Homopolymer Bifunctionalization through Sequential Thiol-Epoxy and Esterification Reactions: An Optimization, Quantification, and Structural Elucidation Study

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ARTICLE TYPE

Homopolymer Bifunctionalization through Sequential Thiol-Epoxy and Esterification Reactions: An Optimization, Quantification, and Structural Elucidation Study

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In this study, we probe various aspects of a post-polymerization double-modification strategy involving sequential thiol-epoxy and esterification reactions for the preparation of dual-functional homopolymers. For this, a general reactive scaffold, poly(glycidyl methacrylate), carrying an aromatic end-group was prepared through an atom transfer radical polymerization (ATRP) process. The glycidyl side-chains of this polymer were subjected to a base-catalyzed ring opening reaction with the thiol nucleophiles. Systematic variation in the catalyst type, catalyst loading, reaction medium, reaction temperature, and reaction time suggested that the choice and amount of catalyst had a significant impact on the outcome of the thiol-epoxy reaction. End-group analysis in ^{1}H-NMR spectroscopy was employed to quantify the degree of epoxy group conversion into the corresponding thio-ether moiety. The secondary hydroxyl groups generated as a result of the first functionalization reaction were then employed in the anchoring of a second functional group to the polymer repeat unit through an esterification reaction. Quantification studies suggested that an excess of the activated acid molecules was necessary to observe quantitative functional group transformation. Elemental analysis confirmed the chemical composition of the functionalized polymers. The obtained bi-functionalized polymers could be converted into a water soluble amphipathic structure in which each polymer repeat unit was substituted with a hydrophilic ammonium cation and a hydrophobic alkyl chain. Besides these, a carefully planned model compound study was also conducted to examine the regio-chemical aspects of the prepared polymers.

Introduction

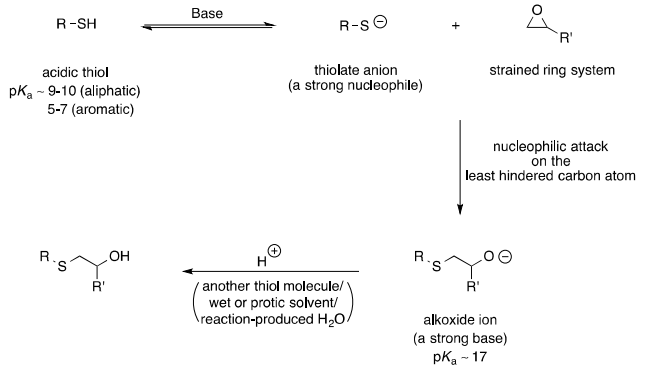
Demand for synthetic polymers displaying a well-defined functional group array has been rising with the pressing need to meet future health and energy issues.[1-2] For instance, in the biomedical arena, well-defined structures featuring multiple functionalities for imaging, tissue targeting, and cell-entry in an all-in-one system are highly desired.[3] Such a multifunctionalization approach is expected to increase the performance and efficacy of the designed systems.[4-6] Synthesis of polymers that carry multiple functionalities at precise locations is however a challenging task. This endeavor requires synthetic methods that proceed with absolute fidelity, high levels of control, and extraordinary functional group compatibility. One way to address this challenge is through post-polymerization modification of carefully designed reactive polymeric scaffolds.[7-18] In this context, various approaches have been established. For example, double, triple, and quadruple post-polymerization modifications on random and alternating copolymers have been demonstrated.[19-37] Block copolymers carrying reactive sites dispersed within one polymer segment or two different types of reactive sites, one in each segment, have been shown to afford well-defined multifunctional materials.[22,30,38-39] The terminal site(s) of a polymer chain have also been addressed for multiple post-polymerization modification processes.[40-44] In a different approach, homopolymer sequences have been designed to carry multiple functionalities. In order to understand the implications of this approach on the structure and the properties of the resulting materials, one has to consider the alternative approach in which a random copolymerization of two or more functionalizable monomers can also lead to polymers carrying multiple functionalities. The random copolymerization process, however, yields polymers with ill-defined monomer sequence (…AAB… or …BAB… or …BBA… or …ABA…) that is subject to change from reaction to reaction even if the total percentage of the two monomers remains constant. Therefore, it is difficult to assume that a direct property comparison, especially in the biomedical applications context in which pharmacokinetic behavior is known to be sensitive to the precise molecular structure,[45] can be made in a multifunctional polymer family that is prepared through a random copolymerization process. In the case of multifunctional homopolymers, however, such direct structure property comparisons can be made due to the identical chemical structure of each polymer-repeat unit involved. Moreover, a reproducible

synthesis and pharmacokinetic behavior can be expected from such molecularly precise materials. The synthetic approach of preparing multifunctional homopolymers is illustrated by the works of Novak, Haddleton, Grubbs, Tao, Meier, and Theato.[46-51] We have contributed to this aspect by introducing a post-polymerization double-modification strategy in which the thiol-epoxy and esterification reactions on a free radically prepared glycidyl scaffold was shown to furnish dual-functional homopolymers in three steps starting from commercially available and inexpensive small molecules.[52] In a later report, this concept was combined with controlled free radical polymerization to yield poly(ethylene glycol) (PEG)-based copolymers[30] and molecular bottlebrushes[53] of low polydispersity and water solubility. Recently, the general nature of this strategy has been applied to prepare a library of bifunctional polymers carrying an ammonium group and a lipophile (an alkyl/aryl moiety).[54] These polymers were capable of forming supramolecular complexes with siRNA and delivering them to human colon carcinoma cells (HT-29-luc). In this design, the positively charged ammonium groups interacted with the negatively charged siRNA and the lipophilic chains allowed the formed complex to cross the cell/endosome membrane. Besides these, collaborative effort among the groups of Haddleton, Davis, Boyer and Whittaker, work from the Gao lab and Nicolaÿ lab, and some work from our group have put the thiol-epoxy coupling chemistry to work in the preparation of a variety of chemically complex yet well-defined materials.[55-59] Despite these advances, a number of questions relating to different aspects of this strategy of polymer functionalization remain, however, unanswered. Regarding the first step, the thiol-epoxy reaction on a polymer substrate, a systematic and comparative study comprehending the available catalyst choices and their consequences, optimum reaction conditions, and optimum catalyst loading is missing. Regarding the second step, the esterification reaction, the most important question perhaps is: can the secondary hydroxyl groups with significant steric demand and known lower reactivity be employed as efficient coupling partners? This question relates directly to the structural precision of the prepared final materials and therefore bears heavily on their description as 'bifunctional homopolymers'. Besides these, the regio-chemistry aspects also need to be considered. The present study, therefore, investigates the aforementioned questions in a systematic fashion. It is anticipated that this work will serve as a guide to researchers interested in employing the thiol-epoxy reaction for polymer synthesis and post-polymerization modification purposes, and for a sequential dual-modifications approach involving thiol-epoxy and esterification reactions to create bifunctional polymeric materials.

Results and Discussion

Thiol-Epoxy Reaction Mechanism

Epoxides are strained three-membered rings. The ring strain comes from the 60° angle between the bonds and renders the molecule susceptible to nucleophilic attacks in order to restore the ideal tetrahedral angle (109°) at all atoms. Thiols can participate in such a ring opening reaction. However, the thiol functionality has to be transformed into an attacking thiolate

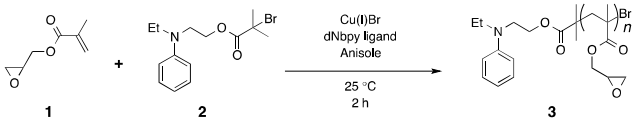


Scheme 1. Thiol-epoxy reaction under basic conditions. The reaction is most likely to proceed by an S_N2 mechanism. Therefore, a step-wise depiction is meant only to simplify the process for a better understanding.

anion. This can be achieved by using a base that is strong enough to deprotonate the thiol group. In chemistry textbooks, this base is most often depicted as lithium or sodium hydroxide. The hydroxide anion can deprotonate thiol molecules quantitatively. In terms of the attack on the epoxide ring, it should be noted, however, that there is no competition between hydroxide and thiol because thiols are more acidic than water (pK_a of RSH is typically 5-10, pK_a of PhSH is 6.4, and pK_a of water is 15.7)[60-61] and therefore a rapid proton transfer occurs from sulfur to oxygen. Once formed, the thiolate nucleophile attacks the less hindered site of the epoxide unit. The alkoxide unit thus formed gets protonated, due to its high basicity ($pK_a \sim 17$),[62] by either the thiol molecules present in the system (due to their acidity as discussed above), by the typical wet/protic nature of the reaction medium, or by the water generated during the reaction (e.g. when using a hydroxide base) (Scheme 1). This thermodynamically driven proton transfer step is critical in quenching the alkoxide anion and hence stopping an anionic ring opening polymerization reaction from commencing. The end product of this reaction, therefore, is a new thioether linkage and a secondary hydroxyl group. This hydroxyl group can be used for a successive second functionalization. A structurally related concept of preparation of secondary hydroxyl group substituted polymers and their post-polymerization modifications can be found in the works of Kiskan and Yagci.[63]

Synthesis of the General Reactive Scaffold

Poly(glycidyl methacrylate) represents a versatile scaffold that has found vast utility in the preparation of functional soft materials.[64-66] To prepare this polymer, glycidyl methacrylate monomer, **1**, was polymerized through an atom transfer radical polymerization (ATRP)[67] using aromatic initiator **2** to yield poly(glycidyl methacrylate) **3** (Table 1, Scheme 2). In order to remove the residual monomer, the resulting polymer was precipitated into isopropanol, passed through a plug of silica gel, and then precipitated again in isopropanol. This treatment was sufficient to obtain pure polymer **3**. In the ^{1}H-NMR spectrum, polymer **3** featured three proton resonances located at 2.6, 2.8, and 3.2 ppm belonging to the reactive epoxide unit of the polymer repeat unit (Figure 1). The aromatic proton resonances arising from the initiating species could be observed at 6.7 and 7.2 ppm. The signal at 6.7 ppm allowed for determination of the



Scheme 2. Polymerization of glycidyl methacrylate monomer **1** with initiator **2** to yield general reactive scaffold **3**.

Table 1. Molecular weight data for polymers **3**, **5**, and **9**.

Polymer	DP $_{(NMR)}$	$M_{n\,(NMR)}$	$M_{n\,(GPC)}$	PDI (M_w/M_n)
3	40	5700	17600	1.3
5	40	12800	23500	1.3
9	40	16700	22000	1.4

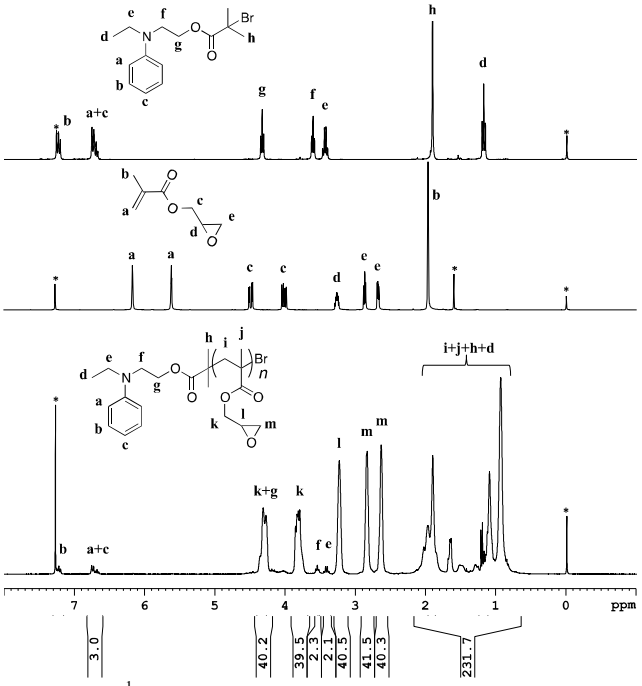


Figure 1. ^{1}H-NMR of the polymerization initiator and the general reactive scaffold **3**. Signals from tetramethylsilane (TMS) and chloroform are marked with an asterisk. The integration values belong to the bottom trace only.

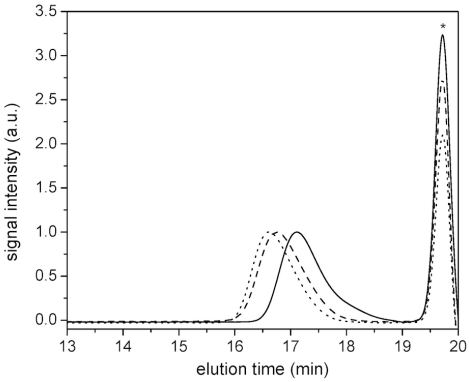
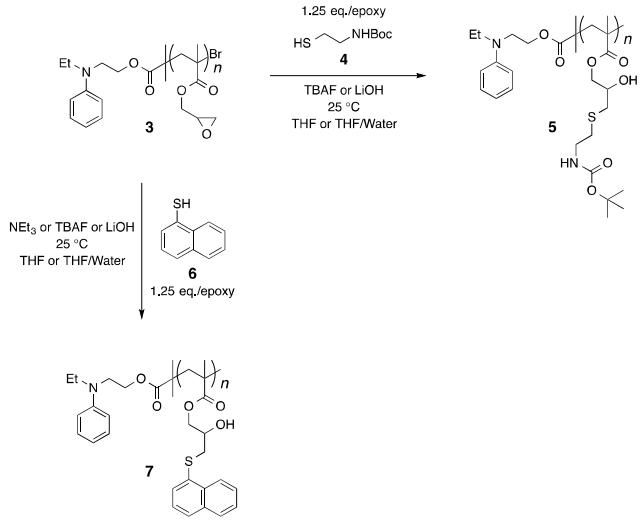


Figure 2. GPC traces of the polymers **3** (solid line), **5** (dot line), and **9** (dash line) in DMF.

degree of polymerization through end-group analysis. According to this, polymer **3** was composed of an average of 40 repeat units. Gel permeation chromatography suggested that the polymerization proceeded under good control, and low polydispersity materials could be obtained (Figure 2 and Table 1).



Scheme 3. First functionalization of the general scaffold **3** with thiols **4** and **6**.

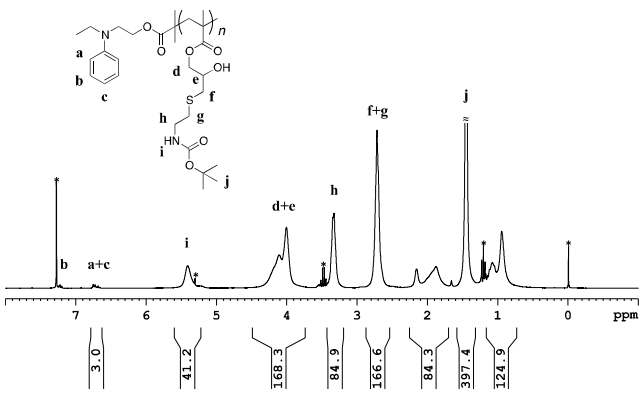


Figure 3. ^{1}H-NMR of poly(glycidyl methacrylate) **3** after functionalization with thiol **4** through thiol-epoxy reaction. Signals from TMS, chloroform, and diethylether are marked with an asterisk.

First Functionalization through the Thiol-Epoxy Reaction

The first functionalization of reactive scaffold **3** was carried out through a thiol-epoxy reaction using thiol **4** (Scheme 3). The epoxy to thiol ratio was kept constant at 1:1.25 and all reactions were carried out at room temperature. The *tert*-butoxycarbonyl (*t*-Boc) unit of **4** provided a good handle in fathoming the degree of functionalization. For this, area integration of the signal arising from the three aromatic protons located at the end-group of polymer **3** (6.7 ppm) was compared to the area integration of the *t*-Boc signal located at 1.5 ppm in the ^{1}H-NMR spectrum of the mono-functionalized polymer **5** (Figure 3). This allowed for determination of the epoxy group conversion, as shown in Tables 2, 3 and 4, into the corresponding thio-ether moiety.

Initially, triethylamine (TEA) was employed as a catalyst and tetrahydrofuran (THF) was used as a solvent. The reaction time was set at one hour at room temperature and with a catalyst loading of 1.2 mol%. However, no reaction was observed at these conditions (Table 2). An increase in the catalyst loading to 3.6,

Table 2. Functionalization of polymer **3** with aliphatic thiol **4**.

Entry	Catalyst	Cat. loading[a] (mol%)	Catalyst (eq./**4**)	Time (h)	Conversion (%)
1	TEA	1.2	0.01	1	-
2	TBAF	1.2	0.01	1	7
3	LiOH	1.2	0.01	1	90
4	TEA	1.2	0.01	3	-
5	TBAF	1.2	0.01	3	12
6	LiOH	1.2	0.01	3	97
7	TEA	3.6	0.03	1	-
8	TBAF	3.6	0.03	1	34
9	LiOH	3.6	0.03	1	>99
10	TEA	3.6	0.03	3	-
11	TBAF	3.6	0.03	3	31
12	LiOH	3.6	0.03	3	>99
13	TEA	5.9	0.05	1	-
14	TBAF	5.9	0.05	1	56
15	LiOH	5.9	0.05	1	>99
16	TEA	5.9	0.05	3	-
17	TBAF	5.9	0.05	3	68
18	LiOH	5.9	0.05	3	>99
19	TEA	8.0	0.07	1	-
20	TBAF	8.0	0.07	1	85
21	LiOH	8.0	0.07	1	>99
22	TEA	8.0	0.07	3	-
23	TBAF	8.0	0.07	3	85
24	LiOH	8.0	0.07	3	>99
25	TEA	8.0	0.07	12	-
26	TBAF	8.0	0.07	12	87
27	TEA	20.7	0.21	1	-
28	TBAF	20.7	0.21	1	95
29	TEA	20.7	0.21	3	-
30	TBAF	20.7	0.21	3	>99

All reactions were carried out at 25 °C using 1.25 equivalents of thiol **4** per epoxy unit. [a]related to the limiting substrate (i.e. an epoxy unit of polymer **3**).

Table 3. Functionalization of polymer **3** with aromatic thiol **6**.

Entry	Catalyst	Cat. Loading (mol%)	Catalyst (eq./**6**)	Time (h)	Conversion (%)
1	TEA	8.0	0.07	12	50
2	TEA	20.7	0.21	12	80
3	TBAF	20.7	0.21	1	>99
4	TEA	34.4	0.42	12	>99
5	LiOH	1.2	0.01	1	90

All reactions were carried out at 25 °C using 1.25 equivalents of thiol **6** per epoxy unit.

Table 4. Thiol-epoxy reaction using DMSO as a solvent.

Entry	Catalyst	Cat. Loading (mol %)	Catalyst (eq./**4**)	**4** (eq./epoxide)	Time (h)	Temp. (ºC)	Conversion (%)
1	TEA	34.4	0.42	1.25	12	25	20
2	TEA	34.4	0.42	1.25	12	50	55
3	TEA	60.9	1.25	1.25	12	50	73
4	TEA	65.2	1.25	1.5	12	50	85
5	TEA	68.6	1.25	1.75	12	50	85
6	TEA	81.3	2.5	1.75	12	50	>90

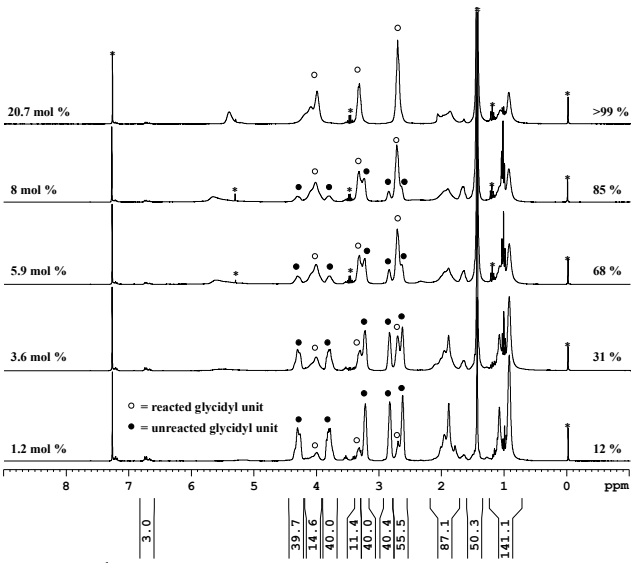


Figure 4. ^{1}H-NMR of polymer **5** prepared upon TBAF catalysis (reaction time = 3 h). The numbers on the left side indicate the amount of the catalyst in mol% and the numbers on the right side indicate degree of epoxide group conversion. Signals from TMS, chloroform, dichloromethane, and diethylether are marked with an asterisk.

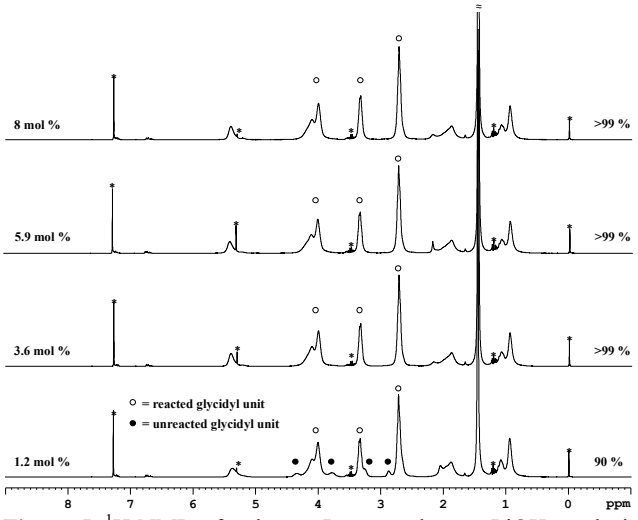


Figure 5. ^{1}H-NMR of polymer **5** prepared upon LiOH catalysis (reaction time = 1 h). The numbers on the left side indicate the amount of the catalyst in mol% and the numbers on the right side indicate degree of epoxide group conversion. Signals from TMS, chloroform, dichloromethane, and diethylether are marked with an asterisk.

5.9, and 8.0 mol% did not change the outcome of the reaction. Therefore, reaction time was increased to three hours. Still, the epoxy groups of polymer **3** remained intact. Therefore, the reaction time as well as the catalyst loading was increased to 12 hours and 20.7 mol%, respectively. These conditions, however, remained unfruitful. It is likely that in the case of aliphatic thiols of relatively low acidity ($pK_a \approx 10$), triethylamine, having pK_a in the similar range (10.7), fails to act as an efficient base at the initial deprotonation step at room temperature and in THF. To

Table 5. Elemental analysis details of the mono-, and bi-functionalized polymers.

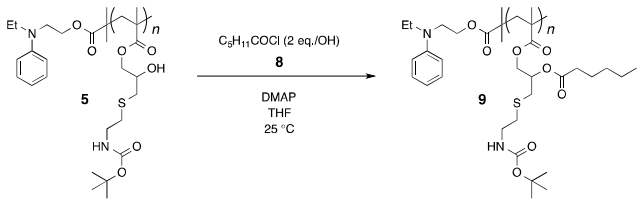
	Polymer **5**		Polymer **9**	
Element	Calculated (%)	Found (%)	Calculated (%)	Found (%)
[C]	52.64	52.47	57.53	57.42
[H]	7.89	7.98	8.45	8.47
[N]	4.39	4.27	3.35	3.29
[O]	25.04	25.31	22.99	23.01
[S]	10.04	9.82	7.68	7.47

check this, aromatic thiol **6**, with relatively higher acidity ($pK_a \approx 6$) was employed. In this case, 50% conversion was observed while using 8 mol% of the catalyst and a reaction time of 12 hours at 25 ºC (Table 3). An increase in the catalyst loading to 34.4% ensured a quantitative conversion of the epoxide units of polymer **3** into the targeted thio-ethers. These results confirmed that TEA could be used in THF as a base for functionalization with aromatic thiols. However, significant amount of time and catalyst were required for full functionalization. To further check the suitability of TEA as a catalyst involving aliphatic thiols, the reaction medium was changed to a more polar solvent dimethylsulfoxide (DMSO). It should be mentioned that due to the toxic nature of DMSO, the present study does not employ it as a primary reaction medium. Nonetheless, 20% conversion of the epoxide units was observed in this case (Table 4). An increase in the reaction temperature to 50 ºC led to a higher degree of conversion (55%). An increase in the amount of the thiol reactant (1.5-1.75 eq./epoxy) and the catalyst loading (68-81 mol%) was necessary to achieve conversions of 85% and higher.

Next, tetrabutylammonium fluoride (TBAF), known for its catalytic properties in the thiol-epoxy reaction,[68] was employed and THF was used as the reaction medium. At 1.2 mol% catalyst loading and 1 hour of reaction time, 7% conversion of the epoxy units was observed (Table 2 and Figure 4). An increase in the catalyst loading to 8% resulted in significant improvement (85%) in the degree of epoxide group conversion. Therefore, the reaction time was increased to 3 and then 12 hours. However, the conversion did not change appreciably. Therefore, an increase in the catalyst loading was applied. In this case, a catalyst loading of 20.7 mol% was sufficient to lead to a quantitative epoxy-group conversion in three hours of the reaction time at room temperature. Use of the aromatic thiol **6** produced similar results. In comparison to TEA, TBAF, therefore, offers a better choice due to its generality (aliphatic and aromatic thiols), low duration for complete consumption of the epoxide units, and the comparatively lower required catalyst loading.

Finally, lithium hydroxide (LiOH) was employed as the reaction catalyst and aqueous THF (10% water) was used as the reaction medium.[69] In this case, at the catalyst loading of 1.2 mol% and a reaction time of 1 hour, 90% conversion was achieved (Table 2 and Figure 5). An increase in the catalyst loading to 3.6 % already resulted in complete conversion of the epoxy groups at 25 ºC and in an hour of reaction time. Similar results were obtained while using aromatic thiol **6** (Table 3). Therefore, in comparison to TEA and TBAF, LiOH performed much better. These results indicated that LiOH was the best choice as a catalyst due to its minimal amount required and the short duration of the reaction time.

GPC analysis confirmed that the thiol-epoxy functionalization



Scheme 4. Esterification of polymer **5**.

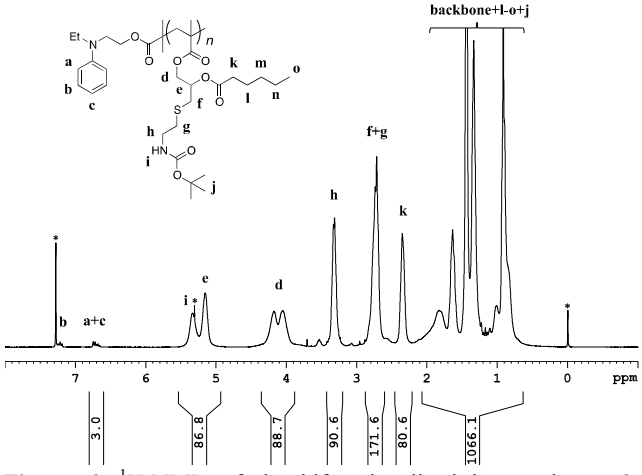


Figure 6. ^{1}H-NMR of the bifunctionalized homopolymer **9**. Residual solvent signals are marked with an asterisk.

reaction did not influence the molecular weight distribution of the precursor polymer (Figure 2). This analysis was deliberately carried out in dimethylformamide (DMF) and at higher temperature (45 ºC) to ensure that the hydroxyl groups and the amide groups of the functionalized polymer **5** did not engage in inter- or intra-molecular hydrogen bonding communications or unfavorable adhesion interactions with the stationary phase. Elemental analysis confirmed the chemical composition of the polymers (Table 5).

Second Functionalization through Esterification Reaction

The hydroxyl groups generated as a result of the first functionalization reaction were used as anchor points for the attachment of a second functional group to the polymer repeat unit (Scheme 4). For this, the hydroxyl groups of polymer **5** were involved in an esterification reaction with an acid chloride molecule **8**. In order to determine the extent of the esterification reaction, once again, the three-proton resonance signal (6.7 ppm) arising from the polymer chain-end was compared with the area integration of the proton located at the methylene carbon atom adjacent to the newly formed ester group (Figure 6). This analysis indicated that use of 1.25, 1.5, and 1.75 equivalents (per hydroxyl group) of the acid chloride molecule led to a 70-80% conversion of the hydroxyl units into the ester moiety. An excess of the activated acid (2 eq./OH) was necessary to achieve a quantitative conversion of the secondary hydroxyl group into the ester moiety. GPC analysis suggested that the polydispersity index remained constant after the second functionalization as well (Figure 2). However, an unexpected shift to a higher retention time was observed for bifunctionalized polymer **9** when compared to the precursor polymer **5**. It is likely that introduction of an alkyl chain at each repeat unit renders the polymer chain with a

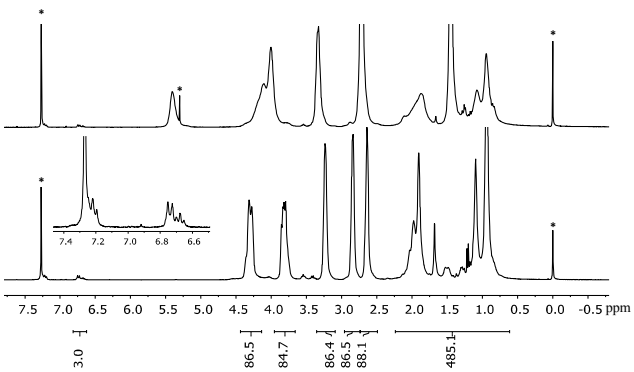


Figure 7. ^{1}H-NMR of the higher molecular weight reactive scaffold (DP = 86) (bottom) upon application of the optimized thiol-epoxy (top) reaction.

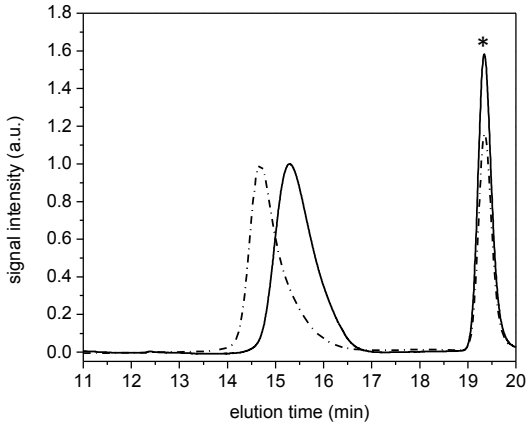


Figure 8. GPC traces of the lower molecular weight (solid line) and higher molecular weight (dash dot line) reactive scaffold **3**.

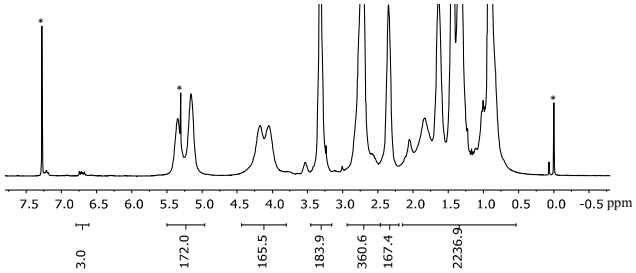


Figure 9. Esterification of the higher molecular weight polymer **5**.

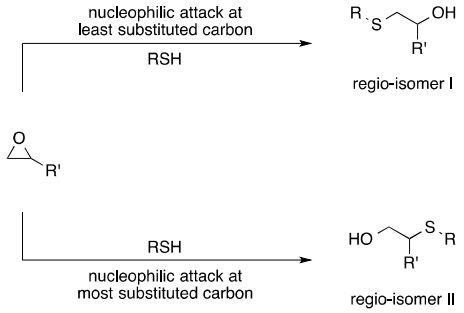
hydrophobic character unlike its precursor polymer. This may result in a decrease in the hydrodynamic volume due to a solvophobically driven collapse of the hydrophobic polymer coil in a polar solvent such as DMF. Once again, elemental analysis confirmed the chemical composition of the bifunctional polymer repeat unit (Table 5).

Application of Higher Molecular Weight Reactive Scaffold

In an attempt to examine the generality of the optimized reaction conditions, the primary reactive scaffold **3** was prepared with higher molecular weight ($DP_{(NMR)}$ = 86, $M_{w(GPC)}$ = 12200, $M_{n(GPC)}$ = 16300, M_w/M_n = 1.3) attributes. Once again, end-group signals from the initiator were used to determine the degree of polymerization through area integration analysis in NMR spectroscopy (Figure 7). This analysis confirmed that the degree of polymerization in the newly synthesized poly(glycidyl methacrylate) was two times higher than the previously used reactive scaffold. GPC analysis also corroborated this conclusion as the retention time of the newly prepared scaffold was significantly shifted to the lower side as compared to the previously studied poly(glycidyl methacrylate) (Figure 8). Once again, a narrow elution curve indicated good control over the polymerization process. Having this higher molecular weight scaffold in hand, initially, the first functionalization reaction through the thiol-epoxy reaction was studied under the optimized reaction conditions. For this, in case of TBAF, 20.7 mol%, and in case of LiOH, 3.6 mol%, of the catalyst loading was employed. The reactions were carried out for 1 (for LiOH) and 3 (for TBAF) hours. ^{1}H-NMR analysis revealed that in both cases complete consumption of the epoxy group could be accomplished (Figure 7).

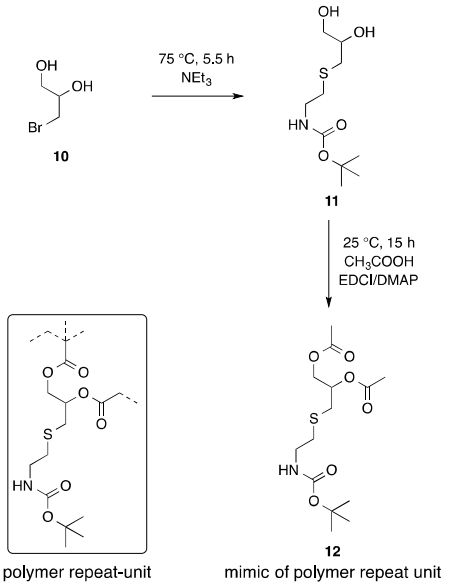
In order to study the next aspect, the resulting higher molecular weight polymers were subjected to the second functionalization through the esterification reaction with molecule **8**. Once again, application of the aforementioned optimized conditions for the esterification reaction resulted in quantitative conversion of the hydroxyl groups into the desired ester functionalities (Figure 9). These experiments established the generality of the optimized conditions.

Regio-chemistry Aspects



Scheme 5. Two possible regio-isomers expected from a thiol-epoxy reaction.

In a nucleophilic ring-opening reaction of asymmetric epoxides, two regio-isomers can form (Scheme 5). It is the reaction conditions that decide the structure of the formed product. In the presence of a strong thiolate anion (under basic conditions) and a poor leaving group (an alkoxide anion), an S_N2 pathway prevails and the best target for the nucleophile to attack is the least hindered carbon atom. Therefore, isomer I is formed under basic conditions. Under acidic conditions, however, the oxygen atom of the epoxide is protonated, creating a good leaving group and building up a positive charge on the most substituted carbon atom as this carbon atom is best suited to stabilize a positive charge. The nucleophilic attack in this case, therefore, comes at the most substituted carbon atom as it holds a greater degree of positive



Scheme 6. Synthesis of a regio-isomer mimic type I of the bifunctional polymer repeat unit.

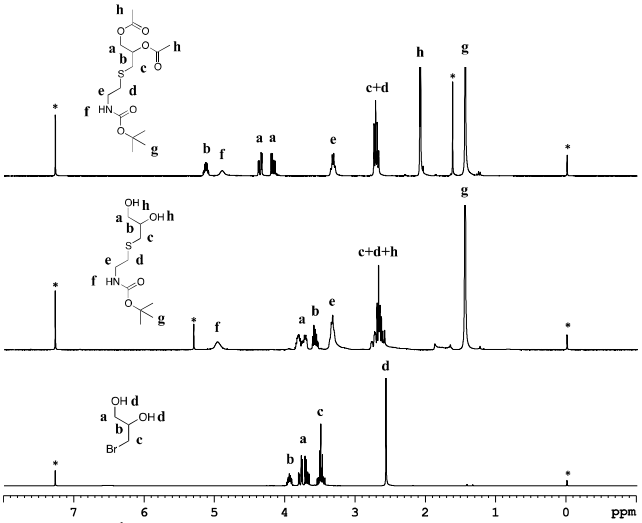
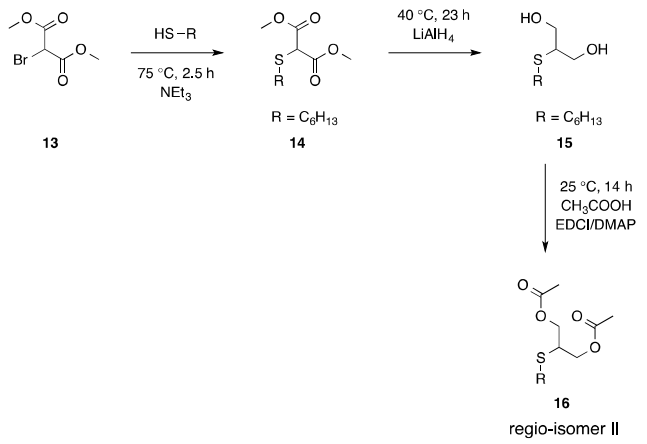


Figure 10. ^{1}H-NMR of the compounds **10**, **11**, and the polymer repeat unit mimic **12**.

charge. This results in the formation of regio-isomer II. It is likely to assume, therefore, that under present conditions, the bifunctional polymer repeat units are composed of regio-isomer I. To experimentally confirm this notion, a model compound study was conducted. In this study, it was decided to prepare an isomer I mimic of the bifunctional polymer repeat unit starting from a non-epoxide precursor so as to have no ambiguity about its structure. To achieve this, the bromine group of compound **10** was displaced by thiol **4** (Scheme 6). The hydroxyl groups of **11** were then modified through an esterification reaction with acetic acid. This led to the formation of compound **12**. The arrangement of the functional group in this molecule was identical to regio-isomer I. The most significant proton resonance of **12** is perhaps from the proton located at the tertiary carbon atom (designated 'b' in Figure 10). This signal could be observed at 5.1 ppm. A comparison with the ^{1}H-NMR of the bifunctional polymer



Scheme 7. Synthesis of a regio-isomer II.

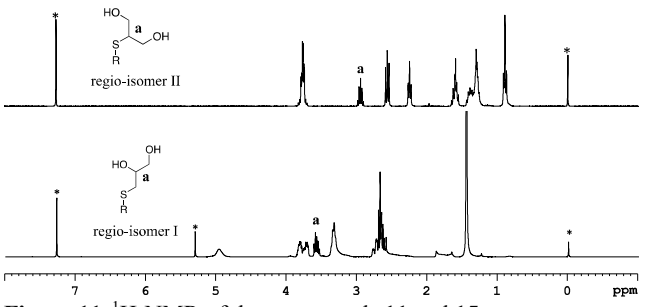


Figure 11. ^{1}H-NMR of the compounds **11** and **15**.

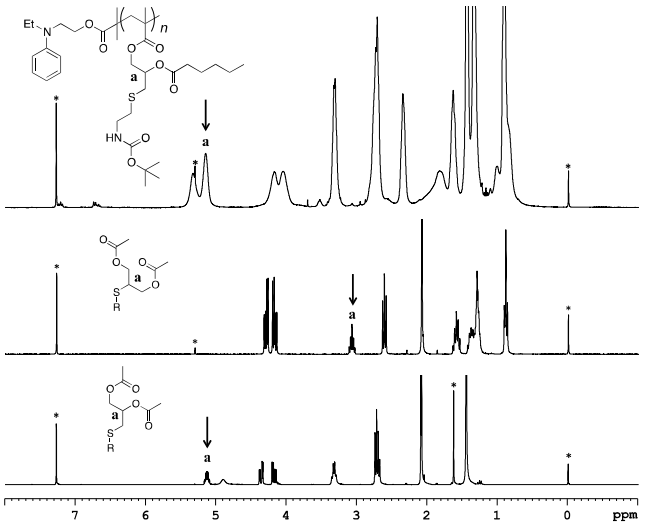


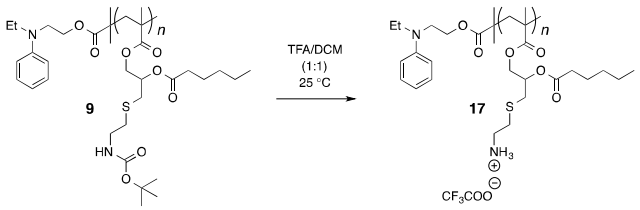
Figure 12. ^{1}H-NMR of the polymer **9** and compounds **12** and **16**.

revealed that this proton resonated at nearly the same position. This suggested that the repeat unit of polymer **9** was composed of regio-isomer I. However, to further prove this, a small molecule mimicking the structure of the regio-isomer II was synthesized (Scheme 7). In this scheme, newly prepared compound **15** represented a mimic of regio-isomer II and could be compared to compound **11** that represented the mimic of regio-isomer I. This comparison revealed that the proton located at the tertiary carbon atom resonated at 2.9 ppm in the case of regio-isomer II (Figure 11). No such signal could be seen in the ^{1}H-NMR of polymer **5** indicating that thiol-epoxy reaction on polymer **3** did not produce

any regio-isomer II. To further confirm this, molecule **15** was esterified with acetic acid because both of these hydroxyl units are present as an ester group in the final bifunctional polymer structure. A comparison could then be performed in the ^{1}H-NMR spectra of polymer **9** and molecules **12** and **16** (Figure 12). This comparison established that the repeat unit of the bifunctionalized structure resembled mimic I (**12**). It can be concluded, therefore, that the thiol-epoxy reaction in the present system exclusively forms regio-isomer I.

Transformation into an Amphipathic Structure

Polymers carrying a positively charged site and a lipophile may display antibacterial and cell penetration properties.[70-71] In the present case, the two active residues will reside on the same repeat unit. To demonstrate this, the *t*-Boc group of polymer **9** was removed under acidic conditions at room temperature in one hour of reaction time (Scheme 8). The signal arising from the *t*-Boc group at 1.5 ppm completely disappeared after the reaction and suggested complete removal of the protective group. This resulted in the formation of the ammonium group at each polymer repeat unit. The signal from the ammonium group could be observed at 8.2 ppm in deuterated dimethysulfoxide (Figure 13). The transformation of the completely neutral polymer **9** into a cationic polymer **17** imparted water solubility to the material. The ^{1}H-NMR, therefore, could also be measured in deuterated water. In water, the signal arising from the ammonium group disappeared due to a fast exchange of the protons with deuterium (Figure 13).



Scheme 8. Removal of the *t*-Boc group and preparation of amphipathic homopolymer **17**.

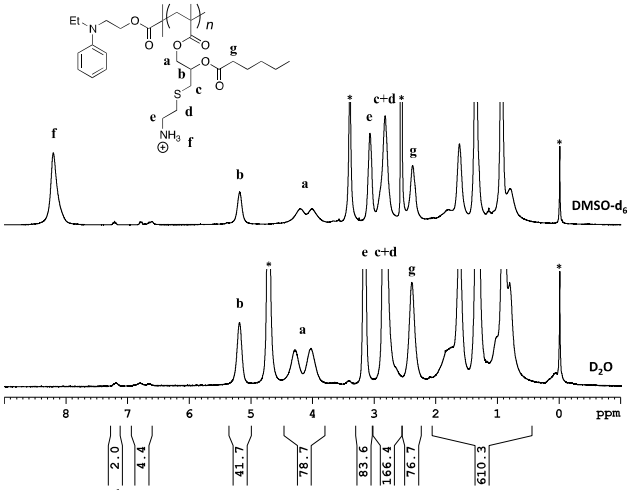


Figure 13. ^{1}H-NMR of the amphipathic polymer **17** in deuterated DMSO and water. Residual solvent signals are marked with an asterisk.

Conclusions

The conclusions drawn from this work can be listed as follows.

1. TBAF in THF, and LiOH in aqueous THF (10% water) are good catalyst choices for thiol-epoxy reactions involving aliphatic and aromatic thiols.
2. Low conversions are observed at a TBAF loading of 1.2-3.6 mol% for reaction times of 1-3 hours. An increase in the catalyst loading to 5.9-8% results in significant conversions (up to 85%). Longer reaction times (12 h) do not improve the extent of reaction. Rather, an increase in the catalyst loading to 20.7 mol% is required to achieve a quantitative conversion of the epoxy groups into the targeted thio-ethers in a reaction time of 3 h.
3. LiOH is the best catalyst as quantitative conversions are obtained at a catalyst loading of 1.2-3.6 mol% and a reaction time of 1-3 hours.
4. TEA can be employed in THF as a catalyst while using aromatic thiols. However, high catalyst loading (34.4%) and long reaction times (12 h) are required for quantitative conversions at room temperature.
5. TEA can also be used in the case of aliphatic thiols, however, even higher catalyst loading (68-81%), higher thiol content (1.5-1.75 eq./epoxy unit), higher temperature (50 ºC), and DMSO as a reaction medium are necessary for achieving high conversions (≥85%).
6. The secondary hydroxyl units can be converted into desired ester functionalities. However, an excess of the activated acid (2 eq./OH) is required to achieve quantitative hydroxyl group conversion.
7. Area integration analysis (^{1}H-NMR) and elemental analysis suggests that structurally precise bifunctionalized homopolymers, carrying a 1:1 functionality ratio per polymer repeat unit, can be obtained through sequential thiol-epoxy and esterification reactions starting from a general poly(glycidyl methacrylate)-based reactive scaffold.
8. A careful model compound study suggested that the attack of the thiolate anion occurs at the least hindered carbon atom of the pending glycidyl unit of the polymer chain and regio-isomer I forms exclusively upon thiol-epoxy functionalization in the present synthetic scheme.

It is anticipated that these guidelines will help the researchers interested in employing the thiol-epoxy reaction for polymer synthesis (from small molecules) as well as for single post-polymerization modification purposes. More importantly, realization that double-modifications involving the thiol-epoxy and the esterification reaction of a general and easily accessible polymer scaffold can produce chemically precise materials in a facile manner is expected to assist in further expanding their use and ascertaining their new properties and applications.

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Notes and references

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