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Liquid-Phase Synthesis of Block Copolymers Containing Sequence-Ordered Segments

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Control over monomer sequences is a crucial topic in modern polymer chemistry.[1] Indeed, polymers with defined macromolecular sequences may exhibit unique conformational and functional properties. For instance, sequence-ordered biopolymers such as nucleic acids and proteins are the keystones of highly organized biological systems. Thus, it seems obvious that sequence-ordered macromolecules could also play an important role in synthetic materials. For example, it has recently been reported that sequenced-defined biooligomers can be efficiently exploited for organizing synthetic materials.[2] In particular, block copolymers containing short oligonucleotide or oligopeptide segments have been shown to be versatile building blocks for guided self-assembly.[3] These promising strategies could certainly be extended to a wider range of nonbiological polymers with controlled sequences (e.g., conducting oligomers, self-sorting segments).

However, our tools for controlling monomer sequences are still limited.[1] To date, Merrifield solid-phase synthesis remains the most suitable route for preparing sequence-ordered macromolecules.[4] This method is certainly efficient for synthesizing short oligomers but somewhat tedious for the preparation of complex macromolecular architectures. For instance, block copolymers containing sequence-defined segments are typically obtained by (*i*) synthesizing an oligomer on a solid support, (*ii*) cleaving and isolating the oligomer, and (*iii*) linking the oligomer with another polymer in solution (i.e., using coupling or macroinitiator strategies).[5] The last step could certainly be bypassed if the sequence-ordered oligomers were directly grown on a soluble polymer segment. Indeed, linear macromolecules can easily be isolated from low-molecular-weight mixtures (e.g., via selective precipitation) and therefore used as efficient supports for organic synthesis.[6] Such soluble polymer supports interestingly combine the advantages of solid-phase synthesis (i.e., facile isolation) and solution chemistry (i.e., accessibility). For instance, some examples of oligonucleotide and oligopeptide synthesis on soluble polymer supports have been described in past years.[7] However, in these approaches, the soluble polymers have principally been used as sacrificial supports. Thus, in most cases, ill-defined commercial polymers have been exploited. However, modern polymer chemistry certainly allows the design of more advanced macromolecular supports. For instance, the recent discovery of controlled radical polymerization techniques[8] such as atom-transfer radical polymerization (ATRP), nitroxide-mediated polymerization (NMP), and reversible addition−fragmentation chain-transfer polymerization (RAFT) open wide possibilities in terms of macromolecular engineering.[9] Nevertheless, these techniques have barely been explored to date for synthesizing tailored polymer supports.[10] In this context, the objective of the present work was to show that well-defined soluble polymer supports can be efficiently utilized to prepare advanced macromolecular architectures containing sequence-ordered segments.

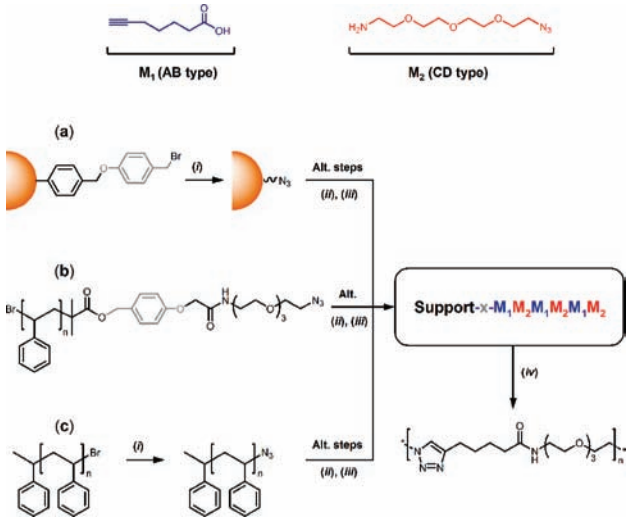


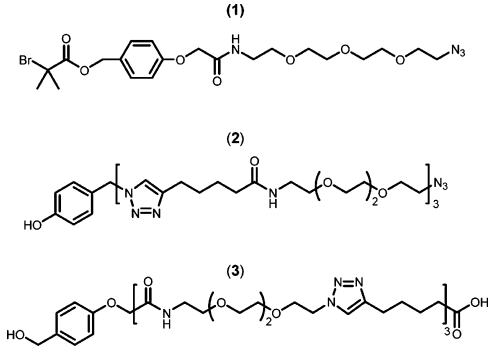
Figure 1. Strategies for synthesizing sequence-defined oligomers via an AB + CD growth mechanism: (a) conventional solid-phase approach based on an azido-functionalized Wang resin; (b) liquid-phase approach based on a linear polystyrene support containing a cleavable linker; (c) direct synthesis of block copolymers using an ω-azido-functionalized polystyrene support. Light-gray colors indicate cleavable moieties. Experimental conditions: (*i*) NaN_3, DMF; (*ii*) M_1, CuBr, dNBipy, THF; (*iii*) M_2, NHS, DCC, THF; (*iv*) TFA, CH_2Cl_2. The last step was used in approaches a and b only.

Herein, linear polystyrene supports were prepared using ATRP and exploited to synthesize model sequence-defined oligomers (Figure 1). In particular, our purpose was to demonstrate that these well-defined supports can be used as either (*i*) cleavable segments [i.e., standard sacrificial supports (approach b in Figure 1)] or (*ii*) permanent segments [i.e., in block copolymer synthesis (approach c in Figure 1)]. In all cases, the model oligomers contained alternating polar and apolar segments and were constructed stepwise via an AB + CD approach (Figure 1). This synthetic strategy relies on two efficient chemical reactions, namely, 1,3-dipolar cycloaddition of terminal alkynes (A) and azides (D) and amidification of carboxylic acids (B) with primary amines (C).[11] These two reactions proceed chemoselectively in an ABCD multifunctional mixture (i.e., A reacts solely with D, whereas B reacts solely with C).[12] As a consequence, sequence-defined oligomers can be prepared easily in the absence of protecting groups. Hence, this straightforward approach seemed adequate for an initial proof-of-principle.

Nonetheless, these alternating oligomers had not been synthesized previously. Thus, a reference oligomer was first prepared using a standard solid-phase procedure (approach a in Figure 1). The bromide moieties of a commercial Wang resin were first transformed into azide functions by nucleophilic substitution in the presence of sodium azide.[13] This modified resin was subsequently

used to initiate the stepwise synthesis of an oligomer composed of three polar and three apolar building blocks (i.e., six consecutive growth steps, including three amidifications and three cycloadditions). After each step, the resin was characterized by FT-IR (Figure S1 in the Supporting Information). These measurements confirmed that the growth steps proceeded in nearly quantitative yields. After the last step, the sequence-ordered oligomer was cleaved from the solid support using a TFA/CH_2Cl_2 mixture, purified, and analyzed using ^{1}H NMR and FT-IR spectroscopy and MALDI and ESI mass spectrometry (Figures S2 and S3 in the Supporting Information). All of the measurements indicated the formation of a monodisperse oligomer with a molecular weight of 1128 g mol^{-1}. This corresponds to the targeted molecular structure containing six building blocks, an azide ω-end group and a 4-hydroxybenzyl α-end group (structure **2** in Scheme 1). The latter is due to cleavage of the aryl benzyl ether.[13] The formed oligomer was found to be soluble in various solvents, including water and methanol. These preliminary results indicated that the AB + CD strategy is rapid and efficient for synthesizing sequence-ordered oligomers.

Scheme 1. Molecular Structures of the Cleavable Azido-Functionalized ATRP Initiator (**1**) and Some Oligomers Prepared in This Study (**2** and **3**)



Thus, oligomer synthesis was then performed on a well-defined soluble polystyrene support. In order to fully demonstrate the viability of this technique, a cleavable support allowing oligomer isolation and characterization was first investigated (approach b in Figure 1). This polystyrene support was synthesized by ATRP in the presence of an azido-functionalized ATRP initiator (**1**) containing a labile *p*-alkoxybenzyl ester linker (Scheme 1).[14] The formed polymer was characterized by ^{1}H NMR and FT-IR spectroscopy and size-exclusion chromatography (SEC). The former methods confirmed the presence of **1** at the α-chain end of the polymer, whereas the latter evidenced the formation of a well-defined macromolecule with a controlled molecular weight ($M_n \approx 4300$ g mol^{-1}) and a narrow molecular weight distribution ($M_w/M_n \approx 1.14$). The azido functionality of this linear polystyrene was exploited to initiate the sequential oligomerization of building blocks M_1 and M_2. Oligomers having different chain lengths were synthesized on this linear support (i.e., using four or five consecutive growth steps). After each step, the modified polymer was isolated by precipitation in methanol. This purification procedure was rapid and allowed efficient removal of the low-molecular-weight reactants together with minimal polymer loss. Thus, the oligomer synthesis on this soluble polystyrene support was overall as fast as on a commercial Wang resin. Moreover, the products of each step were examined by ^{1}H NMR and FT-IR spectroscopy (Figure 2a), which indicated high reaction yields in all cases. After the last step, the modified support was analyzed by ^{1}H NMR spectroscopy and SEC. Both techniques indicated the formation of a well-defined block copolymer, polystyrene-*b*-oligomer.

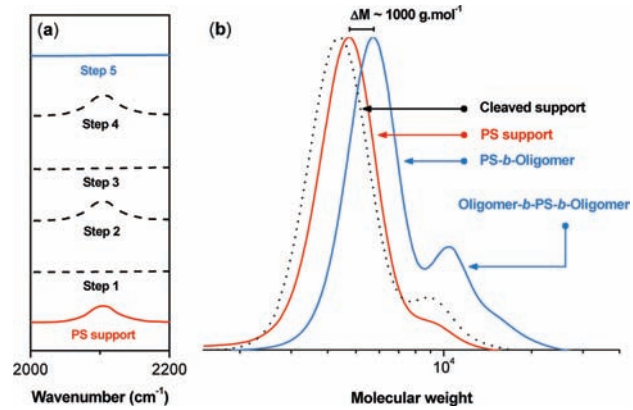


Figure 2. Synthesis on a cleavable soluble polystyrene support: (a) FT-IR spectra (showing the 2000−2200 cm^{-1} region) recorded at room temperature after each step of the stepwise oligomerization process. This graphic highlights the quantitative disappearance (after the cycloaddition step with M_1) or reappearance (after the amidification step with M_2) of the absorption peak of the azide function ($\nu_{N_3} = 2105$ cm^{-1}). (b) SEC chromatograms recorded in THF for the cleavable azido-functionalized polystyrene support (solid red line), the formed polystyrene-*b*-oligomer block copolymers (solid blue line), and the support after cleavage in TFA/CH_2Cl_2 (black dotted line).

For instance, SEC evidenced a clear molecular weight difference between the formed diblock copolymer and the parent support (Figure 2b and Figure S4 in the Supporting Information). Although SEC only gives access to apparent molecular weight values, these differences roughly coincided with the theoretical molecular weights of the targeted oligomers (i.e., ∼900 g mol^{-1} after four growth steps and ∼1000 g mol^{-1} after five growth steps). Additionally, high-molecular-weight shoulders could also be detected on the chromatograms. These signals correspond to triblock copolymers, oligomer-*b*-polystyrene-*b*-oligomer, which were initiated by α,ω-azido telechelic polystyrene (i.e., dead chains formed by bimolecular coupling during the ATRP). In order to fully characterize the formed oligomers, the diblock/triblock copolymers were cut using a TFA/CH_2Cl_2 mixture (Figure 1). After this treatment, the reaction mixture was reconcentrated and poured into a large volume of methanol. The polystyrene support precipitated out, whereas the cleaved oligomers remained in the methanol solution. The former was dried in vacuo and characterized by ^{1}H NMR spectroscopy and SEC (Figures 2b and 3), while the latter were purified by rotary evaporation and characterized by ^{1}H NMR and FT-IR spectroscopy, MALDI-MS, and ESI-MS. The SEC measurements clearly confirmed the quantitative cleavage of the block copolymers (Figure 2b). Indeed, the chromatogram of the precipitate coincided with that of the initial support. In fact, a slight shift of roughly 350 g mol^{-1} between these two molecular weight distributions was observed. This difference corresponds to the *N*-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-2-(4-hydroxymethylphenoxy)acetamide moiety of the initial support (molecular weight 382 g mol^{-1}), which was transferred to the oligomer after cleavage. Furthermore, MALDI-MS and ESI-MS evidenced the formation of monodisperse oligomers. For example, after five growth steps and cleavage, an oligomer with a molecular weight of 1160 g mol^{-1} was detected. This value corresponds to the targeted alternating sequence with a *p*-alkoxybenzyl alcohol α-end group (structure **3** in Scheme 1). However, a second species with a molecular weight of 1174 g mol^{-1} was also identified. This structure could be due to partial esterification of the carboxylate end group during the purification procedure (i.e., methanol + TFA).

Ultimately, soluble polystyrene supports were studied for preparing noncleavable block copolymers containing sequence-defined

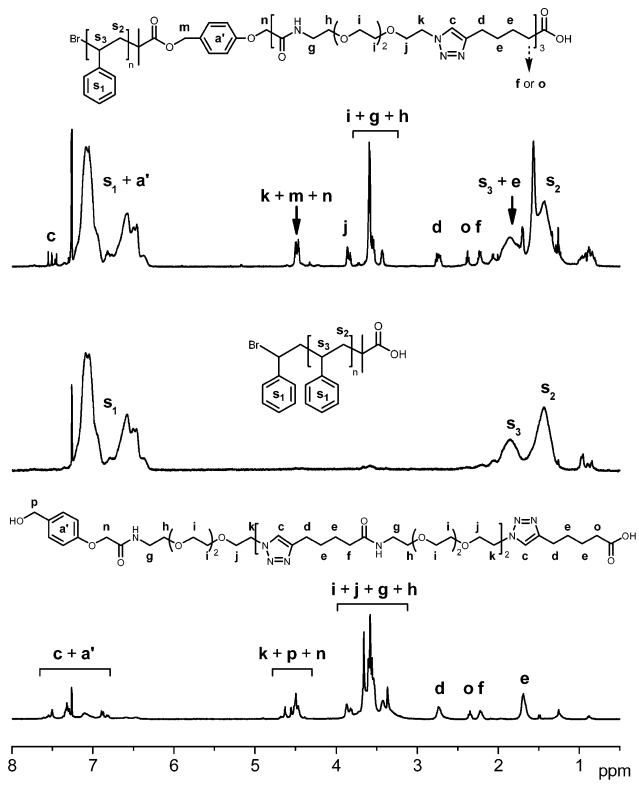


Figure 3. Oligomer synthesis on a cleavable soluble polystyrene support (Figure 1, approach b). ^{1}H NMR spectra recorded in $CDCl_3$ for (top) the formed polystyrene-*b*-oligomer copolymers before TFA/CH_2Cl_2 cleavage, (middle) the polystyrene support after cleavage and filtration, and (bottom) the formed oligomer after cleavage and isolation.

oligomers (approach c in Figure 1). In this case, the bromine ω-end groups of the ATRP polystyrene chains ($M_n \approx 3900$ g mol^{-1}, $M_w/M_n \approx 1.13$) were first transformed into azide moieties by nucleophilic substitution with sodium azide.[15] These functional chain ends were then used as initiating sites. Six alternating growth steps were performed on the soluble polystyrene support (three amidifications and three cycloadditions). As for the previous approach, the sequential growth of the oligomer was monitored by ^{1}H NMR spectroscopy. This technique evidenced high reaction yields in each step. After synthesis, the ^{1}H NMR spectra and SEC data indicated the formation of a well-defined diblock copolymer containing a sequence-ordered segment with a molecular weight of $\sim$1000 g mol^{-1} (Figures S6 and S7 in the Supporting Information). Contrary to what occurred with approach b, no triblock copolymers were formed in the present case. Indeed, approach c relies on ω-chain end initiation, in which dead chains are simply inactive (i.e., they initially have no bromine terminal groups and therefore no azide-initiating sites).

In conclusion, tailor-made linear macromolecules synthesized by ATRP appear to be robust and versatile supports for the synthesis of sequence-ordered oligomers. Indeed, these macromolecular supports can be used not only for the conventional synthesis and cleavage of defined oligomers but also for the preparation of advanced macromolecular architectures containing sequence-defined segments.

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Supporting Information Available: Full experimental section and Figures S1−S7. This material is available free of charge via the Internet at http://pubs.acs.org.

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