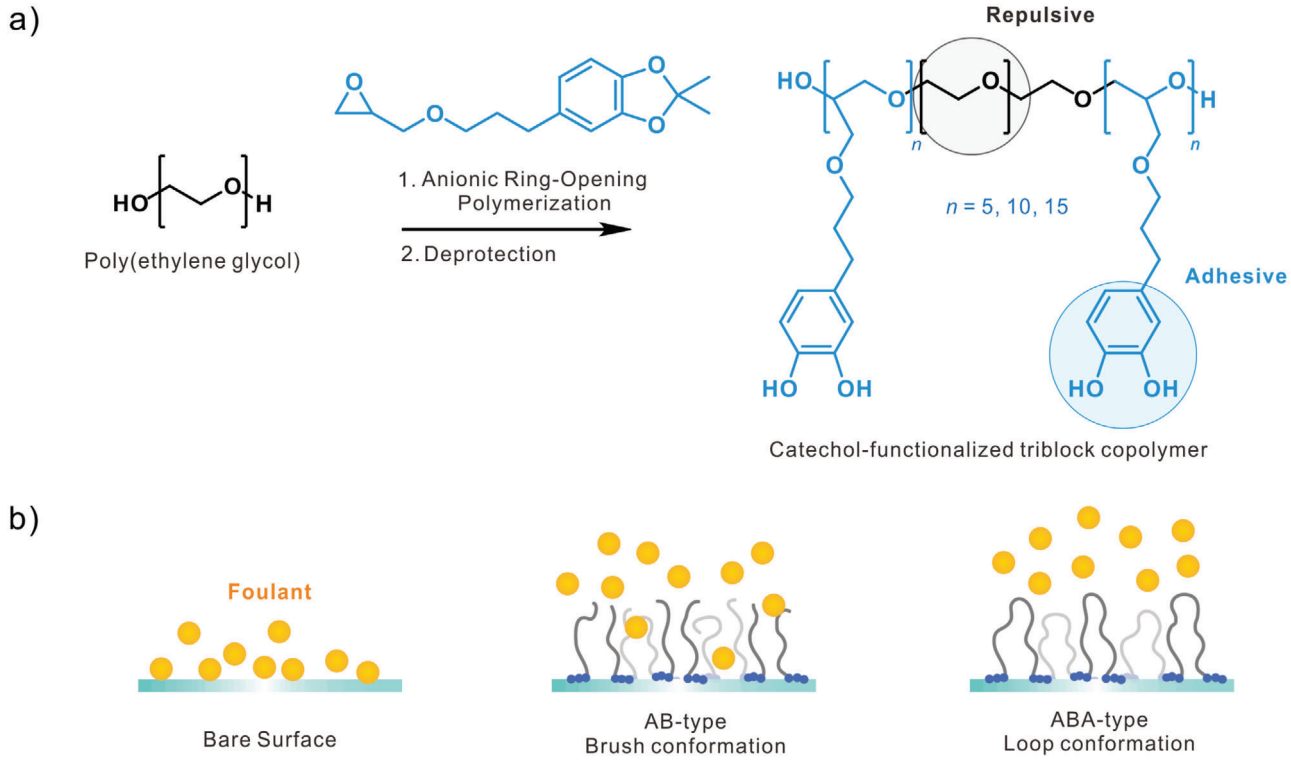

Figure 8. Polymerization and utilization of mussel-inspired CAGE monomer. a) Synthetic scheme of triblock copolymers composed of PEG and catechol-functionalized CAGE. b) A schematic process of antifouling surface using polymer brushes and polymer loops with a model protein. Reproduced with permission.[53] Copyright 2020, American Chemical Society.

the resulting PGs, this system has provided a potential opportunity in biomedical applications.[54–56] Depending on the type of acetal moiety, it is also possible to control the degradation kinetics in physiological pH windows. In this section, we cover recent progress in acetal-bearing epoxide monomers and their pH-responsive degradation for potential biomedical applications.

3.2.1. GEGE

The synthesis of GEGE was first presented by Frey and coworkers (**Figure 9**a).[25] As an AB_2-type monomer, GEGE has a similar structure to EEGE except for one additional hydroxyl group at the end of the acetal bond with which GEGE can be used as an inimer that can act as both initiator (free hydroxyl group) and monomer (epoxide group). Therefore, AROP with GEGE as an inimer enables the facile preparation of hyperbranched polymers (Figure 9b). By taking the pH-responsive nature of the labile acetal bond present within the hyperbranched polymers, the latter can undergo controlled hydrolytic degradation under acidic conditions. ^{1}H NMR-based kinetic analysis proved that the pH-dependent degradation follows first-order kinetics. In addition, size exclusion chromatography trace of the hydrolyzed hyperbranched polymer revealed that it could be selectively degraded under acidic conditions.

The unique pH-responsive degradation behavior of the GEGE inimer has been further demonstrated in a drug delivery system.[57] Lipid-like macromolecules possessing a cholesterol head group with a degradable hyperbranched polymer tail have been produced using cholesterol as the initiator and glycidol and GEGE as the monomers (Figure 9c). Lipid-like macromolecules possessing a cholesterol head group with a degradable hyperbranched polymer tail have been produced using cholesterol as the initiator and the glycidol and GEGE as the monomers (Figure 9c). Hydrophobic cholesterol head group enables the formation of stable liposome for drug carrier in which the hydrophilic tail prolongs the circulation time of liposome. Moreover, the tail group consisting of cleavable acetal linkages permits the degradation of liposome near acidic sites like tumor cell and inflammation tissues. It is of note that the GEGE monomer has opened a facile route for the preparation of hyperbranched polymers with pH-responsive groups that will be beneficial for potential drug delivery systems.

3.2.2. α-Epoxy-ω-hydroxyl KetalMmonomers

Kizhakkedathu group investigated the relationship between the structural difference of acetals and the hydrolysis rate of the resulting polymers (**Figure 10**). They prepared a series of acetal monomers with varying structure and hydrophobicity. Each monomer with additional hydroxyl groups was polymerized with glycidol and initiated with glycerol, resulting in hyperbranched polymers with acetal linkage in their structures. The differences between the structures and hydrophobicity values of the acetal bonds creates exceptional divergence of

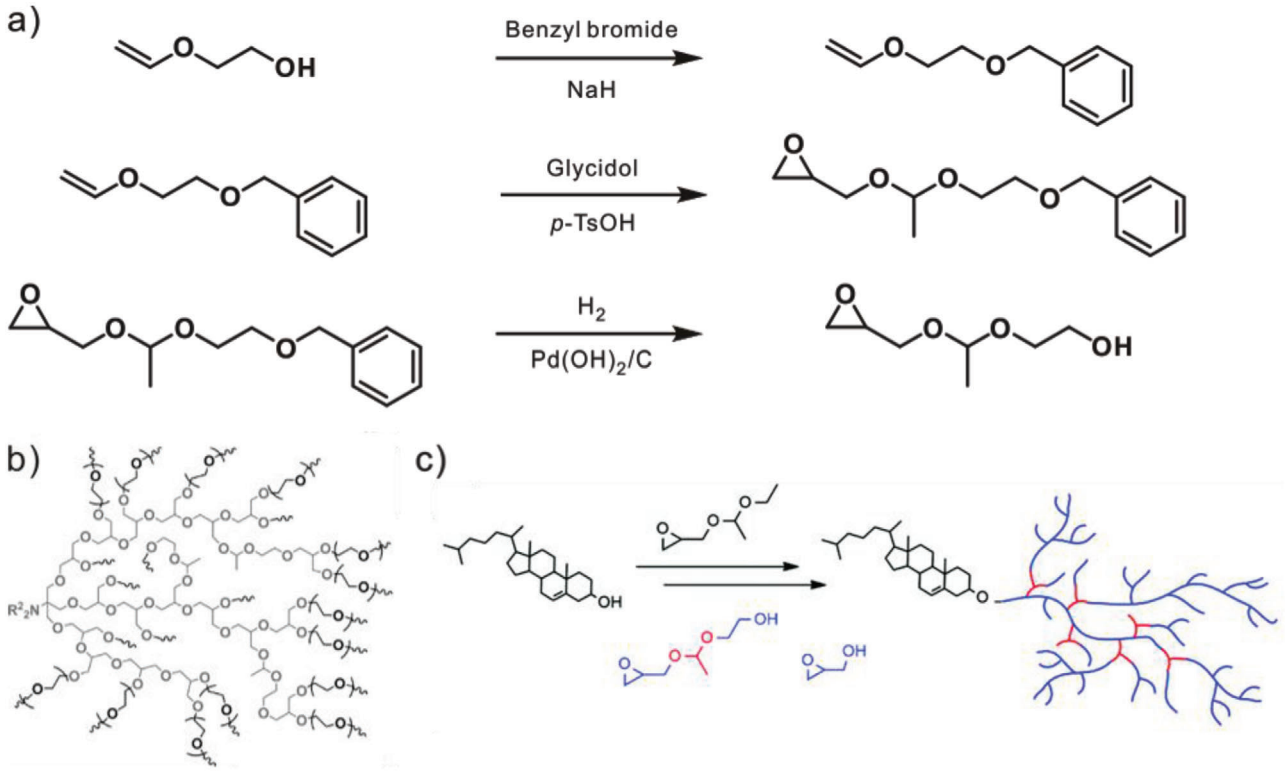

Figure 9. a) The overall synthetic scheme of the GEGE monomer and b) an acetal-incorporated hyperbranched polymer prepared from the GEGE monomers and ethylene oxide (EO). Reproduced with permission.[25] Copyright 2012, American Chemical Society. c) A lipid like polymer using cholesterol as alkoxide initiator and GEGE and glycidol as feeding monomers. Reproduced with permission.[57] Copyright 2016, The Royal Society of Chemistry.

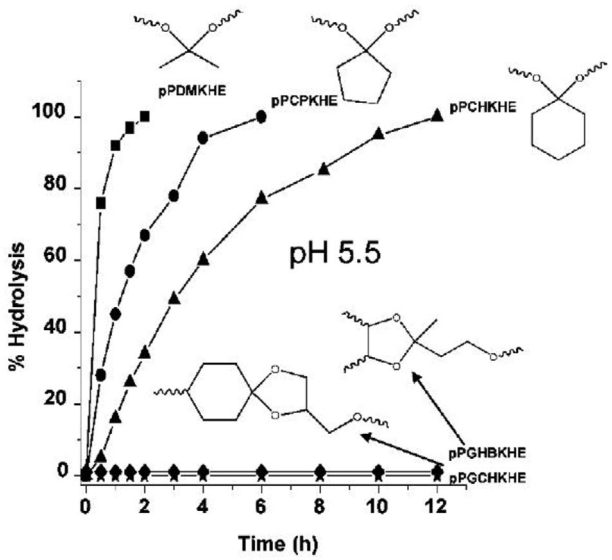

Figure 10. Comparison of the degradation of various acetal group linkages in multifunctional hyperbranched polyethers. Poly(dimethylketal hydroxyether) (PDMKHE), poly(cyclopentylketal hydroxyether) (PCPKHE), poly(cyclohexylketal hydroxyether) (PCHKHE), poly(glycerol hydroxybutanone ketal hydroxyether) (PGHBKHE), and poly(glycerol cyclohexanone ketal hydroxyether) (PGCHKHE). Reproduced with permission.[37] Copyright 2012, American Chemical Society.

their hydrolysis rates ($t_{1/2}$) ranging from a very short 6.3 min to over 400 d, with the latter showing exceptional stability. The hydrophobicity of the acyclic acetal group determined the hydrolysis rate, as was revealed by comparing the values of the resulting polymers, including poly(dimethylketal hydroxyether) (PDMKHE), poly(cyclopentylketal hydroxyether) (PCPKHE), poly(cyclohexylketal hydroxyether) (PCHKHE), poly(glycerol hydroxybutanone ketal hydroxyether) (PGHBKHE), and poly(glycerol cyclohexanone ketal hydroxyether) (PGCHKHE). In contrast, the hydrolysis rates of the cyclic and spiro acetal group-based polymers were not related to the hydrophobicity values of the monomers but instead, to the torsional strain induced by the acetal group; both were highly stable under acidic conditions with a more than 10^5-fold increase compared to the least-stable acetal structure. In accordance with a previous report, the endocyclic cleavage during acetal hydrolysis significantly delayed the process due to intramolecular ring closure reaction.[58] It is significant in that the hydrolysis rate of pH-responsive linkers can be considerably modulated by controlling the structure of them without introducing additional functional groups.

Shenoi et al. prepared biodegradable hyperbranched polyglycerols (BHPGs) consisting of various acetal-incorporated monomers (**Figure 11**).[59] Among their monomer pool, they chose cyclopentylketal (CPK), cyclohexylketal (CHK), and glycerol hydroxybutanone ketal (GHBK) as building blocks for endowing the moderate degradation of the resulting polymers under mild acidic conditions. The resulting polymers' high

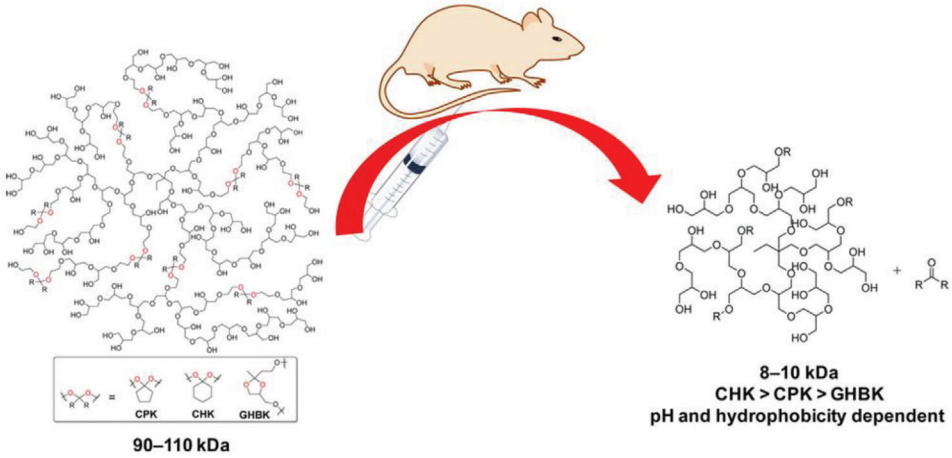

Figure 11. The structure of BHPGs and a schematic illustration of the degradation of high molecular weight BHPGs upon degradation of acetal bonds in vivo system. BHPGs were prepared with using cyclopentylketal (CPK), cyclohexylketal (CHK), and glycerol hydroxybutanone ketal (GHBK) as building blocks. Reproduced with permission.[59] Copyright 2016, American Chemical Society.

molecular weights of more than 92 kDa prevented them from being excreted after being introduced intravenously. After injection, the BHPG made from the GHBK monomer gradually fractured into smaller molecular weight fragments due to the pH-responsive degradation of acetal bonds, which could then be cleared from the body. Furthermore, they also envisioned that the degradation time of this system could be controlled through adequate design of the degradable parts. As revealed by Li and co-workers the pH of internal organs varies from site to site,[60] therefore, it will be critical to achieve a tunable degradation and release profiles for a target delivery site.

3.2.3. TPGE

Independently from previous research, our group reported the preparation of TPGE modulate the hydrolysis rate of the acetal linker (**Figure 12**a).[26] 3,4-Dihydropyran (a widely utilized protecting group for alcohols) was used to shield the free hydroxyl group of glycidol, which resulted in the TPGE monomer at a high yield. As TPGE is a hydrophobic moiety, amphiphilic polymers can easily be prepared through its block copolymerization initiated with *m*PEG (Figure 12b). Comparing to the existing EEGE monomer with a similar structure, the cyclic TPGE monomer shows significantly enhanced hydrophobicity. For instance, diblock copolymer micelles prepared from the self-assembly of *α*-methoxypoly(ethylene glycol)-*b*-poly(tetrahydropyranyl glycidyl ether) (*m*PEG-*b*-PTPGE) displayed a considerably lower critical micelle concentration value than that of *m*PEG-*b*-PEEGE.

For environment-responsive drug delivery systems, pH-sensitive polymeric micelles have attracted considerable attention due to the wide range of pH changes in many specific compartments. In this study, owing to the nature of acetal linkages placed in the side chain of both the PTPGE and PEEGE blocks, we pursued the degradation of the amphiphilic block copolymers upon treatment with acid to dissociate the acetal linkages, which resulted in the changes of the hydrophobic PTPGE or PEEGE block to its corresponding hydrophilic linear PG block possessing superior biocompatibility (Figure 12c). Using pyrene as a model hydrophobic probe, the degradation of *m*PEG-*b*-PTPGE and *m*PEG-*b*-PEEGE micelles (i.e., T1, T2, and E2) was monitored (Figure 12d). As the relative fluorescence excitation intensity ratio between 339 and 332 nm (I_{339}/I_{332}) tends to increase when pyrene is located in hydrophobic environment,[61,62] it has been widely utilized for determination of critical micelle concentration and the degradation properties of polymeric micelles.[63,64]

Interestingly, the I_{339}/I_{332} plots of T1 and T2 micelles showed sustained degradation over time, which can help maintain therapeutic doses for extended periods within the desirable concentration window for effective drug delivery. These results suggest that the release kinetics can be easily controlled by the number of hydrophobic TPGE units. In clear contrast, E2 micelles prepared from $m\text{PEG}_{114}$-*b*-PEEGE_{22} showed a rapid decrease in I_{339}/I_{332} which illustrates burst release of pyrenes. Taking these results together, it is important to highlight that the type of functional acetal monomer within the structure is critical for modulating the degradation of the acetal group which directly related to control over the degradation and release kinetics of the prepared micelles.

Encouraged by our previous findings, we further tailored the rate of hydrolytic degradation of the hydrophobic acetal groups via the copolymerization of TPGE and EEGE (**Figure 13**a).[65] A series of block copolymers, *m*PEG-*b*-P(EEGE-*co*-TPGE)$_n$, with a varying ratio of EEGE and TPGE monomers (T0–T4, increasing fraction of TPGE from 0% to 100%) were synthesized by AROP through controlling the ratio of EEGE and TPGE as acyclic and cyclic acetal moieties, respectively. The critical micelle concentration values, loading efficiencies, and degradation kinetics of the micelles prepared from the series of *m*PEG-*b*-P(EEGE-*co*-TPGE) copolymers were precisely controlled by varying the fractions of TPGE and EEGE. As similar to the previous approach, pH-triggered release of encapsulated pyrene was used to monitor the degradation and subsequent release kinetics of the micelles under acidic conditions (Figure 13b). The intensity ratio of pyrene for the T0–T4 micelles did not change significantly, suggesting that the micelles were stable under neutral

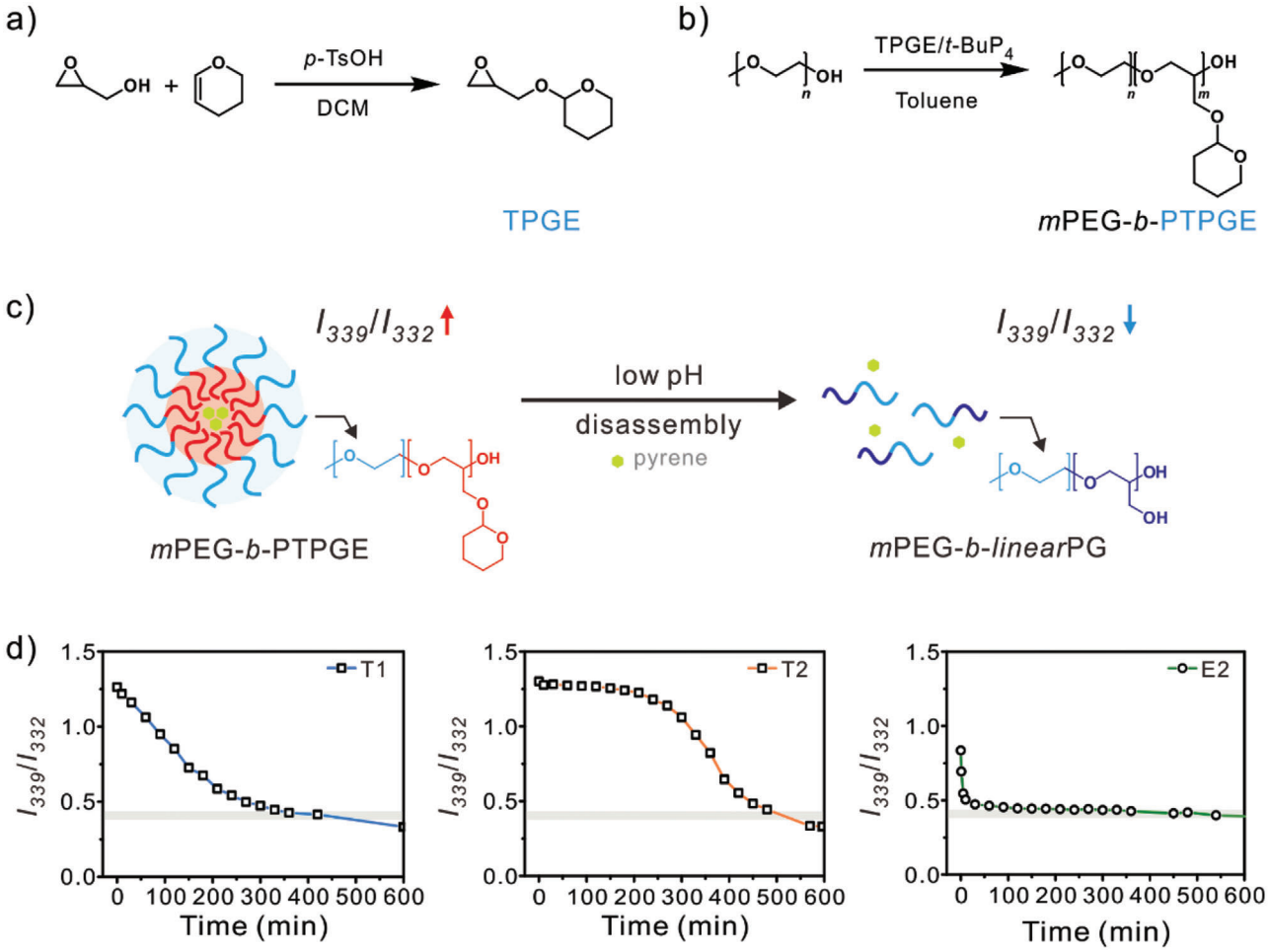

Figure 12. The synthetic scheme for preparation of a) TPGE monomer and b) amphiphilic block copolymer of *m*PEG-*b*-PTPGE. c) A schematic illustration of pyrene released under acidic conditions and structure of resulting polymer *m*PEG-*b*-linearPG after hydrolysis of acetal bond. d) The degradation percentage of each micelle with different number and type of hydrophobic blocks which was plotted using the I_{339}/I_{332} values of pyrene calculated from fluorescence excitation spectra. T1: $m\text{PEG}_{114}$-*b*-PTPGE_{18}, T2: *m*PEG-*b*-PTPGE_{37}, and E2: $m\text{PEG}_{114}$-*b*-PEEGE_{22}. Reproduced with permission.[26] Copyright 2017, The Royal Society of Chemistry.

conditions. However, upon switching to pH 5.0, the I_{339}/I_{332} value of pyrene was shifted and decreased with time as the encapsulated pyrene was released. The rate of degradation and release of pyrene was slow for the copolymers that included a higher percentage of the TPGE monomer. It is worth noting that the micelle from the T4 copolymer displayed the slowest release profile, suppressing the initial burst and extending the release over two weeks.

Furthermore, Förster resonance energy transfer (FRET)-analysis was conducted to prove whether the stability of micelle can be maintained under in vitro system (Figure 13c,d). In this case, the FRET pair comprised of the donor, dioctadecyloxacarbocyanine perchlorate (DiO), and the acceptor, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI), was loaded into the micelle and treated to HeLa cells. When both FRET pair molecules were encapsulated inside the micelle and the DiO donor was excited at 488 nm, energy transfer occurred because of the proximity of the molecules within the micelle, which resulted in the emission of the DiI acceptor at 564 nm (red color). In contrast, when the micelles disintegrated and the dyes were released, the FRET molecules diffused apart and eliminated the FRET effect, which resulted in the emission of the DiO donor at 501 nm (green color). It was found that as the fraction of TPGE is increased in the copolymer micelles as in the case of T4, intense red fluorescence emission was observed resulting from FRET effect, indicating a high stability of the micelles in vitro condition. On the other hand, green fluorescence of DiO could be seen in micelle with a lower fraction of TPGE system (i.e., T2) from decoupling of DiO and DiO in the course of dissociation of micelle. It is notable that a wide range of degradation kinetics can be achieved via simple copolymerization of two acetal-based monomers of different degradation rate. Considering highly tunable properties and superior biocompatibility of resulting polymers, this study clearly showed the immense potential for the development of versatile platform for smart drug delivery systems.

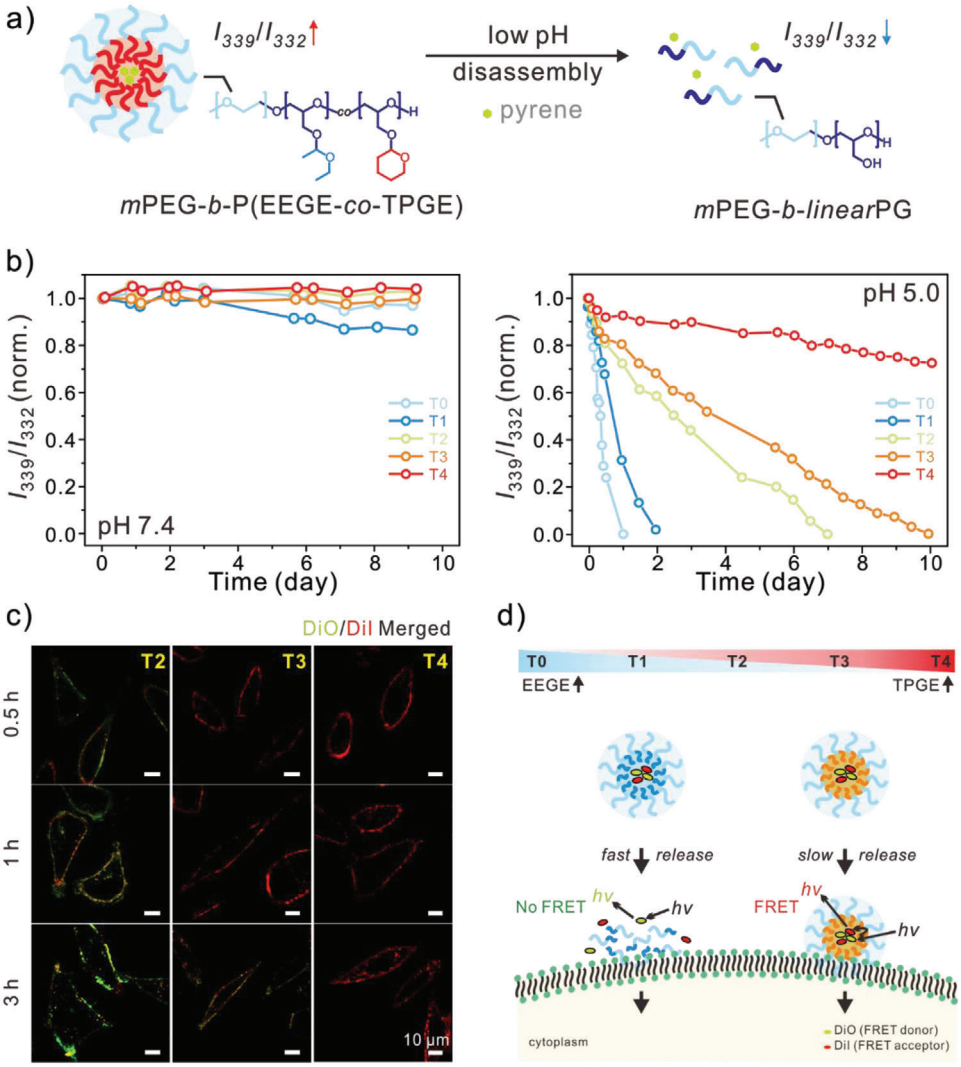

Figure 13. a) Schematic illustration of the degradation of the amphiphilic *m*PEG-*b*-P(EEGE-*co*-TPGE)$_n$ copolymers. b) The release profiles of pyrene from the degradation of block copolymer micelles over time at (left) pH 7.4 and (right) pH 5.0. The degradation percentage was plotted using the I_{339}/I_{332} values of pyrene calculated from fluorescence excitation spectra. *m*PEG$_{114}$-*b*-P(EEGE-*co*-TPGE)$_n$ with a varying ratio of EEGE and TPGE monomers (T0–T4, increasing fraction of TPGE from 0% to 100%). c) In vitro Förster resonance energy transfer (FRET)-based analysis of amphiphilic *m*PEG-*b*-P(EEGE-*co*-TPGE)$_n$ copolymer micelles (T2–T4) after incubation in HeLa cells for different time period. The green and red colors represent the DiO and DiI signals, respectively, and the yellow color indicates the overlapped signals of both FRET dyes. d) Schematic illustration of the different release mechanisms for the micelles. Reproduced with permission.[65] Copyright 2019, The Royal Society of Chemistry.

3.2.4. TFGE

In continuation of our effort in the development of novel acetal-based functional epoxide monomers, we prepared the TFGE monomer from the reaction of glycidol and dihydrofuran (**Figure 14**a).[27] While TFGE retains its cyclic structure similar to TPGE, the polymer prepared from TFGE demonstrated remarkably low hydrophobicity and a fast hydrolysis rate; these phenomena were rationalized via a computational simulation program in detail (Figure 14b). Here, we used a series of model compounds to accessing the hydrolysis kinetics of different acetal groups. In particular, considering the structure of side chain structures after the ring-opening reaction of the epoxide group, we prepared the following three model compounds: tetrahydropyranyl propyl ether (TPPE), tetrahydrofuranyl propyl ether (TFPE), and ethoxyethyl propyl ether (EPEE).

BLIP/6-GAG* level of theory was performed to calculate activation energy in the course of hydrolysis of each acetal and they found that activation energy of TFPE was much lower than that of TPPE. Specifically, in the course of the degradation of the acetal groups of the side chain of the TFGE monomer (depicted as the model side chain in Figure CA), the inner water shell that directly envelops the TFGE monomer assists in the protonation step whereas the protonation of TPGE is assisted by the outer water shell that envelops the inner water shell (Figure did). As a result, the activation energy levels of the protonation step for both monomers are significantly different, which eventually leads to a much faster hydrolysis rate for the acetal group in the TFGE

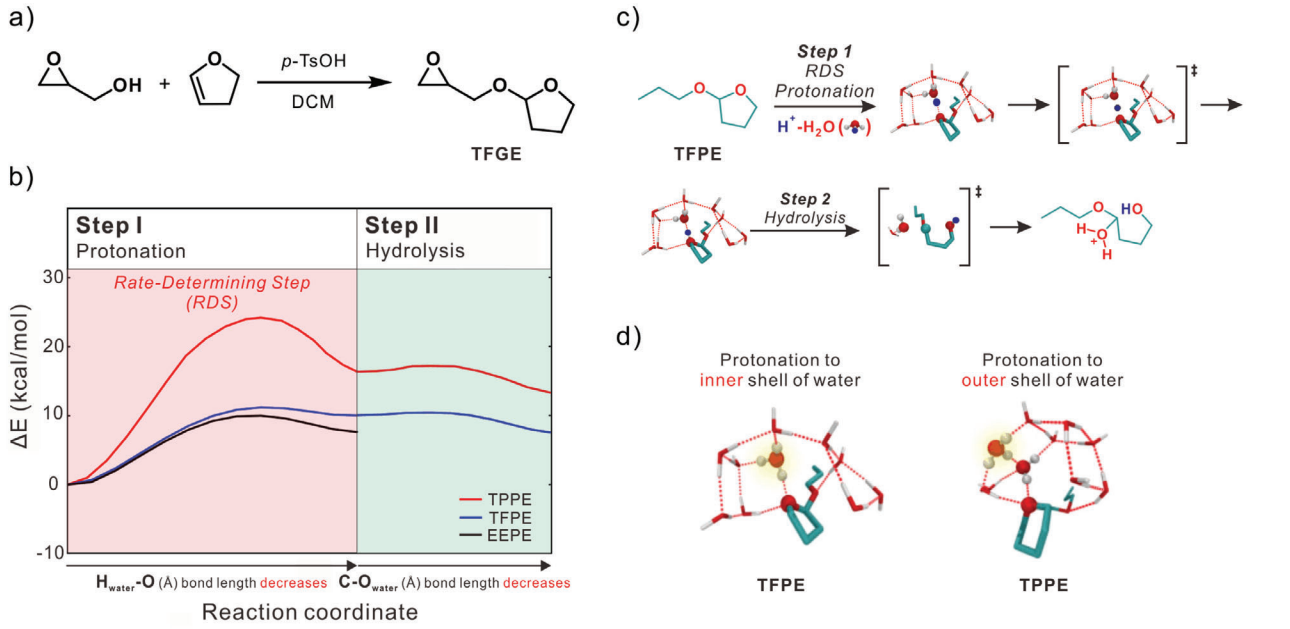

Figure 14. a) Synthetic scheme of the pH-responsive acetal-based monomer, TFGE. b) An energy diagram based on bond length during the acetal hydrolysis reactions of model molecules, such as TPPE, TFPE, and EEPE. c) The resulting hydrolysis mechanism of TFPE. d) The protonation steps for TFPE and TPPE, which receive a proton from the inner and outer shells of water, respectively. Tetrahydrofuranyl propyl ether (TFPE); tetrahydropyranyl propyl ether (TPPE); ethoxyethyl propyl ether (EEPE). Reproduced with permission.[27] Copyright 2019, American Chemical Society.

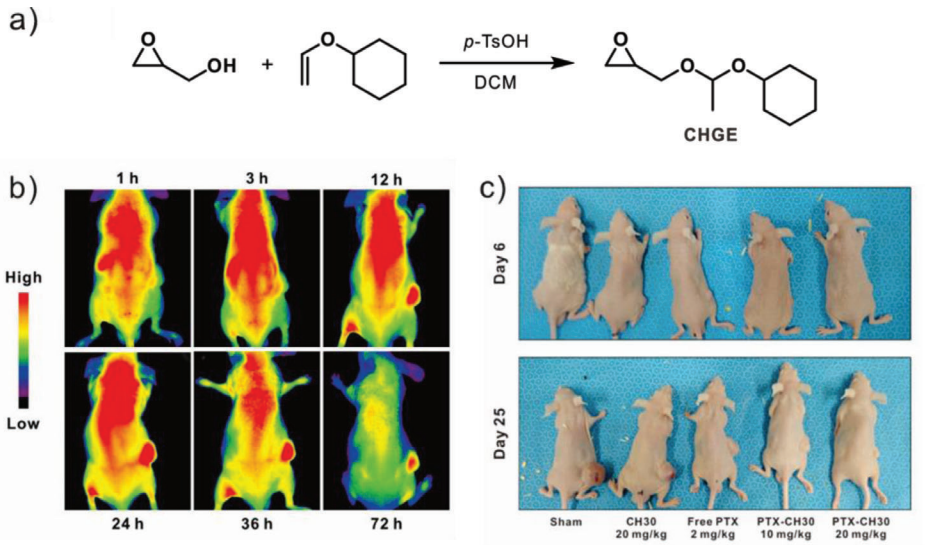

Figure 15. a) The synthetic scheme for the preparation of the pH-responsive CHGE monomer. b) Near-IR fluorescence imaging of mice with tumors 3 h post injection with IR 780-loaded *m*PEG-*b*-PCHGE$_{30}$ (CH30) micelles. c) Representative images of mice with tumors at day 6 and day 25 after treatment with drug-loaded micelles containing different amounts of PTX (paclitaxel) with and without CH30 and a control (sham). Reproduced with permission.[28] Copyright 2021, American Chemical Society.

monomer. This result was also proved again with NMR analysis, which showed much lower value of rate constant in TPPE hydrolysis reaction than TFPE hydrolysis.

3.2.5. CHGE

Most recently, CHGE presenting the highest hydrophobicity among acetal-based monomers has been prepared (**Figure 15**a).[28] For example, the log *P* value (the most widely utilized measure for determining hydrophobicity) of the CHGE monomer is 1.82, which is considerably higher than other acetal-based monomers due to the presence of an exocyclic cyclohexyl side chain. As a result, the block copolymer of *α*-methoxypoly(ethylene glycol)-*b*-poly(cyclohexyloxy ethyl glycidyl ether) (*m*PEG-*b*-PCHGE) can form self-assembled micelles at a very low critical micelle concentration value. A FRET analysis

proved that micelles of *m*PEG-*b*-PCHGE are highly stable in phosphate-buffered saline and slowly degrade under acidic conditions.

Fluorescence imaging analysis after injection of IR 780-loaded *m*PEG-*b*-PCHGE$_{30}$ (CH30) micelles showed an accumulation of dye at the tumor site, which can be interpreted as the enhanced degradation of the micelles under the acidic conditions created by the tumor cells (Figure 15b). Moreover, due to the enhanced hydrophobicity of *m*PEG-*b*-PCHGE, the cores of the micelles formed with it can significantly load the hydrophobic anticancer therapeutic paclitaxel (PTX), thereby demonstrating their delivery of effective cancer therapeutics at low toxicity (Figure 15c).

4. Conclusion and Outlook

In this review, we have presented the recent progress in the development of acetal-incorporated epoxide monomers from their synthesis and polymerization to their application, particularly in the biomedical field. While early development was focused on their use as a simple protecting group during the harsh conditions during AROP, recent progress has been made in the use of their polymers in pH-responsive hydrophobic delivery systems for therapeutic drugs. Degradation of the acetal linkage within the polymer is highly dependent on the chemical structure and hydrophobicity of the acetal-carrying monomer. Moreover, the degradation rate of the polymer can be precisely controlled by both the type of acetal group and the degree of polymerization of the hydrophobic blocks. It is thus anticipated that these monomers will offer a convenient means to produce a versatile drug delivery system to cover a broad spectrum of release profiles from a rapid burst release for reducing pains to a sustained release for cancer therapy.

While most of the examples presented in this review deal with frameworks of hyperbranched polymers and polymeric micelles, exploiting these unique pH-responsive degradable polymers in injectable hydrogels for cosmetic application such as instant filler or tissue engineering scaffolds for mimicking in vivo system and cell delivery will be an area for future endeavor. By taking advantage of the excellent biocompatibility of polyethers, we anticipate that acetal-based functional epoxide monomers will be used in an even wider range of applications than covered in this review.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

acetals, epoxide monomers, polyethers

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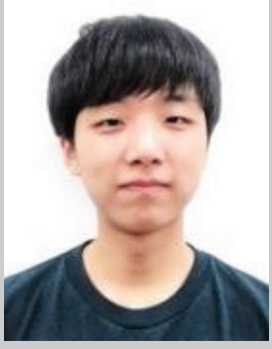

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