Sequence-Controlled Polymers

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Precision PEGylated Polymers Obtained by Sequence-Controlled Copolymerization and Postpolymerization Modification**

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Abstract: *Copolymers containing water-soluble poly(ethylene glycol) (PEG) side chains and precisely controlled functional microstructures were synthesized by sequence-controlled copolymerization of donor and acceptor comonomers, that is, styrene derivatives and N-substituted maleimides. Two routes were compared for the preparation of these structures: a) the direct use of a PEG–styrene macromonomer as a donor comonomer, and b) the use of an alkyne-functionalized styrenic comonomer, which was PEGylated by copper-catalyzed alkyne–azide cycloaddition after polymerization. The latter method was found to be the most versatile and enabled the synthesis of high-precision copolymers. For example, PEGylated copolymers containing precisely positioned fluorescent (e.g. pyrene), switchable (e.g. azobenzene), and reactive functionalities (e.g. an activated ester) were prepared.*

The development of synthetic polymers with controlled sequences of monomers is a topic that has received increasing attention in recent fundamental polymer science.[1] Indeed, as shown in many recent studies,[2] monomer-sequence regulation opens up previously unexplored avenues for controlling the structure, properties, and functions of synthetic macromolecules. Consequently, a number of methods have been described for the preparation of sequence-controlled polymers. Many of them aim at making perfectly monodisperse sequence-defined polymers. Such structures can be obtained by using iterative syntheses,[3] templates[4] or complex molecular machines.[5] An alternative strategy consists of regulating monomer feeds and reactivity in conventional polymerization methods, such as chain-growth or step-growth polymerization.[6] Such approaches are usually not perfect but allow some degree of control over comonomer sequence distribution.

The earliest example of such a strategy was reported by our research group.[7] It is a one-pot kinetic process that enables the precise incorporation of *N*-substituted maleimides (MIs) in specific regions of styrene-based polymer backbones.[8] In this approach, the polymers are prepared by using a controlled/living radical polymerization (CRP) method, such as atom-transfer radical polymerization and nitroxide-mediated polymerization (NMP), in which all chains are initiated in the early stages of the reaction and grow simultaneously at the same rate.[9] When different comonomers are used in such a controlled/living mechanism, their incorporation in the growing chains depends on their chemical reactivity. For example, acceptor comonomers (e.g. MIs) and donor comonomers (e.g. styrene) have usually a very strong tendency to copolymerize (i.e. cross-propagation is kinetically favored over homopolymerization). Thus, under CRP conditions, MIs are usually incorporated in the chains directly after their addition to the reaction mixture, even if the donor comonomer is used in large (e.g. 20–100-fold) excess.[10] Hence, by the time-controlled addition of MIs, it is possible to create polymers with complex microstructures in a one-pot process.[7,11] The macromolecules synthesized by this process are donor homopolymers containing positionable functional MI "patches". Of course, these copolymers are not perfectly sequence-defined. Owing to the statistical nature of chain-growth copolymerization, chain-to-chain sequence inhomogeneity is still present in these polymers.[10] Thus, these copolymers are generally referred to as "sequence-controlled" rather than "sequence-defined".[12] Nevertheless, the method is simple and versatile, and therefore enables the synthesis of macromolecular structures of unprecedented complexity.[13]

Although most of the polymers prepared by this approach have been based on hydrophobic polystyrene backbones, the method can also be extended to the preparation of sequence-controlled water-soluble polymers. For example, we recently reported the synthesis of sequence-controlled copolymers based on poly(4-vinylbenzoic acid) (PVBA)[14] and poly(4-hydroxystyrene) (PHS)[15] backbones. However, although interesting, these examples were not fully satisfying. Indeed, only limited control over comonomer sequence distribution was possible in the case of PVBA, and PHS-based copolymers could only be dissolved in water under highly alkaline conditions. Thus, to date, there is no example of nonionic sequence-controlled copolymers that can be dissolved in water at a neutral pH value. Such polymers could be of high fundamental importance. For example, it is known that graft polymers with oligo(ethylene glycol) (OEG) side chains are

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very useful alternatives to traditional linear poly(ethylene glycol) (PEG) for applications in biology and medicine.[16] Moreover, these polymers often exhibit interesting stimuli-responsive properties in aqueous media.[17] Thus, the placement of functional groups (e.g. hydrophobic moieties, fluorescent markers, or reactive groups) at specific locations on such polymers could enable the fine-tuning of their properties in water.

In this context, we describe herein a facile method for preparing sequence-controlled PEGylated polymers. These macromolecules were prepared by sequence-controlled copolymerization of styrene derivatives and *N*-substituted maleimides. We compared two different strategies for the synthesis of these polymers (Figure 1). The most obvious approach is the direct use of a PEG-functionalized styrenic macromonomer (Figure 1, approach a).[18] Thus, the nitroxide-mediated polymerization (NMP) of vinyl benzyl ethers of OEG **1** was first investigated (see Table S1 in the Supporting Information). Different macromonomers with 7, 9, and 10 OEG units were tested. These experiments were performed with the commercial alkoxyamine BlocBuilder MA (see Scheme S1 in the Supporting Information) in anisole. Although a broad range of experimental conditions was screened (results not shown), the radical homopolymerization of **1** could not be well controlled. Polymers with a broad molecular-weight distribution (see Table S1) were obtained in all cases. These results are not suitable for the sequence-controlled copolymerization of styrenes and *N*-substituted maleimides. Indeed, as mentioned previously,[10] our strategy requires that the polymerization of the styrenic monomer, which is used in large excess (20–100 molar equivalents as compared to the initiator), is perfectly controlled to minimize chain-to-chain structural inhomogeneity.

An alternative postpolymerization modification strategy was studied for the preparation of sequence-controlled PEGylated polymers (Figure 1, approach b). This concept relies on the use of alkyne-functionalized styrenic monomers that are first copolymerized with *N*-substituted maleimides and afterwards PEGylated by copper-catalyzed azide–alkyne cycloaddition (CuAAC).[19] The first crucial point in this strategy was the choice of the appropriate alkyne-containing monomer. The most tempting option was to use a styrene derivative bearing an unprotected terminal-alkyne substituent at the *para* position of its aromatic ring, for example, 4-propargyloxystyrene (**2**).[20] However, the NMP of this monomer is in general poorly controlled (see Table S1). Although the experimental kinetics fulfilled the criteria of a controlled/living mechanism, the formed polymers exhibited a broad molecular-weight distribution. This behavior is most probably due to radical addition to the unprotected acetylene groups.[21] Confronted with these limitations, we selected TMS-protected propargyloxystyrene **3** as a donor monomer.[20,22] The NMP homopolymerization of **3** was studied at different concentrations in anisole (see Table S1). In all cases, the polymerization proceeded well according to first-order kinetics with reasonable conversion (results not shown). However, it was found that the control of the homopolymerization was significantly influenced by the initial concentration of monomer **3**. Under semidilute conditions (monomer/solvent 1:0.5 v/v), the formed homopolymers exhibited broad bimodal molecular-weight distributions ($M_w/M_n \approx 1.8$). Better control was observed at higher monomer dilution (with an initial monomer/solvent ratio of 1:1 v/v). The best results were observed at a monomer/solvent ratio of 1:2 v/v. Under these optimized conditions, well-defined polymers with controlled molecular weights (see Table S2 and Figure S1) and narrow molecular-weight distributions (e.g. $M_w/M_n \approx 1.14$) were obtained.

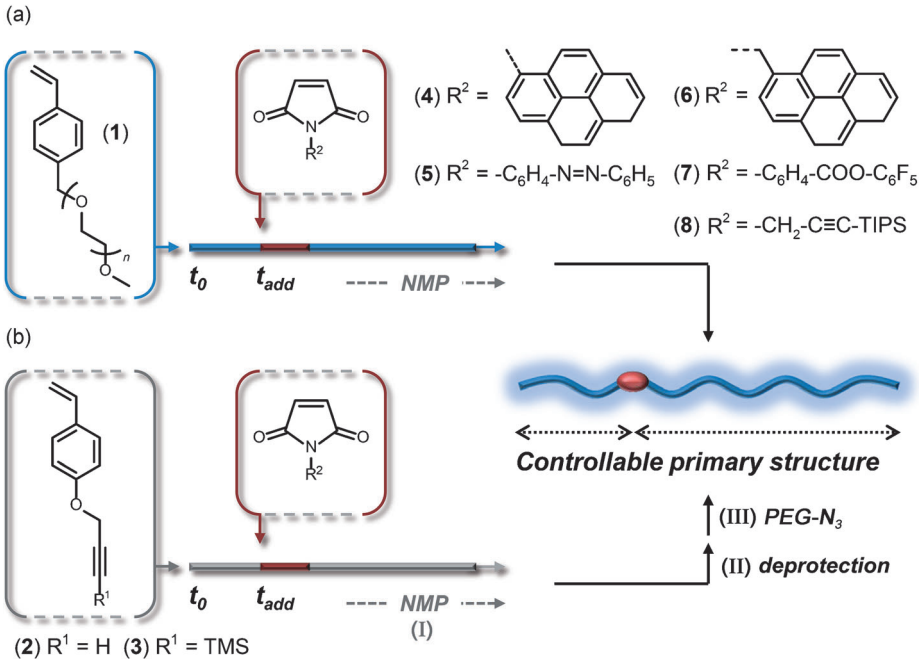

Figure 1. Strategies investigated in the present study for the preparation of sequence-controlled PEGylated copolymers. a) Direct copolymerization of a PEG–styrene macromonomer with *N*-substituted maleimides. b) Postpolymerization-modification approach, in which azido-PEGs were grafted on alkyne-functionalized sequence-controlled precursors. The acronym NMP denotes nitroxide-mediated polymerization. Experimental conditions: I) [styrenic monomer]/[*N*-substituted maleimide]/[BlocBuilder MA] = 20:1:1, anisole, 115 °C; II) TBAF, THF, room temperature, overnight (this procedure was only applied to copolymers based on monomer **3** and MIs **4**–**7**); III) CuBr/dNBipy, THF, room temperature. dNBipy = 4,4′-dinonyl-2,2′-bipyridine, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

These optimal experimental conditions were selected for the sequence-controlled copolymerization of **3** with *N*-substituted maleimides (Table 1). In particular, five acceptor comonomers were tested in this study (Figure 1): *N*-(1-pyrenyl)maleimide (**4**), 4-(*N*-maleimi-

Table 1: Copolymers of **3** with *N*-substituted maleimides.[a]

	M	t_{add} [min][b]	t_{end} [min][c]	Conv.[d]	M_n[e]	$M_{n,th}$	M_w/M_n[e]
C1	**4**	120	315	0.72	4050	4000	1.14
C2	**5**	0	300	0.75	3900	3800	1.20
C3	**6**	120	240	0.71	4800	3600	1.14
C4	**7**	180	340	0.81	5000	4500	1.13
C5	**8**	120	240	0.78	4700	4200	1.18

[a] Experimental conditions: 115 °C, [**3**]/[MI]/[BlocBuilder MA] = 20:1:1, solution in anisole (**3**/anisole = 1:2 v/v, except for the synthesis of **C2**, in which case a 1:1 ratio was used). [b] Time at which the MI was added to the polymerization medium. [c] Final polymerization time. [d] Conversion of **3** at the end of the reaction. [e] The number-average molecular weight (M_n) and the mass-average molecular weight (M_w) were determined by SEC in THF. $M_{n,th}$ = theoretical number-average molecular weight.

do)azobenzene (**5**), *N*-(1-pyrenemethyl)maleimide (**6**), pentafluorophenyl 4-maleimidobenzoate (**7**), and TIPS-protected *N*-propargylmaleimide **8**. Monomers **4** and **6** were chosen since they enable the precise incorporation of a pyrene group in the polymer chain. It is known that such fluorescent and hydrophobic moieties are particularly useful for the characterization of water-soluble polymers.[23] Monomer **5** bears a photoswitchable azobenzene group, which is also of interest for tuning the hydrophilic–hydrophobic balance of PEG-based polymers.[24] Monomers **7** and **8** contain reactive functionalities that can be used after polymerization for local chain modification.[19,25]

The NMP copolymerization of a large excess of **3** (20 molar equivalents as compared to the initiator) with discrete amounts of *N*-substituted maleimides (an equimolar amount with respect to the initiator) enabled sequence control. As demonstrated previously,[8] by time-controlled addition, the MIs can be positioned at any desired location in the chains (i.e. the red bar in Figure 1 can be placed virtually anywhere). Thus, various copolymers with different microstructures were prepared (Table 1). In all cases, kinetic monitoring of the copolymerization by ^{1}H NMR spectroscopy evidenced a sequence-controlled copolymerization behavior. For example, Figure 2 shows the copolymerization kinetics recorded for the copolymerization of **3** and **7**. In this example, **7** was introduced into the reaction medium after the homopolymerization of **3** for 3 h (i.e. at a conversion of 52%). Directly after its addition, **7** was quantitatively polymerized within 10 min, whereas the conversion of **3** increased by only 5%. Afterwards the homopolymerization of **3** was pursued for an additional 2 h. These kinetic results show that **7** can be incorporated at very precise positions along the polymer backbone. Comparable kinetic trends were observed for all other copolymers (see Figures S2–S5). Moreover, all formed copolymers exhibited a controlled molecular weight (Table 1) and a narrow molecular-weight distribution (Table 1, Figure 2; see also Figures S2–S5). In general, polymers prepared by the sequence-controlled copolymerization of donor and acceptor comonomers exhibit a narrow composition distribution.[10]

Afterwards, PEGylation of the sequence-controlled copolymers was investigated. Emrick and coworkers reported a few years ago that CuAAC is an efficient reaction for preparing graft copolymers with PEG side chains.[26] Indeed, it enables a high-yielding "grafting-onto" process. Thus, we tested this method for grafting PEG side chains on the sequence-controlled backbones. The TMS groups of the pendant alkyne groups of the homopolymers and copolymers were cleaved with TBAF. In all cases, ^{1}H NMR spectroscopy showed quantitative TMS deprotection and the formation of terminal-alkyne units (see Figure S6). This result was also confirmed by size-exclusion chromatography (SEC). The deprotected copolymers appeared at a higher elution volume than their protected precursors (Figure 3). In most cases, the apparent weight loss after deprotection was about 25%, which suggests complete removal of the TMS groups. Moreover, all copolymers remained well-defined after deprotection (see Table S3).

The alkyne-functionalized copolymers were PEGylated by CuAAC with α-methoxy-ω-azido-PEG ($M_n \approx 2000\ g\,mol^{-1}$). ^{1}H NMR spectroscopic analysis indicated a nearly quantitative modification step (see Figure S7). Indeed, the signal of the terminal alkyne hydrogen atoms of the polymer fully disappeared after CuAAC, and characteristic signals due to the formation of a triazole ring appeared at 4.5 and 7.8 ppm. SEC also indicated the formation of well-

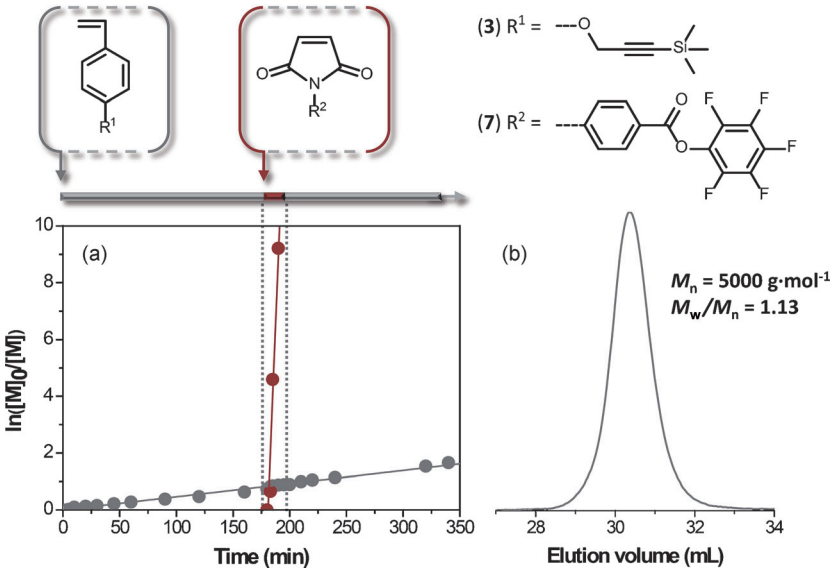

Figure 2. Example of sequence-controlled copolymerization: NMP of donor comonomer **3** and acceptor comonomer **7** with BlocBuilder MA in anisole. a) Semilogarithmic plots of comonomer conversion versus time. b) SEC chromatogram of the final copolymer after isolation. This example corresponds to copolymer **C4** in Table 1.

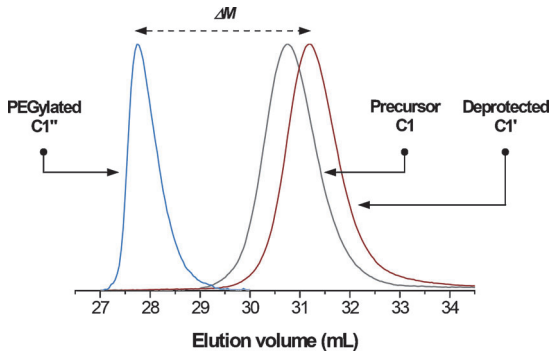

Figure 3. SEC chromatograms recorded in THF for the sequence-controlled copolymer **C1** before modification (gray), after removal of the TMS protecting group (**C1′**, red), and after CuAAC PEGylation (**C1″**, blue). For clarity, the signal of the remaining PEG-N_3 chains eluting at 30.7 mL was removed from the blue chromatogram. (See Figure S10 for the raw chromatograms of the PEGylated copolymer before and after dialysis.)

defined PEGylated graft copolymers (Figure 3; see also Table S3). Indeed, a significant molecular-weight increase was observed in all cases. This apparent gain in molecular weight (ΔM) was, however, lower than expected in most cases (e.g. for **C1**, a gain of 18000 g mol^{-1} was measured instead of 30000 g mol^{-1}). This underestimation is most probably due to the grafted topology of the formed copolymers. It is well-known that the hydrodynamic volume of PEG-grafted copolymers is smaller than that of linear SEC standards of similar molecular weight.[27] This assumption is also supported by an apparent decrease in the molecular-weight distribution after PEGylation (see Table S3). In all cases, the formed copolymers were found to be readily soluble in neutral water. Furthermore, ^{1}H NMR spectroscopy indicated that the sequence-controlled microstructure of the copolymers remained intact after PEGylation (see Figure S7).

The results described in the previous paragraph show that approach b (Figure 1) is simple and efficient for the preparation of sequence-controlled PEGylated copolymers. Moreover, this approach is compatible with additional postmodification steps. The functional microstructure of the copolymers can be tuned by using double-modification protocols.[28] For example, the sequence-controlled copolymer **C4**, which contains a pentafluorophenyl-activated ester group, was first locally modified by treatment with hexylamine (see Figure S8).[25] Afterwards, the TMS protecting group of the backbone was removed, and the polymer was PEGylated (see Figure S9). Site-selective CuAAC can also be performed on these copolymers.[13d] For example, copolymer **C5** contains a TMS-protected propargyloxystyrene backbone and a TIPS-protected local succinimide site. Owing to the larger excess of TMS groups in the copolymer, selective deprotection was only possible by using a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-based protocol instead of the conventional procedure with K_2CO_3.[29] Subsequently, the polymer was selectively PEGylated by CuAAC (see Table S3). After PEGylation, the TIPS protecting groups were removed with TBAF, thus making the alkyne site accessible for further modification.

In summary, the sequence-controlled copolymerization of donor and acceptor comonomers enables the preparation of PEGylated polymers with precisely controlled functional microstructures. However, the use of vinyl benzyl ethers of OEG as the donor monomer is not recommended. A finer control of the primary structure was possible with a CuAAC postpolymerization-modification strategy. This method enables the synthesis of a wide range of tailored functional PEGylated copolymers. This new class of macromolecules opens interesting avenues in the field of water-soluble polymers. Indeed, as elegantly shown by Terashima, Sawamoto, and co-workers,[30] precise microstructure variations (e.g. inclusion of discrete hydrophobic sites) in hydrophilic copolymers allow the fine-tuning of their properties in water. It is also clear that the present strategy is not restricted to PEGylation. Indeed, as shown in numerous studies, CuAAC postmodification can be used to prepare a wide variety of functional backbones (e.g. glycopolymers, polyelectrolytes, and polymers with high glass-transition temperatures).[19,31] Thus, the present method is probably the most versatile approach reported to date for the preparation of functional sequence-controlled copolymers.

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