Synthesis of Multifunctional Homopolymers via Sequential Post-Polymerization Reactions

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Multifunctional homopolymers, homopolymers with multiple pendent functionalities, can offer unparalleled properties not possible with traditional polymers. Preparation of multifunctional homopolymers has been a challenge, but one promising approach involves sequential and selective post-polymerization modification of macromolecular precursors. Approaches considered thus far include the use of polymers that contain monomer units with masked reaction sites for successive functionalization or the use of orthogonal or chemoselective reactions. In this mini-review, we highlight recent developments in synthesis of multifunctional homopolymers via these routes and offer insight into the promise and utility of the resulting macromolecules for materials applications.

Introduction

As polymers find roles in virtually every aspect of our lives, methods for modifying and enhancing their utility have also developed.[1] Many reports describe new, innovative routes to furnish useful functional macromolecular materials; modifications can be made pre- or post-polymerization to introduce functionality to the backbone units or the polymer end-group.[2-4] Such progress in the field of functional polymers not only improves the properties of existing commercial polymers, but can also provide access to new, previously inaccessible materials. Among the various types of functional polymers, multifunctional homopolymers—defined here as homopolymers with multiple functionalities in every repeat unit—offer distinct characteristics due to their structural features and unique arrangement of functional moieties. Multifunctional homopolymers can offer several advantages over their monofunctional counterparts. As polymers continue to play an increasing role in more advanced applications, they are often called upon to demonstrate more than one property.[5, 6] For example, multifunctional homopolymers are excellent candidates for modifying surface properties because one moiety in each repeat unit can immobilize the polymer on the surface while the other group endows the substrate with a specific quality, such as anti-fouling character. Incorporating these distinct functional groups within a homopolymer microstructure, instead of a statistical copolymer, ensures that the two functionalities are incorporated uniformly, densely, and in an equimolar ratio.

Multifunctional homopolymers are typically prepared through post-polymerization modification, a useful approach for functionalizing polymers in which desired groups are introduced after the polymers are synthesized.[7-10] This modification strategy circumvents possible compatibility issues between desired functional groups and polymerization or processing conditions. Furthermore, an array of functional polymers can be prepared from a single reactive polymer. This modularity is advantageous because preparation of various functional polymers from one source allows for a systematic structure-property relationship study in which samples of identical degree of polymerization and backbone composition have varying functionality. One major requirement in this modification approach is that the transformation is efficient, a feat which is often challenging to achieve for polymers but is critical for obtaining a uniform product distribution.

Preparation of multifunctional homopolymers *via* post-polymerization modification comes with various challenges. Introduction of two functionalities can be sequential or simultaneous. The two most common strategies to achieve sequential introduction of two or more functionalities have been reported: either the use of polymers with a latent reaction site for successive functionalization or an orthogonal/chemoselective functionalization. Additionally, multi-component reactions, the subject of multiple reviews, have been extensively studied to simultaneously incorporate multiple functionalities within polymers.[11, 12] Furthermore, the introduction of amino acid moieties into polymer side chains can also simultaneously install more than one functional group.[13-15]

In this mini-review, we focus on various polymer modification techniques for obtaining multifunctional homopolymers *via* sequential reactions such as (i) a ring-opening of thiolactone followed by thiol-ene reaction, (ii) a ring-opening of glycidyl group followed by esterification, (iii) double orthogonal "click" reactions, and (iv) chemoselective nucleophilic aromatic substitution reactions (Figure 1). Several

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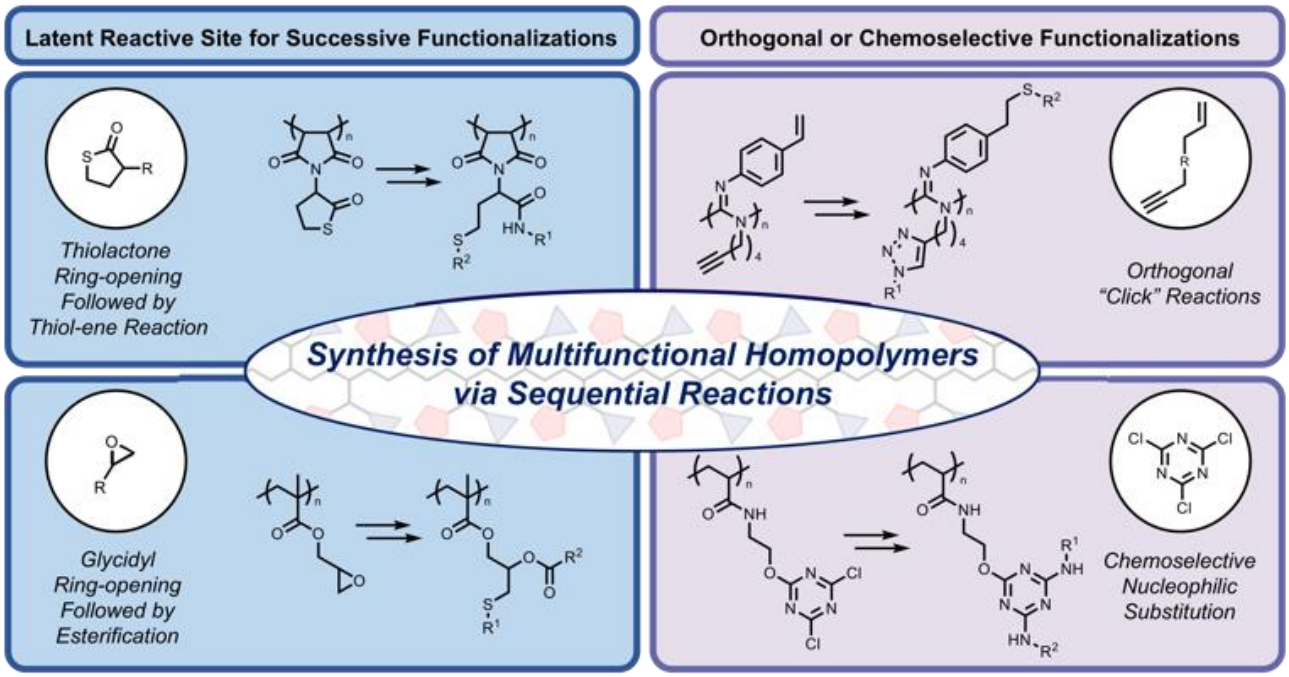


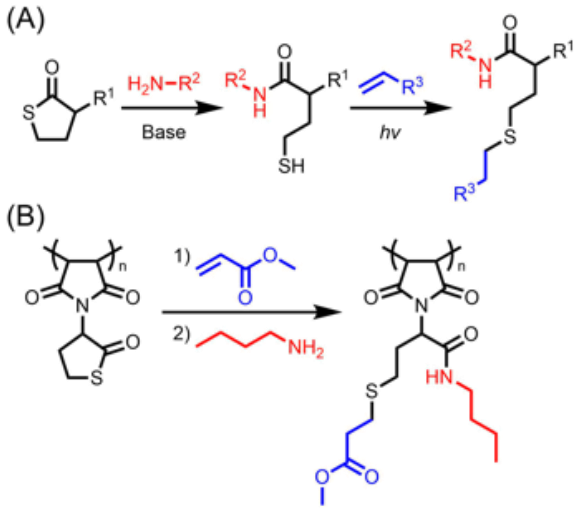
Figure 1. Various strategies for multifunctional homopolymer synthesis via sequential reactions

examples of applications utilizing these chemistries are discussed.

Polymers with a latent reaction site for successive functionalization

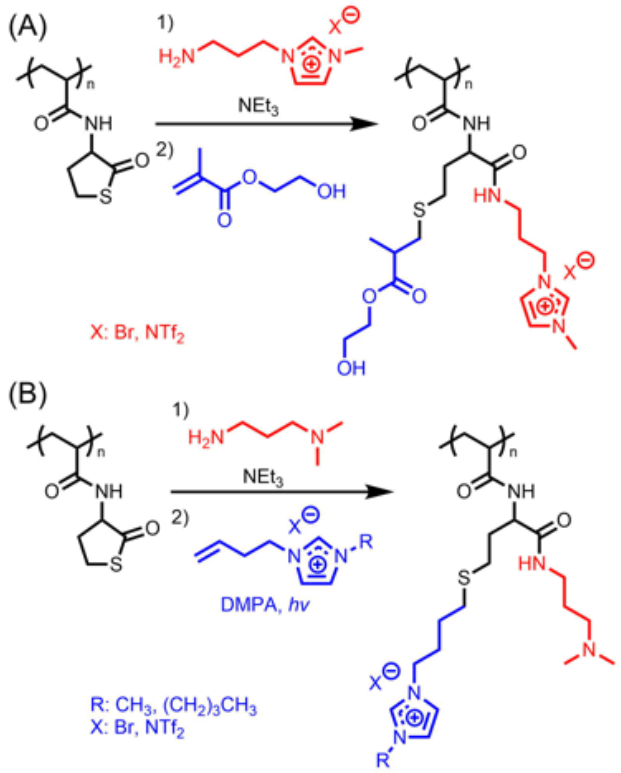
Espeel, Goethals, and Du Prez established the double modification strategy in polymers using thiolactone in 2011 (Scheme 1A).[16] Thiolactone, an analogue of a cyclic ester in which the endocyclic oxygen is replaced with sulfur, can undergo sequential functionalization. Specifically, an amine ring-opens the thiolactone to generate a thiol that can then react with acrylates (i.e., thiol-ene reaction) or thiols (i.e., disulfide formation). The sequential reactions can be performed metal-free, in one pot, and with high efficiency. Additionally, *in situ* generation of thiols upon ring-opening and rapid capping with a reactive partner circumvents potential issues associated with thiols such as undesirable odor formation and oxidative coupling. Using this thiolactone synthetic strategy, the authors synthesized both linear polymers and networks, thus demonstrating its utility in the synthesis of polymeric materials.

Scheme 1. (A) Double modification strategy using thiolactone group. (B) synthesis of multifunctional homopolymers through one-pot, double modification of thiolactone-containing polymers



Initial attempts to homopolymerize thiolactone-containing monomers with the ability to yield multifunctional homopolymers were not fruitful due to low solubility during the polymerization.[17] However, copolymerization with *N*-isopropylacrylamide was successful, and a variety of tunable stimuli-responsive polymers were synthesized *via* one-pot double modification of pendent thiolactone with amines and acrylates.[18] Rudolph and coworkers later demonstrated successful homopolymerization of a maleimide-based thiolactone-containing monomer (Scheme 1B). This development led to the formation of multifunctional homopolymers *via* double functionalization of thiolactone.[19] To modify thiolactones in each repeat unit, aliphatic amine (10 equiv) was added to a solution containing homopolymer (1 equiv) and acrylate (10 equiv). Efficient sequential functionalization *via* ring-opening of thiolactones with amines followed by thiol-Michael addition gave multifunctional homopolymers in one pot.

This thiolactone-based double modification strategy has also been applied for the preparation of ionic liquid multifunctional homopolymers (Scheme 2).[20] Polymeric ionic liquids demonstrate useful properties and have been studied for various applications, such as polymer electrolytes and fuel cell membranes. Despite general challenges associated with dealing with ionic liquids, incorporation of ionic liquids onto thiolactone-derived polymers was achieved by two approaches: (i) aminolysis with an ionic liquid containing a reactive amine

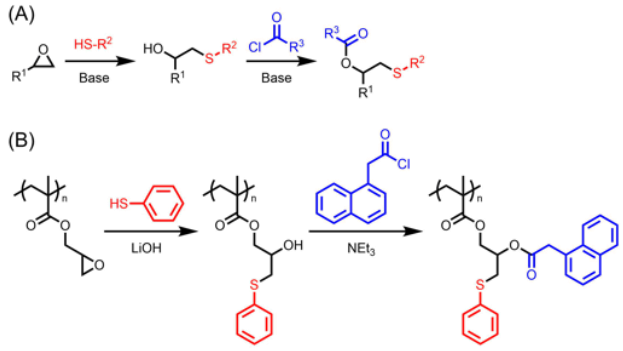


Scheme 2. Synthesis of polymeric ionic liquid multifunctional homopolymers *via* (A) ring-opening with an ionic liquid containing a reactive amine functionality and (B) thiol-ene reaction with an ionic liquid containing a reactive alkene functionality

functionality and (ii) thiol-ene reaction with an ionic liquid containing a reactive alkene functionality. Each approach successfully enabled the introduction of ionic liquids within polymers, thus extending the scope of multifunctional homopolymers and demonstrating the versatility of thiolactone chemistry for complex functional polymer synthesis.

In 2012, De and Khan reported the synthesis of a side-chain and chain-end multifunctionalization strategy using thiol-epoxy click reactions (Scheme 3A).[21] The authors envisioned that various advantageous features of thiol-based reactions—high efficiency, water and oxygen tolerance, benign reaction conditions, and versatility of thiol nucleophiles—could be exploited for functional polymer synthesis. To achieve the synthesis of multifunctional homopolymers, pendent glycidyl groups were conveniently installed through free-radical polymerization of glycidyl methacrylate (Scheme 3B). Base-

Scheme 3. (A) Double modification strategy using glycidyl group. (B) synthesis of multifunctional homopolymers *via* successive thiol-epoxy click reaction and esterification

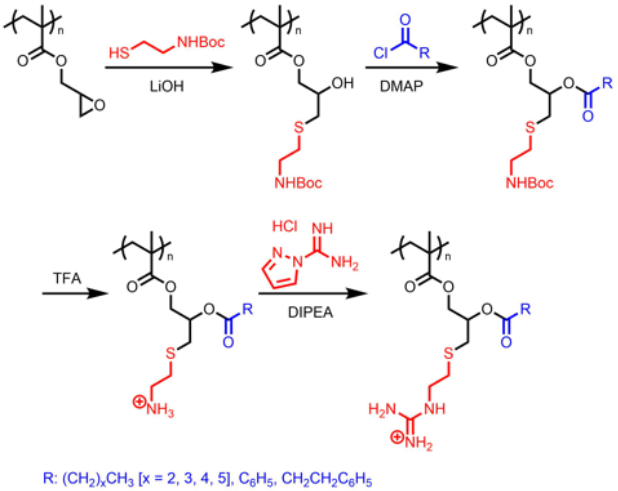


catalyzed ring-opening of the glycidyl group was performed using 2 equiv of thiols to introduce thioether functionalities while simultaneously furnishing a reactive secondary alcohol. Subsequent acylation with acid chlorides resulted in the successful introduction of the second group to furnish multifunctional homopolymers. Importantly, due to its versatility and ease of preparation, poly(glycidyl methacrylate) has been widely used as an effective scaffold to prepare a variety of well-defined functional polymers via sequential functionalization (e.g., azidation followed by copper-catalyzed azide-alkyne cycloaddition (CuAAC)).[22-24] Applications of poly(glycidyl methacrylate)s and their derivatives have been extensively studied and were the subject of another review.[25]

One application of this strategy is the synthesis of amphiphilic homopolymers for siRNA delivery (Scheme 4).[26] Amphiphilic homopolymers have been studied for various biomedical applications such as protein sensing and extraction.[27] Studies of cell viability and transfection capability were performed to elucidate how different hydrophobic and hydrophilic structures affect the performance of the polymer. Generally speaking, increasing the length of the hydrophobic segments resulted in a higher transfection efficiency, while ammonium-containing polymers demonstrated superior performance over guanidinium-containing polymers. Systematic study of this class of amphiphilic homopolymers was made possible through the preparation of various well-defined amphiphilic homopolymers *via* sequential post-polymerization modification reactions.

Each functionalization reaction was optimized, and the regioselectivity of ring-opening was determined to investigate the distribution of possible products.[28] LiOH generally outperformed TEA and TBAF as a catalyst for the thiol-epoxy ring-opening reaction. For the esterification reaction, 2 equiv of activated acid were required to achieve quantitative conversion. Lastly, ring-opening of the glycidyl group under basic conditions proceeded *via* a nucleophilic attack of the thiol to a less-substituted carbon of the epoxy ring, which was corroborated by a small molecule study.

Scheme 4. Synthesis of amphiphilic homopolymers through post-polymerization modification of glycidyl group-containing polymers



Other architectures, including side-chain functional polymers, bottlebrushes, hydrogels, and (segmented) hyperbranched polymers have been prepared by using the same sequential technique.[29-33] In each case, the thiol-epoxy reaction shows high efficiency and selectivity which enables the successful preparation of a variety of well-defined functional macromolecules.

Another example in which new functionality is formed after the first functionalization was reported by Kakuchi and Theato (Scheme 5).[34] Styrenic-based polymers containing pentafluorophenyl sulfonate esters were treated with primary amines to afford mono-substituted sulfonamides, which can then undergo a Mitsunobu reaction with an alcohol to yield pendent heterodifunctional homopolymers. Quantitative conversion of each functionalization was observed by ^{1}H NMR analysis for various substrates.

Orthogonal or chemoselective functionalization

The use of click reactions has dominated the field of post-polymerization modification due to their impeccable efficiency.[3] Another advantage of click reactions is the specificity of the reaction, and this characteristic can be applied for orthogonal polymer functionalization.[10, 35-37] For example, Lyon and co-workers demonstrated the orthogonal functionalization of microgels *via* simultaneous CuAAC and carbodiimide coupling.[38] The authors demonstrated that CuAAC reactions proceeded in the presence of carboxylic acids, amines, and amide functional groups, which illustrates the high functional group tolerance and chemoselectivity of CuAAC click reactions for polymer functionalization.

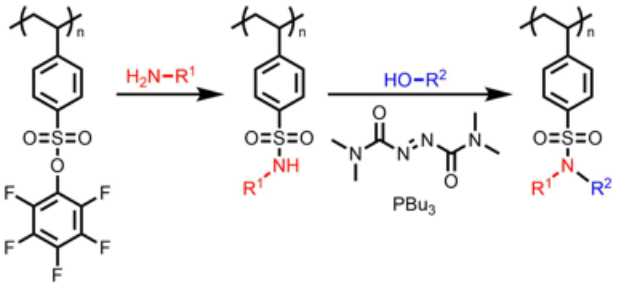
Despite the high chemoselectivity of this and other click reactions, the application of this orthogonal approach to synthesize new homopolymers has not been extensively explored. Novak et al. demonstrated sequential CuAAC followed by thiol-ene reactions on polymers to afford heterodifunctional homopolymers without necessitating protecting groups (Scheme 6).[39] This approach enabled the incorporation of pendent groups in a controlled manner and the study the structure-property relationship of helical alkyne polycarbodiimides.

More recently, our group reported that 2,4,6-trichloro-1,3,5-triazine (TCT) can be used to afford chain-end and side-chain heterodifunctional polymers.[40, 41] TCT has been extensively studied as a building block for dendrimer synthesis due to high efficiency, stability, availability, and multifunctionalization ability.[42, 43] These advantageous features were highlighted by Simanek and coworkers who demonstrated the synthesis of large dendrimers that match the size of small viruses.[44] TCT can undergo chemoselective, sequential functionalization with three different nucleophiles to conjugate three components onto the triazine core (Scheme 7A). Each successive reaction is performed at increasing temperatures to overcome high energy barriers, which are induced from a replacement of σ-withdrawing chlorine atoms with π-donating nucleophilic heteroatoms. This unique concept of utilizing kinetically differentiated reactivity for multifunctionalization has also led to a design of new multifunctionalization-capable scaffolds and further development of novel, functional macromolecular materials.[45-47]

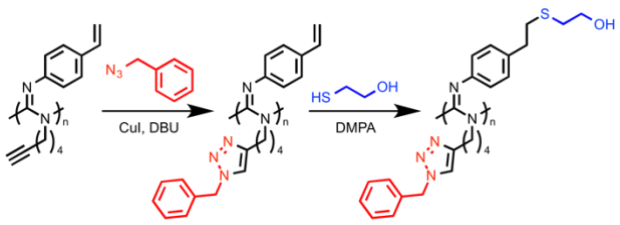
Multifunctional homopolymer synthesis was achieved by first polymerizing a dichlorotriazine-containing monomer by RAFT polymerization (Scheme 7B).[41] Successive nucleophilic aromatic substitution with amines or thiols afforded the desired products. The substitution of chlorine with a nitrogen or sulfur-based nucleophile during the first step of polymer functionalization stabilizes the triazine core through enhanced electron donation. To overcome this stabilization, a higher temperature is required for the substitution of the last chlorine on the triazine which allows for chemoselective functionalization. High chemoselectivity was indicated by a small molecule model study as well as MALDI analysis of the chain-end functionalized polymer. This example demonstrates that a high chemoselectivity can be applied to prepare multifunctional homopolymers. In our recent report, we demonstrated that this TCT-based post-polymerization modification approach can be applied for multifunctionalization of degradable polyesters that were afforded via radical ring-opening polymerization.[48]

This synthetic approach has also been used for amphiphilic homopolymer synthesis (Scheme 8).[49] Installation of a hydrophobic group and a latent hydrophilic group, followed by hydrolysis of the ester, afforded two amphiphilic

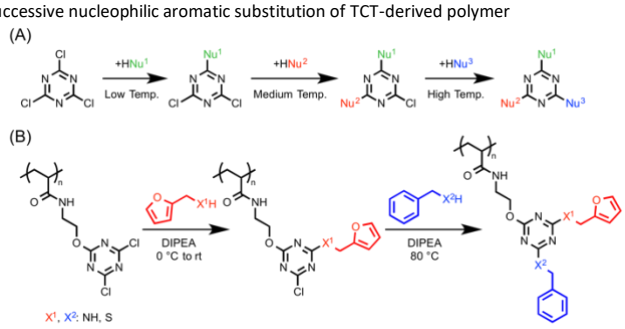
Scheme 5. Successive sulfoamidation and Mitsunobu reaction



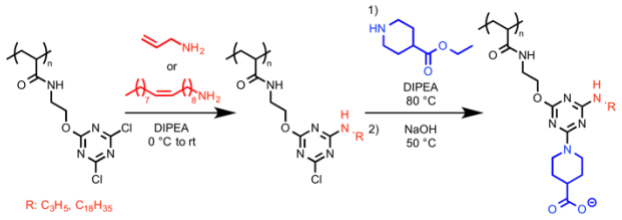
Scheme 6. Synthesis of multifunctional polycarbodiimide *via* orthogonal click reactions



Scheme 7. (A) Sequential and chemoselective nucleophilic aromatic substitution on 2,4,6-trichloro-1,3,5-triazine (TCT). (B) Synthesis of multifunctional homopolymer *via* successive nucleophilic aromatic substitution of TCT-derived polymer



Scheme 8. Synthesis of amphiphilic homopolymers from 2,4,6-trichloro-1,3,5-triazine-derived polymer



homopolymers with distinct hydrophobic segments. We found that the size of the nanoparticles and the dynamics of self-assembly were greatly influenced by the size of the hydrophobes. These amphiphilic homopolymers successfully reduced the interfacial tension between 1-dodecene and water, demonstrating their potential utility as polymeric surfactants.

Conclusions and future outlook

Several strategies to synthesize multifunctional homopolymers have been developed. A common trait of these routes is that each approach features highly efficient and selective transformations. In some approaches, a second functionality is masked within the polymer to prevent undesired reactions, while other techniques rely on orthogonal or highly chemoselective transformations. We have also shown that the techniques described here are generally applicable to the synthesis of polymers with more complex architectures and functionalities.

Despite the enormous potential that multifunctional homopolymers have, the number of well-established approaches to afford such macromolecules remains limited. Additionally, applications of multifunctional homopolymers remain scarce, likely due to the limited number of available synthetic technologies. Recent developments of new functionalization scaffolds would potentially enable expansion of the realm of polymer multifunctionalization.[45, 46] We hope that the previous examples described herein allow us to identify underexplored territories in polymer functionalizations and exploit new chemistries tailored to our current needs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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