Poly(ß-hydroxy thioether)s: Synthesis through Thiol-Epoxy ‘Click’ Reaction and Post-Polymerization Modification to Main-Chain Polysulfonium Salts

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Poly(ß-hydroxy thioether)s: Synthesis through Thiol-Epoxy ‘Click’ Reaction and Post-Polymerization Modification to Main-Chain Polysulfonium Salts

The base-catalyzed reaction between thiol and epoxide functionalities is a simple process that can be carried out under ambient conditions. The base catalyst can be organic or inorganic. The reaction medium can be organic or aqueous. A variety of the required mercapto/oxirane-containing building blocks can be obtained from commercial sources. The reaction is highly efficient and regioselective. It is due to these attributes the thiol-epoxy reaction is referred to as a ‘click’ reaction. It produces a ß-hydroxy thioether linkage upon completion. The thioether group can be modified by a post-polymerization alkylation reaction to access antibiofouling and antibacterial ß-hydroxy sulfonium salts. Overall, therefore, the thiol-epoxy reaction is highly utilitarian in the context of polymer synthesis. Our aim in this article is to trace our own steps in this area of research and document the journey from initial simple synthetic efforts to the current functional materials prepared by the thiol-epoxy ‘click’ reaction.

Keywords: Polythioethers; Polysulfonium Polyelectrolytes; Thiol-Epoxy Reaction; Click Chemistry; Sulfur Alkylation

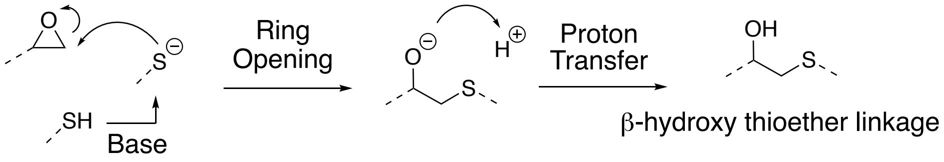
Introduction

The advent of ‘click’ chemistry revolutionized the manner in which polymeric materials are being prepared.[1] A ‘click’ reaction is a modular and efficient process with ease of operation and a broad scope.[2] In 2012, we observed that poly(glycidyl methacrylate)s containing a number average of 12,000 repeating units (P_n) could be quantitatively modified into side-chain thioethers through ring-opening reaction with the thiol nucleophiles.[3] This process required only three hours of reaction time under ambient conditions. The polymeric glycidyl scaffolds are commercially available and could also be prepared by free radical polymerization techniques.[4-5] Furthermore, the thiol reactants could also be polymeric in nature thus giving rise to molecular bottlebrushes upon ring-opening reaction.[6] Later studies involved a systematic optimization of the reaction conditions,[7] confirmation of regiochemistry,[7] preparation of dendrimers,[8] and establishment of 1:1 stoichiometry of the reactants.[9] Recently, sterically demanding thiol reactants based upon a fragment of fullerene C_{60}, corannulene, is also shown to be applicable in this synthetic strategy.[10-11] Overall, these results confirmed the 'click' nature of the thiol-epoxy reaction.[12]

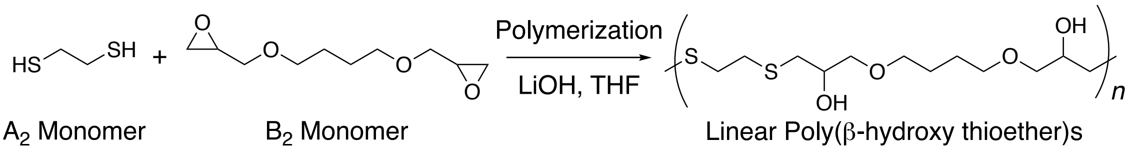
In parallel to the aforementioned post-polymerization modification efforts of glycidyl polymers,[13-15] we also considered the potential of the thiol-epoxy reaction as a polymerization process. Since a variety of small molecules carrying thiol and epoxide groups are commercially available, we reasoned that such a polymerization would be highly practical and would lead to the formation of a polythioether backbone. Due to the presence of a ß-OH group, we named the new polymer family as poly(ß-hydroxy thioether)s.[16] In this review article, our aim is to discuss this particular aspect of the thiol-epoxy 'click' chemistry, i.e., its application as a polymerization process. The discussion is not meant to be an exhaustive treatment of the topic but rather a personal account of the developments in the field.

Linear Polymers

Prior to discussing concrete examples, a brief mention of the polymerization mechanism appears to be reasonable. We often refer to the polymerization process as a 'proton transfer polymerization'. This is because protonation of the alkoxide anion, formed from the nucleophilic attack of thiolate on the epoxide group, is the critical step that stops an anionic ring-opening polymerization from occurring (Scheme 1). The anionic polymerization would have given rise to a poly(ethylene glycol)-based polymer backbone. Therefore, the protonation of the alkoxide anion is critical in determining the polymerization mechanism and forming a polythioether backbone. Hence, the polymerization is often referred to as a ‘proton transfer polymerization’.

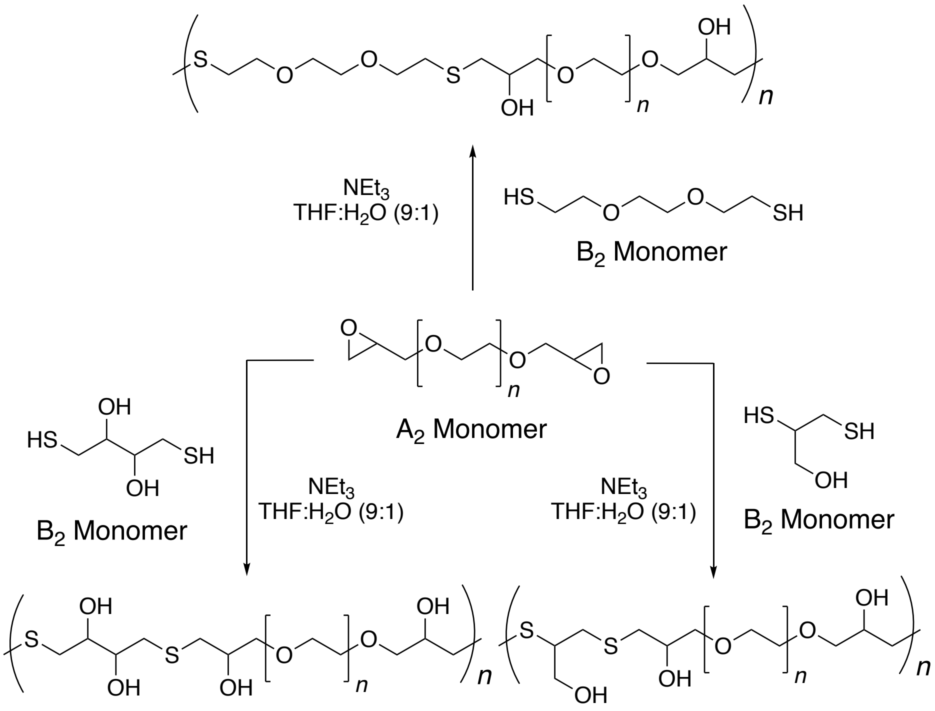


Scheme 1. The sequence of ring-opening and proton transfer gives access to the thioether linkage.



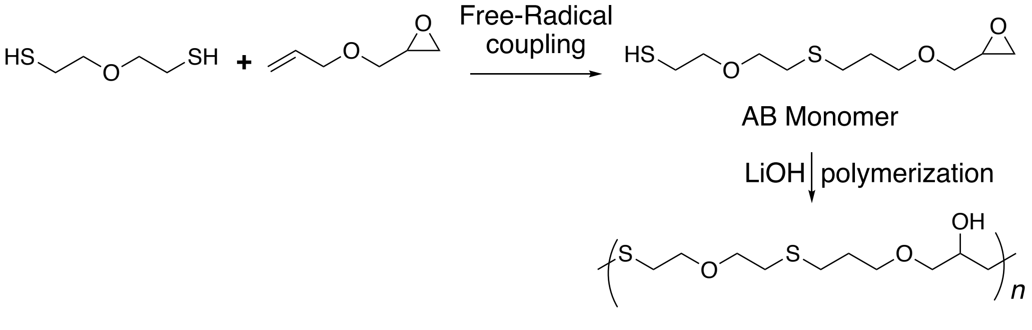
Scheme 2. Synthesis of a linear polymer through application of an A_2/B_2 monomer system.

In terms of monomers, a number of bis-thiol and bis-epoxide molecules are commercially available. In 2012, we used 1,2-ethanedithiol and 1,4-butanediol diglycidyl ether as A_2- and B_2-types of monomers (Scheme 2).[16] In terms of the base catalyst, we utilized lithium hydroxide. The resulting polymer was a viscous low T_g material with number average molecular weight of approximately 5000 g/mol and a dispersity index (PDI = M_w/M_n) of 2.3. The low molecular weight and broad dispersity was not unreasonable. It is typical of a step growth polymerization process utilizing an A_2/B_2 monomer system. Such a system is highly sensitive to a 1:1 functional group balance. A failure to meet this requirement prevents the formation of high molecular weight polymers as the excess functionality can act as a chain terminator.[17] In the present system where we used commercially available monomers without any further purification, the functional group imbalance is a surety due to impurities present in the monomers. On the positive side, however, direct use of an A_2/B_2 system translates to a practical polymer synthesis as a number of monomers can be accessed from the commercial suppliers. For instance, poly(ethylene glycol)-based di-glycidyl ethers can be combined with dithioerythritol, dithioglycerol, and dioxaoctanedithiol to make water-soluble poly(ß-hydroxy thioether)s in a large scale (Scheme 3).[18]



Scheme 3. Synthesis of a hydrophilic polymer family through use of ethylene glycol-based diglycidyl ether as a monomer.

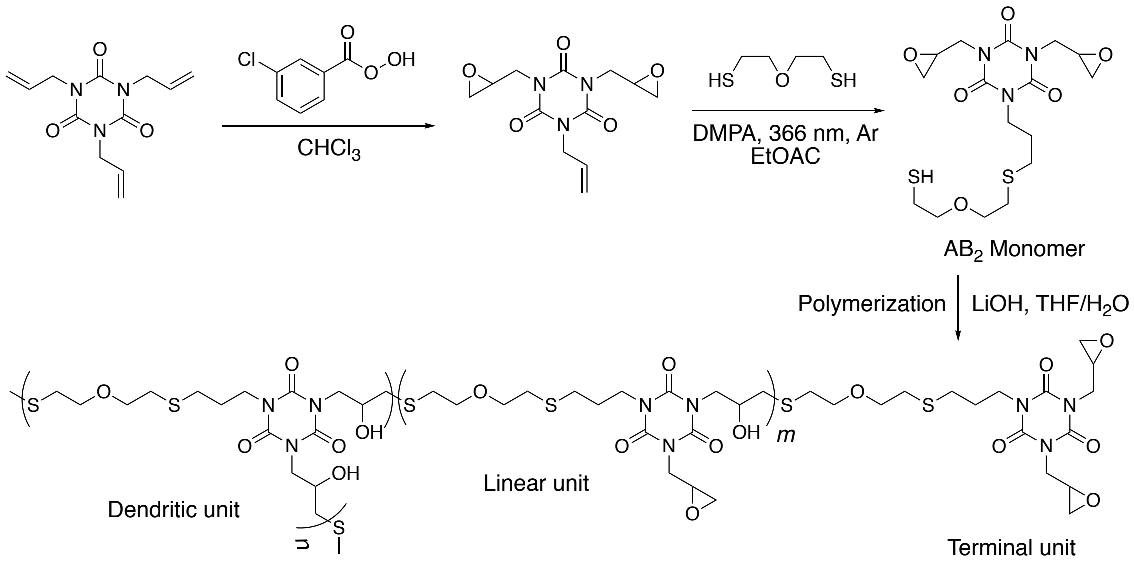
The A_2/B_2 monomer system, therefore, is clearly useful and practical. However, for the sake of academic curiosity, an AB monomer system that inherently ensures a 1:1 functional group balance attracted our attention. To synthesize such a molecule, the active functionalities must be placed on the same molecule. This poses issues during preparation, purification, and storage as the monomer contains mutually reactive sites. However, higher degrees of polymerizations are expected due to the functional group balance in the monomer.[17] Therefore, we set out to synthesize a molecule carrying both the thiol and the epoxide functionalities.[19] Thiols are good nucleophiles under basic conditions and epoxides are sensitive to acidic conditions. Therefore, acidic or basic conditions could not be used in the preparation of the required AB monomer. We, therefore, turned our attention to the free radical chemistry. Free radical chemistry offers chemically neutral reaction conditions and thiols are known to participate efficiently in such processes especially with olefins as the coupling partner. Therefore, to access an AB monomer, a thiol group of bis-mercaptoethyl ether was allowed to couple with an alkene functionality of allyl glycidyl ether under ambient light and aerobic conditions at room temperature. Such chemically neutral conditions furnished the desired AB monomer (Scheme 4). As anticipated, polymerization of the AB monomer led to polymers with relatively higher molecular weights. The best results were obtained using solvent-less (bulk) polymerizations. The precipitation in ethyl acetate and hexane mixture furnished the polymers in quantitative yields. This meant that no fractionation happened during the precipitation process. The polymers possessed number average molecular weight of 23-24 kDa. In terms of number average degree of polymerization (P_n), the average number of repeating units in these polymers is calculated to be about 100. These numbers indicate that the high molecular weight fraction must boast much larger degree of polymerizations.



Scheme 4. Synthesis of a linear polymer through application of an AB monomer system.

Hyperbranched Polymers

A more complex monomer structure is an AB_2-type of monomer containing two epoxides and a thiol group (Scheme 5).[20] The branching in the monomer leads to introduction of branching points in the polymer chain. Thus highly branched structures can be synthesized. Once again, free radical synthesis paved the way to the required monomer and the thiol-epoxy polymerization gave access to the hyperbranched structures with 69% degree of branching. The polymers also contained about 5% of disulfide-based structural defects. Since the polymerization is carried out under air, such structural defect formation is unavoidable. However, as shown in a recent study, use of sodium borohydride would ensure that disulfide defects could be activated in-situ to give back the thiolate anion.[9] Such a procedure, however, is only applied thus far for side-chain modification purposes.

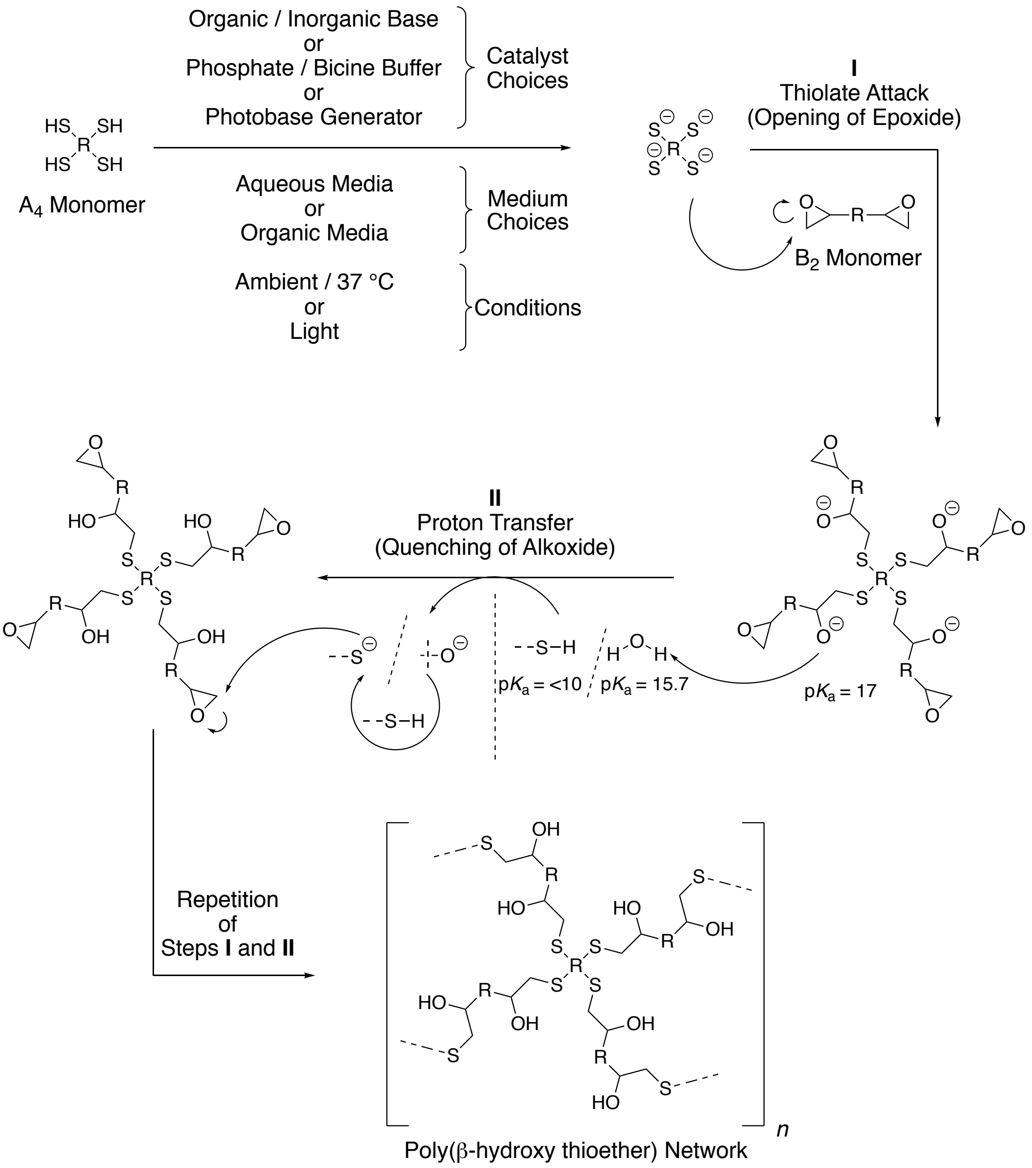


Scheme 5. Synthesis of a hyperbranched polymer through application of an AB_2 monomer system.

Polymer Networks

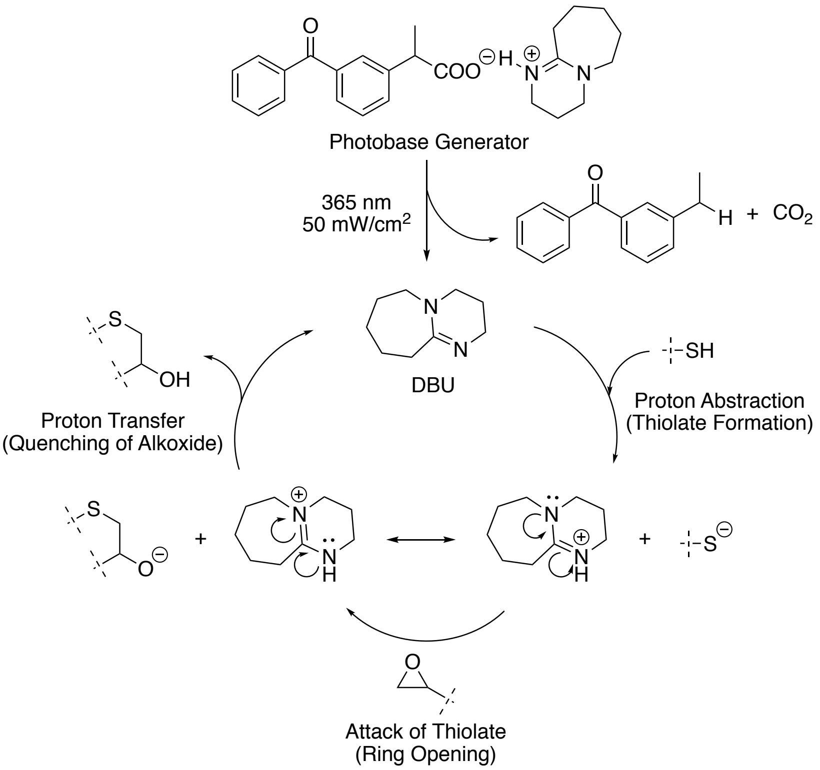
A natural evolution of the aforementioned chemistry is to increase the number of reactive functionalities (A/B) further (>3) to prepare network polymers (Scheme 6). For instance, a tetra-thiol would represent an A_4 monomer and a bis-epoxide would represent a B_2 monomer.[21] In such a case, inter-chain crosslinking can lead to gelation and formation of a network polymer. To test feasibility of such a concept, initially, a poly(ethylene glycol)-based bis-epoxide monomer was employed. Due to the hydrophilic nature of this monomer, the networks can be regarded as hydrogels as they are capable of holding a large amount of water. Interestingly, introduction of poly(dimethyl siloxane) (PDMS)-based bis-epoxide monomers into the networks enhances the mechanical properties of the hydrogels.

This initial study was encouraging and motivated us to study the gelation in more depth.[22] Initially, we scanned gelation medium and found that phosphate and bicine-based buffer systems are efficient gelation media in which a catalyst is not required for the gelation due to the alkaline nature of the buffers. Alternatively, pure water can also be employed for this purpose. However, a base catalyst is required for the gelation to happen in water. The base can be organic such as 1-methylimidazole and triethylamine or inorganic such as lithium hydroxide. The strength of the base catalyst ultimately controls the gelation kinetics and the latter two systems are much faster with gelation time of a few minutes. Besides ambient and thermal crosslinking, a photochemical method is also applicable in the present synthesis. For example, photochemical release of a biguanide base allowed the gel formation under irradiation with UV light. The modularity of the synthesis allowed for use of polymeric as well as small molecule-based thiol and epoxide precursors. The small molecules, however, are insoluble in aqueous medium. Therefore, the nature of the polymerization medium can be adjusted to include organic solvents such as tetrahydrofuran or acetonitrile. The mechanical and water-uptake properties are adjustable and can be controlled by the chemical structure of the precursors and the gelation conditions.



Scheme 6. Synthesis of a network polymer through application of an A_4/B_2 monomer system in a thiol-epoxy 'click' polymerization process.

The aforementioned photochemical crosslinking encouraged us to investigate this aspect of the thiol-epoxy 'click' reaction in a more systematic fashion (Scheme 7).[23] For this, we prepared a photolabile salt through complexation of diazabicycloundecene (DBU) with benzoylphenylpropionic acid (ketoprofen). Under illumination at a wavelength of 365 nm (50 mW/cm^2), the salt underwent a photodecarboxylation reaction to release DBU as a base. The base-catalyzed ring-opening reaction then created the crosslinked poly(ß-hydroxy thioether) patterns. The application of soft lithography techniques such as micro-molding in capillaries or imprint could be applied to fabricate micro- and nano-sized features under open-air and bench-top conditions.



Scheme 7. Photochemical activation of the thiol-epoxy ‘click’ polymerization process.

Availability of the ß-hydroxy Groups

Under basic conditions, the thiolate attacks the less-hindered site of the oxirane ring. Therefore, a ß-hydroxy group is created upon ring-opening reaction. The secondary nature of this functional group indicates its lower reactivity as compared to a primary hydroxy group. The steric hindrance caused by the polymer chain may cause a further lowering of chances for modification of such hydroxy groups. We noticed, however, that an access of an activated acid (acid chloride or anhydride) was enough to fully react the ß-hydroxy groups through an esterification reaction.[16,19-21] This strategy of post-polymerization functionalization could be successfully carried out on linear polymers, hyperbranched polymers, and hydrogels (Figure 1).[16,19-21] In linear polymers, the esterification reaction allows an opportunity to place a side-chain to the polymers. In hyperbranched polymers, the interior scaffold can be functionalized. In hydrogels, owing to the issues of the diffusion inside the crosslinked network, it is likely that the hydrogel surface is functionalized predominantly.

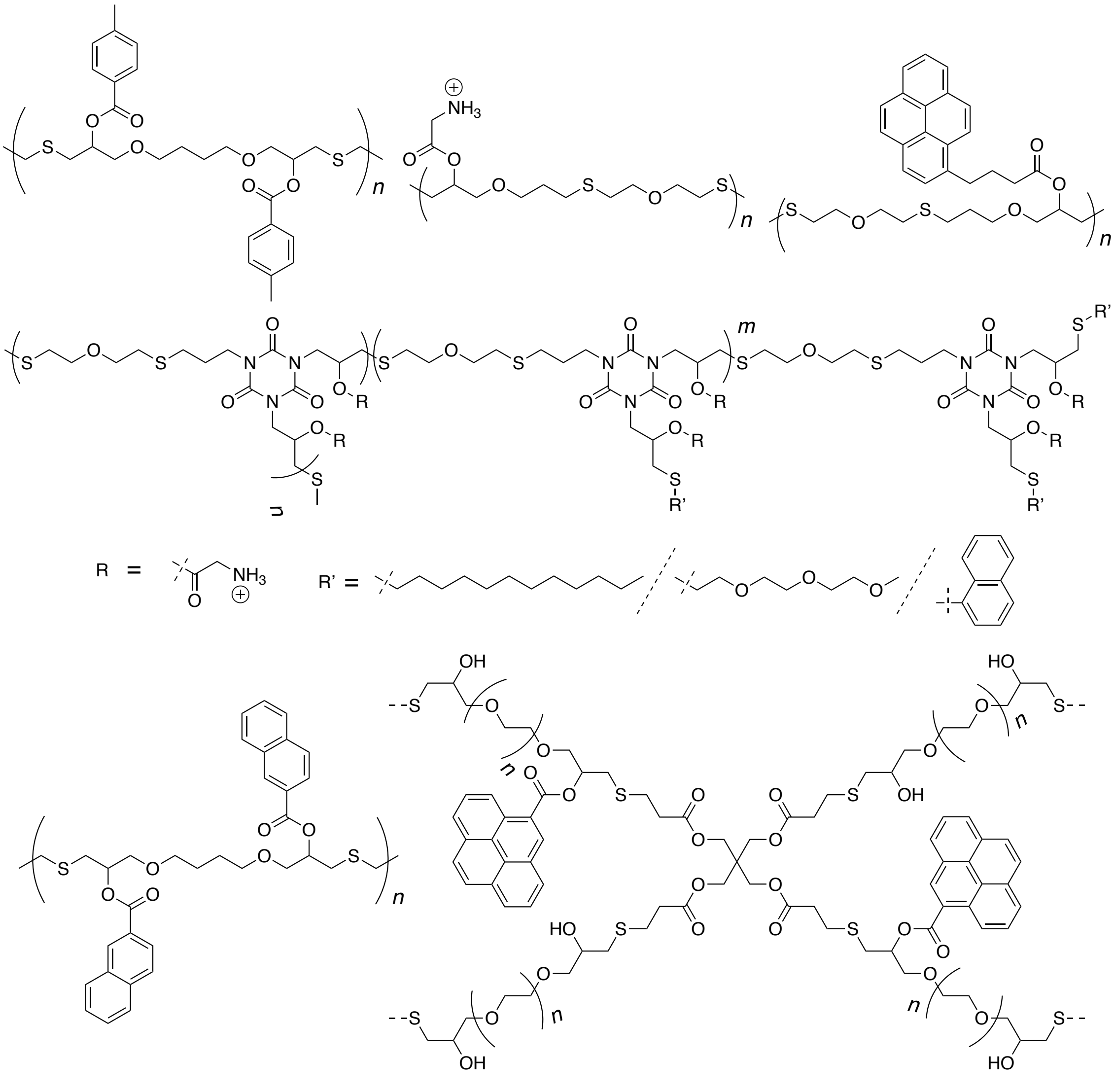
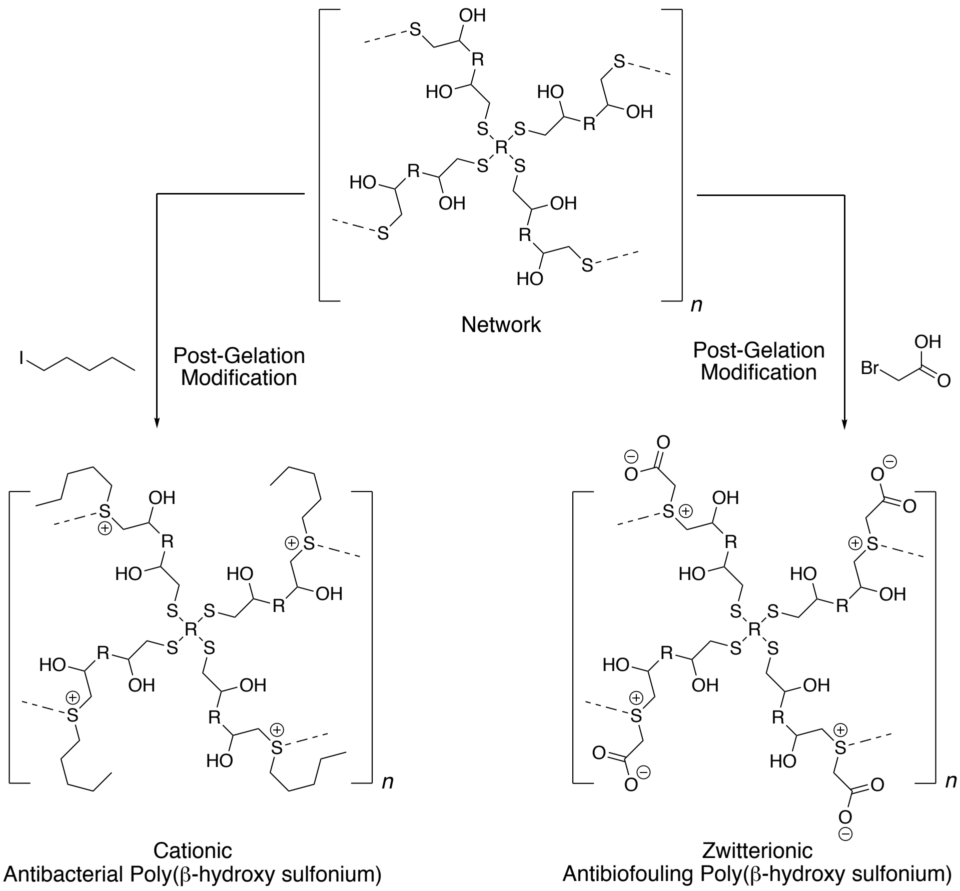


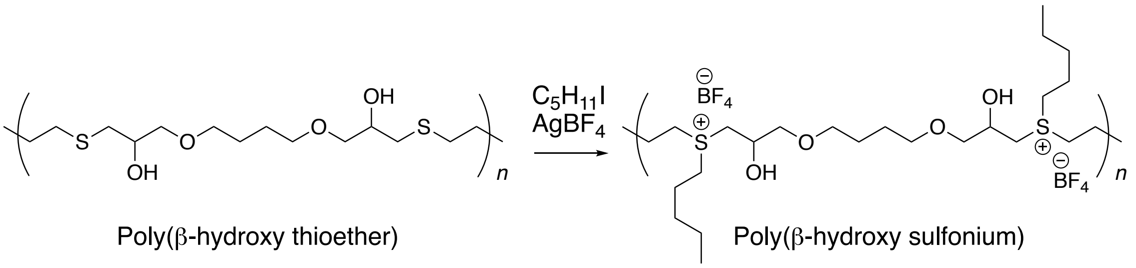
Figure 1. Employing the ß-hydroxy groups to functionalize poly(ß-hydroxy thioether)s.

Poly(ß-hydroxy sulfonium)s

In 2018, we reported an example of the main-chain poly(ß-hydroxy sulfonium)s through post-gelation alkylation of the sulfur atoms in the hydrogels discussed above (Scheme 8).[22] Naturally, The alkylation efficiency of these post-gelation modifications remains low (29-36%) due to the crosslinked nature of the network which hinders the reactants to fully diffuse and react in a uniform manner with the macroscopic materials. However, even with this low efficiency, the hydrogels exhibited potency against the negative bacterial strain *Escherichia coli* (*E. coli*). Thus far, polysulfonium salts were limited in their potency against only the positive bacterial strain such as *Staphylococcus aureus (S. aureus)*. This study, therefore, was the first study in indicating the antibacterial potential of the main-chain polysulfonium salts.[22] A later study further reinforced this notion by preparation of a large library of linear and soluble poly(ß-hydroxy sulfonium) salts (Scheme 9 and Figure 2).[24] These salts were highly effective against positive and negative both bacterial strains as only very little amounts of the polymers (10 μg/mL) were required to inhibit bacterial cell growth.



Scheme 8. Post-gelation modification of the thioether networks created by the thiol-epoxy ‘click’ reaction to access cationic and zwitterionic sulfonium salts.



Scheme 9. Antibacterial polysulfonium salt preparation through alkylation of thioether linkages.

The alkylation chemistry is modular and alkyl halides carrying a carboxylate or a sulfonate anion can be utilized for the post-polymerization modification purposes.[23] In such cases, since the sulfur alkylation result in the formation of the sulfonium cation, and an anion (carboxylate/sulfonate) is already part of the alkylating agent, a zwitterionic structure comes into being (Scheme 8). This concept is shown to work on patterned surfaces discussed before.[23] For example, reaction with bromoacetic acid produced a sulfonium/carboxylate-based zwitterionic motif. The functionalization efficiency was found to be 43%. The zwitterions endowed antibiofouling capability to the micropatterns. For instance, the unfunctionalized and functionalized patterns were both exposed to fluorescent protein bovine serum albumin (BSA) for a period of 24 hours and then examined with the help of fluorescence microscopy. This inspection indicated that the nonfunctionalized patterned surface allowed protein adsorption and appeared green upon photoexcitation. The modified patterned surface, however, did not allow protein adsorption and remained nonfluorescent under photoexcitation.

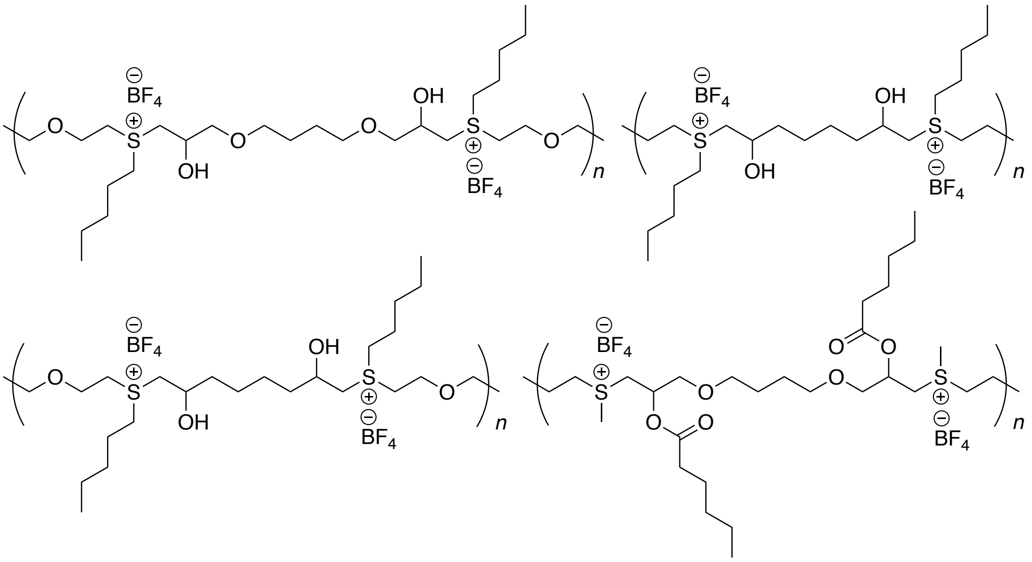


Figure 2. Chemical structures of sulfonium polyelectrolytes.

Conclusions

The examples discussed thus far indicate that the thiol-epoxy ‘click’ reaction is a useful synthetic tool in the preparation of main-chain polythioethers. In synthesis of linear polymers and networks, a number of commercially available monomers can be utilized. To access an AB or AB_2 monomer, however, requires monomer synthesis. The discussed free-radical chemistry is useful in achieving this goal. However, storage of the monomers carrying mutually reactive thiol and epoxide functionalities is impractical. Therefore, new synthetic strategies must be developed that allows a practical synthesis and storage capabilities of such monomers. A potential route is to protect the thiol group so that it does not interfere in monomer synthesis and renders stability to the monomer during purification and storage. However, once subjected to the polymerization conditions, the protective group can come off thus allowing the thiolate anion to form and the polymerization mechanism to be activated. Recent work from Gadwal and coworkers on the use of acetyl protective group is particularly interesting in this context.[25] The formation of disulfide defects is unavoidable in the present system as the polymerization reaction is carried out under ambient conditions. The recent use of sodium borohydride as an in-situ activating agent for the formation of thiolates in the thiol-epoxy ‘click’ reaction can be explored further to obtain defect-free thioether polymers.[9] Finally, the photochemical activation of the polymerization process and the use of poly(ß-hydroxy thioether)s as precursors to sulfonium salts can be combined to access patterned antibiofouling and antibacterial surfaces.

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