Sequence-Controlled Polymers

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Sequence Control in Polymer Chemistry through the Passerini Three-Component Reaction**

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Abstract: *A new strategy to achieve sequence control in polymer chemistry based on the iterative application of the versatile Passerini three-component reaction (P-3CR) in combination with efficient thiol–ene addition reactions is introduced. First, stearic acid was used as a starting substrate to build up a sequence-defined tetramer with a molecular weight of 1.6 kDa. Using an acid-functionalized PEG allowed for an easier isolation of the sequence-defined macromolecules by simple precipitation and led to a sequence-defined pentamer in a block-copolymer architecture. Importantly, this new strategy completely avoids protecting group chemistry. By following this strategy, a different side chain can be introduced to the polymer/oligomer backbone in a simple way and at a defined position within the macromolecule.*

Nowadays, several methods are known for the precise synthesis of macromolecular architectures with defined molecular weights and end groups. Of these, the controlled radical polymerization methods, such as RAFT,[1] ATRP,[2] and NMP,[3] enable the synthesis of defined and complex architectures. In contrast, the synthesis of polymers bearing well-defined monomer sequences only recently gained more interest.[4] The development of solid-phase peptide synthesis by Merrifield in 1963 can be considered the most important milestone in the synthesis of sequence-defined macromolecules.[5] In addition, the solid-phase oligonucleotide synthesis is well established.[6] Inspired by the natural synthesis of DNA strands, several approaches making use of DNA-templated reactions, for instance nucleotide coupling,[7] Wittig olefinations,[8] reductive aminations,[8a] and Huisgen cycloadditions have been described.[9] The DNA-templated Wittig olefination was also utilized for the synthesis of sequence-defined oligomers by stepwise addition of different monomers.[8b] Moreover, the DNA-templated synthesis was used for the synthesis of polymers. Saito et al. oligomerized five DNA pentamers by photoinduced cyclobutane formation[10] and Liu et al. introduced a DNA-templated translation system enabling the enzyme-free translation of DNA templates into sequence-defined synthetic polymers.[11] Leigh and co-workers reported on the synthesis of sequence-specific peptides by a rotaxane-based small-molecule machine; here the peptide chain was elongated by successive native ligation reactions in a non-DNA-templated approach.[12]

In addition, other non-DNA-templated approaches[12,13] and step-growth polycondensation[14] approaches can be employed to achieve sequence control. In contrast, chain-growth-based approaches mainly rely on the high cross-propagation reactivity of styrene with maleic anhydrides[15] or maleimides in radical polymerizations.[16] By application of living polymerization techniques, the maleimides can be incorporated in certain regions (within the first monomer units, the middle of the chain, or within the last monomer units) of the polymer chains.[16b,17] Due to the N-substitution of the maleimides, the introduction of specific moieties into the polymer chain can be realized. Furthermore, it is possible to sequentially add different maleimides to the polymerization system, leading to a polymer with diversely substituted maleimides in the polymer chain.[16d] It should be noted that these polymers are formed in a radical process, which implies that the maleimides cannot be introduced at an absolutely defined position in each chain. Additionally, due to statistic processes and the simultaneous growth of many chains, it is unavoidable that some chains will remain nonfunctionalized and others will carry more than one functional group. Therefore, in order to obtain highly defined sequence-controlled materials, the above-mentioned sequential approaches are inevitable.

Our novel approach is based on the efficient P-3CR. Such multicomponent reactions (MCR) have been known since 1850, when Strecker discovered the formation of α-aminonitriles from aldehydes, ammonia, and hydrogen cyanide.[18] One important subclass of MCRs are the isocyanide-based multicomponent reactions (IMCR), of which the P-3CR[19] and the Ugi 4CR are most famous.[20] The P-3CR, first described in 1921, is a three-component reaction of an oxo component with a carboxylic acid and an isocyanide (isonitrile), forming an α-acyloxy carboxamide.[19] Although MCRs are widely used in organic chemistry,[21] they were only recently introduced to polymer chemistry. In 2011, our group developed a novel Passerini polymerization method; the use of a bifunctional carboxylic acid and a bifunctional aldehyde in combination with structurally diverse isocyanides led to the formation of high-molecular-weight polymers.[22] Recently, our group reported on the preparation of acrylate monomers by the P-3CR. After polymerization, the resulting materials showed tunable thermoresponsive properties.[23] Within this contribution, we describe the synthesis of a sequence-defined tetramer as well as the synthesis of a block copolymer bearing

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a sequence-defined pentamer block. In order to achieve sequence control, we applied orthogonal reactions iteratively to synthesize the sequence-defined macromolecules in a stepwise manner without the utilization of protecting groups. In this aspect, the versatile P-3CR and the efficient thiol–ene addition reaction proved to be a powerful combination. Applying this approach, the introduction of different side chains to each monomer unit was

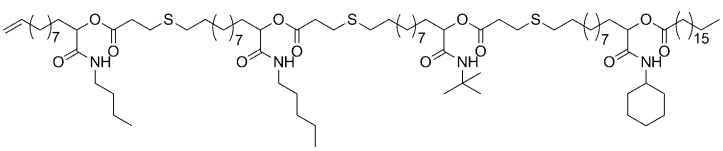
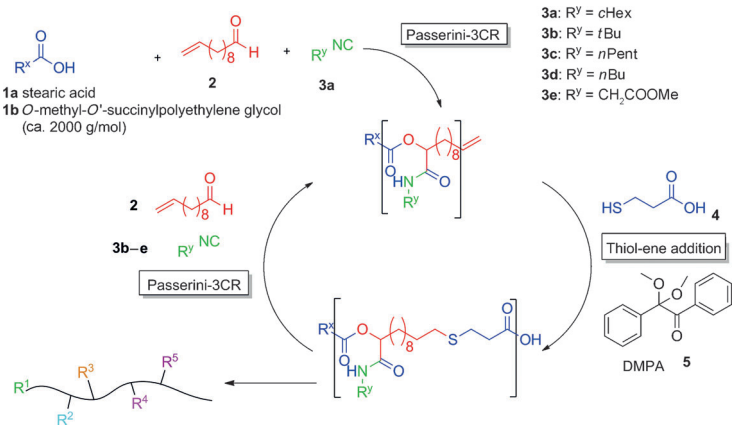


Figure 1. Structure of the obtained sequence-defined tetramer having four different side chains.



Scheme 1. Synthesis of a sequence-defined tetramer (starting from **1a**) or a sequence-defined block copolymer (starting from **1b**) by iterative application of the P-3CR and the thiol–ene addition reaction.

achieved by simply employing different isocyanides in each step of the P-3CR (Scheme 1).

This strategy has several advantages over other sequential approaches (i.e. polypeptide synthesis). The use of coupling/activating reagents is avoided and protecting groups are not necessary for the backbone synthesis. As a result our approach is more versatile (easy choice of side groups) and scaleable, as well as more efficient and sustainable since less waste is produced. Furthermore, the chemical diversity in the field of sequence-defined macromolecules is enlarged by this novel approach.

First, the P-3CR of stearic acid (**1a**), **2**, and **3a** was investigated. THF and dichloromethane were tested as solvents in different molarities (see Table S1 in the Supporting Information). The results revealed that high concentrations of the reactants resulted in higher conversions, shorter reaction times, and higher yields. However, when an equimolar ratio of the reactants was used, traces of **1a** were observed in the obtained product. Therefore, in order to ensure full conversion of the carboxyl groups, we used **2** and **3a** in a 1.5-fold excess. After this brief optimization, we examined the conditions for the thiol–ene addition reaction and found that the highest yields can be obtained by using a tenfold excess of the thiol **4**, 5.0 mol% DMPA **5** as an initiator, and irradiation with UV light for two hours.

These optimized conditions were used in the further synthesis steps of the oligomer and in the synthesis of the block copolymer. Thus, a sequence-defined tetramer (Figure 1) with a molecular weight of 1.6 kDa was prepared in seven steps in an overall yield of 26%.

The results obtained after each synthesis step of the sequence-defined tetramer (Table S2) as well as all analytical data and further details can be found in the Supporting Information. The NMR data of the obtained products show the success of each experimental step by the appearance of characteristic signals and appropriate integrals for the introduced amide protons after the P-3CR and the absence of signals for olefin protons after the thiol–ene addition reaction, respectively. Furthermore, mass spectrometry of the obtained products proves the existence of the desired products. GPC analysis (Figure 2) further indicates the successful formation of the desired products and verifies the high purity of the products by the shifting towards higher molecular weights after each step and the absence of low-molecular-weight by-products.

The successful synthesis of **12** provided valuable details about the synthesis procedures and also about the behavior and stability of the oligomers. In order to improve the yields and to significantly simplify the workup, we changed the initial acid substrate. As also reported earlier,[24] the use of a soluble polymer support significantly facilitates the purification of the sequence-defined products by straightforward precipitation and also speeds up the overall synthesis. Therefore, a PEG acid was synthesized from a commercially available PEG. Starting from the PEG acid **1b**, the sequence-defined block was synthesized according to the aforementioned procedure. As anticipated, complicated purification steps were not required in this case: the

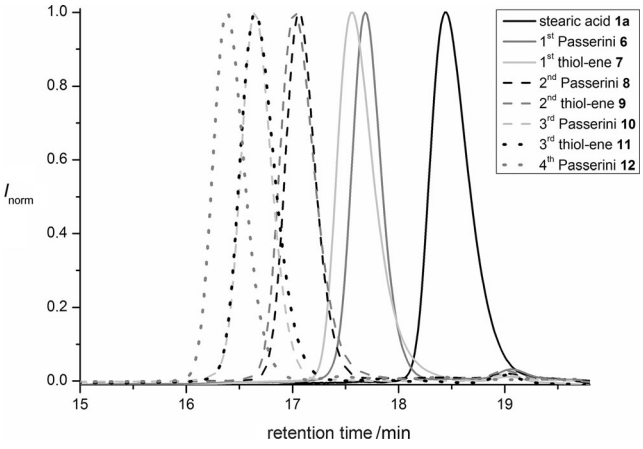


Figure 2. GPC traces obtained after P-3CR and thiol–ene addition reactions in the synthesis of the sequence-defined tetramer.

products were isolated by simple precipitation. For the block copolymer synthesis, the GPC results (Figure 3) also revealed a shift of the complete molecular weight distribution towards higher molecular weights, which is in agreement with the

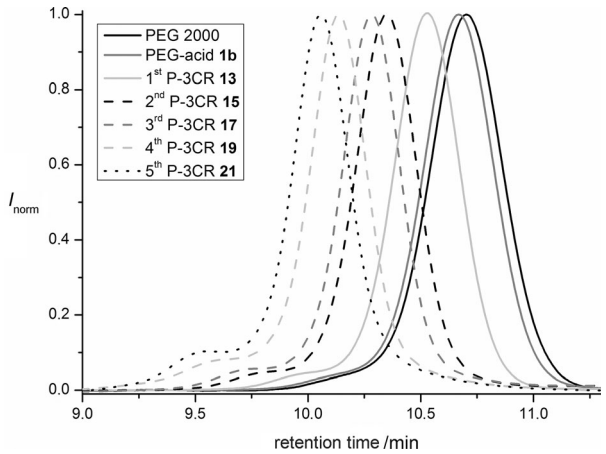


Figure 3. GPC traces of the PEG copolymer after each P-3CR.

successful formation of the desired sequence-defined products. In all GPC traces a small shoulder is observed, which was already present in the initially used PEG and probably arises from bis-OH-functionalized PEG chains. Additional GPC/ESI-MS measurements confirm the success of each reaction step.

Figure 4 shows the mass spectra of **13** and **15** obtained after the first and the second P-3CR, respectively. It is obvious that all polymer chains are functionalized, owing to the shift of the whole molecular weight distribution by 357.3 Da [$\Delta(m/z)$ 119.1], which corresponds to the mass of **4**, **2**, and **3b**.

Furthermore, the introduction of the desired functional groups can be followed by NMR spectroscopy. The presence or absence of the terminal double bond and the presence of amide signals also verify full conversion of the starting

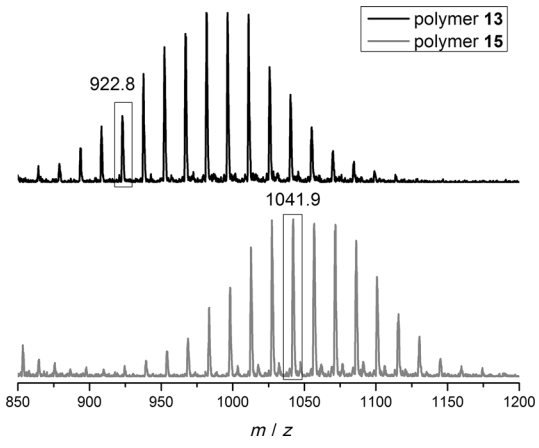


Figure 4. ESI mass spectra of **13** and **15**, showing a shift of the molecular weight distribution towards higher molecular weights. The peaks shown in the spectra correspond to chains carrying three sodium ions and the selected peaks correspond to polymer chains having 51 PEG monomer units.

material to the desired products in each reaction step. Moreover, the integration of the ^{1}H NMR signals of the modified polymer endgroups are in good agreement with those of the desired products and confirm the success of the synthetic steps. Table S3 summarizes the results obtained for each polymer after precipitation.

The synthesis of the block copolymer was much easier than the oligomer synthesis thanks to the time-saving purification by precipitation. Moreover, higher yields can be obtained in the synthesis of **21**, which has a sequence-defined pentamer structural motif. An overall yield of 34% was obtained after nine reaction steps.

All in all, the synthesis of the sequence-defined block utilizing the PEG acid is more efficient with regard to ease of purification and reaction efficiency, and also the overall preparation procedure is significantly accelerated. Moreover, it represents a more desirable polymeric architecture, since the combination of defined polymers obtained by controlled/living polymerizations with sequence-defined oligomeric blocks might ultimately lead to the development of polymers that can mimic proteins and other biopolymers.

In conclusion, a novel synthesis approach towards sequence-defined polymers was successfully applied to the synthesis of a tetramer as well as a block copolymer containing a sequence-defined block of five units and bearing five different side chains. The products were obtained in high yields and purity. Thereby, the iterative utilization of the P-3CR and the thiol–ene addition reaction proved to be a powerful combination for the preparation of sequence-defined materials and enabled an easy and versatile introduction of different side chains. Moreover, the use of a PEG acid allowed for a straightforward isolation of the sequence-defined products by precipitation. It should be emphasized that this novel synthesis protocol does not require any protecting groups or activating reagents due to the orthogonal reactions.

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