Solid-Phase Synthesis of Polymers Using the Ring-Opening Metathesis Polymerization

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The ring-opening metathesis polymerization (ROMP) can generate polymers with diverse attributes.[1] The characteristics and therefore function of a polymer can be tailored by altering its length and the substituents displayed on the backbone. Methods for the combinatorial synthesis of polymers using ROMP could accelerate the production of materials with novel properties. To this end, polymer scaffolds that can be readily modified in solution have been devised.[2,3] The rapid synthesis of polymer libraries from these scaffolds is hindered by purification of the resulting functionalized polymers. Purification methods depend on the physical properties of the reactants used and the polymers that result.[4] The complications of isolating diverse polymers render the solution-phase synthesis of libraries impractical. Solid-phase synthesis has been used to simplify purification steps en route to libraries of small molecules; reaction products remain immobilized, and soluble byproducts are washed away.[5] The application of solid-phase methods to polymer chemistry, however, is more complex. Developing such a strategy involves attaching a soluble polymer to an insoluble one. The immobilized polymer can be derivatized and subsequently released from the resin. To implement such an approach is challenging: an immobilization method that is orthogonal to the polymer modification chemistry is required, as is a process for polymer release that affords minimal byproducts. Here, we report a general method for the solid-phase synthesis of polymers using ROMP that surmounts these barriers.

Immobilized polymers have been synthesized by ROMP from a surface-anchored monomer or catalyst.[3,6,7] The kinetics of such polymerization reactions will be complex; consequently, the resulting polymers will be more heterogeneous than those generated in solution. We sought to preserve the high level of control over polymer structure that can be obtained with ROMP in solution. Under these conditions, ROMP effected using metal carbene initiators can be "living", that is, termination or chain transfer processes do not compete with initiation or propagation. Thus, following monomer consumption, a metathesis-active metal carbene exists at the polymer terminus.[8] The presence of this reactive moiety facilitates the introduction of unique functionality at the terminus[9] or the synthesis of block copolymers by continued polymerization with a different monomer.[10] When the rate of initiation significantly exceeds that of propagation, polymers of defined lengths and narrow polydispersity indices can be generated. Our goal, therefore, was to develop a solid-phase synthetic strategy that would retain these advantages.

Our synthetic strategy has three critical features. First, we wanted to immobilize a polymer that could be readily diversified. We had demonstrated that polymers bearing reactive *N*-hydroxysuccinimidyl (NHS) esters can be modified using an efficiency of polymer capture by presenting multiple copies of a group that can participate in the immobilization process of a variety of amines[2] (Figure 1). Second,
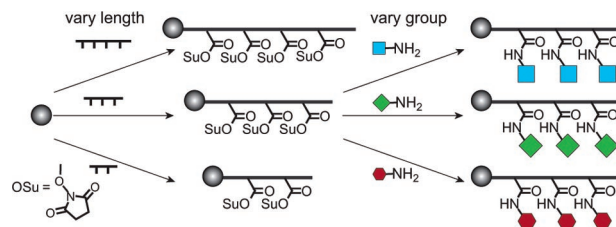
Figure 1. Strategy for the solid-supported synthesis of polymers displaying diverse functional groups. Polymers of different lengths can be immobilized, and substituents can be conjugated to the *N*-hydroxysuccinimidyl ester (OSu)-substituted polymer.
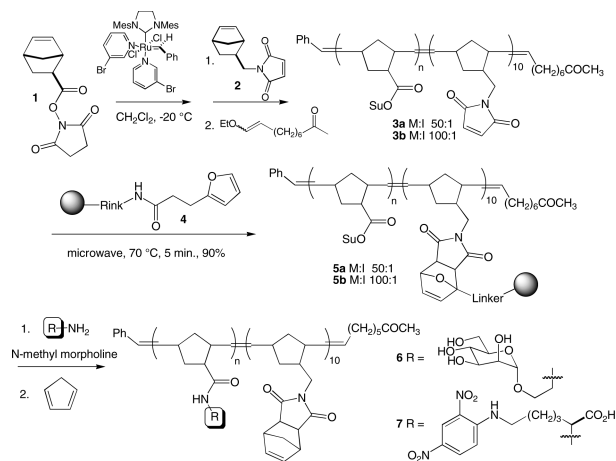
we sought to increase the immobilization efficiency using a short block containing functional groups that can be captured on a reactive resin. Third, we needed an immobilization strategy that allows facile purification of the cleaved polymers. We envisioned that a reversible Diels—Alder reaction could be used to append polymer to resin. The reactivity of NHS esters is orthogonal to that of typical diene/dienophile pairs. Moreover, we anticipated that the linkage between the resin and the polymers could be severed under mild conditions.[11,12]

To test our synthetic strategy, we generated block copolymers using ROMP. One block was designed for immobilization, the other for presenting functionality of interest. We reacted a ruthenium carbene initiator[13] first with a monomer bearing an NHS ester and then with one bearing a maleimide dienophile. The length of the block of activated ester groups was varied by controlling the ratio of NHS ester-substituted monomer to initiator (M:I); 50:1 and 100:1 ratios were employed. When the initial monomer was consumed, a maleimide-substituted norbornene was added (10:1 M:I ratio) to afford polymers **3a,b**. This order of monomer polymerization ensures that all living polymer chains possess the key functionality required for immobilization; any chains that have undergone premature termination will remain in solution. To test the Diels—Alder immobilization strategy, we exposed the polymers to Rink amide polystyrene resin substituted with furan groups (**4**) under microwave irradiation. Microwave irradiation can promote Diels—Alder reactions,[14] and we found that it facilitated the linkage of the polymer to the resin. Indeed, this process resulted in highly efficient polymer immobilization. Over 90% of the polymer was captured.[15] Attempts to immobilize polymers using a single end-group were inefficient. Specifically, when polymers bearing a single end-group dienophile were exposed to resin, the immobilization yield was only 30%.[16] The excellent yields we obtained for block copolymers attests to the advantages of their use.

With immobilized polymers in hand, we explored conditions for their functionalization. We conjugated two amines with very different structures, a mannose derivative and 2,4-dinitrophenyl (DNP) lysine. The amide bond-forming reactions were conducted using a 10:1 ratio of amine to NHS ester in the presence of base. Spectroscopic analysis of the polymer products generated upon

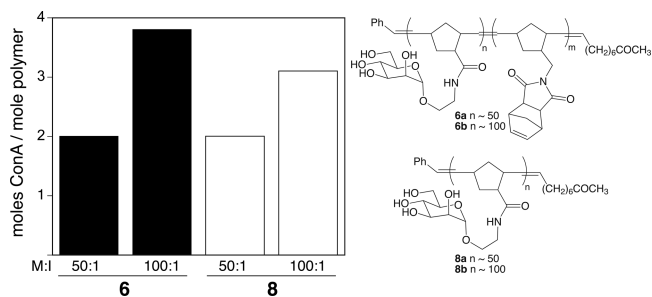† Department of Chemistry.
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Scheme 1. Strategy for Polymer Synthesis[a]

[a] Polymers displaying *N*-hydroxysuccinimidyl esters (M:I 100:1 or 50:1) and a short maleimide-substituted block (M:I of 10:1) were generated. A Diels—Alder reaction between polymer maleimide and a resin-bound furan results in immobilization. After conjugation of amine-bearing groups, cleavage can be effected using a diene, which irreversibly traps the incipient polymer maleimide groups in solution.

cleavage[15] indicates that the amide bond-forming reaction is efficient; it appears to proceed in quantitative yield based on the NHS ester. To complete our solid-phase synthesis, a method to liberate polymer from the resin was required. The tendency of furan to engage in reversible Diels—Alder reactions underlies our cleavage strategy. Treatment of the resin with cyclopentadiene, which forms irreversible Diels—Alder adducts with dienophiles, such as maleimide, resulted in polymer cleavage. To verify that the majority of the polymer was liberated, we exposed the resin to acid to sever the Rink amide linker. No additional polymer was detected in the resulting eluent. Additionally, chromatographic analysis of the functionalized polymers indicated that they have the expected molecular masses and possess narrow polydispersity indices.[15] These investigations demonstrate the utility of our synthetic strategy.

The properties of block copolymers and homopolymers can vary. To determine whether our method affords functional polymers with activities similar to their homopolymer counterparts, we compared the ability of polymers **6a,b** and **8a,b** to interact with the target protein, concanavalin A (ConA). Multivalent displays of saccharides can cluster and thereby precipitate lectins.[17,18] We found that the initial rates of ConA precipitation mediated by polymer **6a,b** are comparable to those obtained with **8a,b**.[15] To test whether differences in activities that depend on polymer length are preserved, we used quantitative precipitation to estimate the stoichiometric composition of precipitated polymer cross-linked lectin complexes.[17,19] The concentration of ligand required to completely precipitate the ConA was extrapolated to determine the relative stoichiometry of ConA and polymer[15] (Figure 2). Our results indicate that activities of the polymers do not depend on the method used for their synthesis. Thus, our solid-phase synthetic method can be used to generate polymers with desired properties.

The data presented suggest this solid-phase route can be used for the synthesis of libraries of soluble polymers. Our conjugation strategy is effective for generating polymers of the lengths needed to probe biological systems. Moreover, use of the Diels—Alder reaction of furan offers many advantages for immobilization.[11,12] As discussed, the reactivity of the reaction partners is orthogonal

Figure 2. Quantitative precipitation of ConA with mannose-bearing polymers. Stoichiometric composition of precipitate was calculated as previously described.[15,18] Ratios depicted are the number of ConA tetramers estimated to be clustered with each mannose polymer.

to that of many other functional groups. In addition, the reversibility of the furan Diels—Alder reaction provides a means to release the polymer from the solid support *and* a handle for further functionalization. We postulate that the strained alkene that results can participate in additional ROMP reactions to build branched copolymers. Alternatively, other reactive species could be used to trap the dienophile (e.g., thiolates) to produce block copolymers that display a range of functionality. We anticipate that the flexibility of this strategy will markedly accelerate the synthesis of soluble polymers with novel functions.

Supporting Information Available: Synthetic methods and experimental details for the development of the methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA053931P