Sequence-Regulated Polymers

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Sequence-Regulated Radical Polymerization with a Metal-Templated Monomer: Repetitive ABA Sequence by Double Cyclopolymerization**

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In nature, macromolecules are generated by elaborate mechanisms, often involving a template, in which the sequence of repeating units (i.e., monomers) along a main chain is perfectly programmed or regulated. In peptides, for example, the repeat unit sequence is well-defined, although as many as 20 amino acid comonomers are involved in the polymerization process. Thanks to these well-defined sequences, even a single molecule of a biologically formed polypeptide (protein) forms a specific structure through hydrogen-bond-directed folding to efficiently function as, for example, an enzyme.

From this viewpoint, the "sequence" should be the most essential structural factor for polymers, but no one thus far can regulate the sequence of synthetic polymers. An exception is the solid-phase synthesis of "artificial" peptides;[1] however, this strategy of circumvention based on repetition of stepwise reactions of monomers requires complicated procedures such as protection, deprotection, and purification. Therefore, manipulation of the polymerization through templates, as observed for natural polymers, is promising for regulating the sequences of artificial polymers.

Herein, we provide a strategy for such a template-based sequence-regulated artificial polymer synthesis by radical polymerization.

Radical polymerization, a chain-growth polymerization of vinyl monomers, is important for industrial polymer production. The majority of products from radical polymerization is in fact copolymers in which the composition of the repeat units statistically depends on the reactivity ratio of the monomers or on an "average" within molecules of varying compositions. Accordingly the "absolute" sequence is ill-defined, not precisely controllable, and often statistically distributed. An exception is the so-called alternating copolymerization, giving an ABABAB… regular sequence, by modulating the reactivity ratio of the monomers by, for example, the addition of a Lewis acid.[2]

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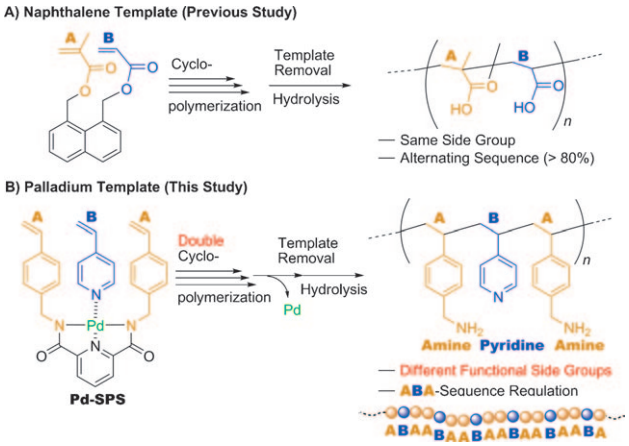
Now that such primary structural factors as, for example, the chain length, finally can be controlled in recently discovered living radical polymerizations,[3] the sequence of polymers is recognized as the next structural factor that can be controlled precisely in artificial polymerizations to express advanced functions of polymers as observed in nature.[4]

We have thus focused on template-based sequence regulation in living polymerization by designing initiators[4g–i] and monomers.[4j] A recent example which is in line with the design of monomers is to employ a naphthalene framework as a template that anchors two monomeric units (e.g., methacrylate and acrylate) spatially close to each other in the peri-position through a "cleavable" ester linkage (Scheme 1 A).[4j] Such an AB-templated divinyl monomer can be polymerized by a metal-catalyzed living radical polymerization under diluted conditions to give soluble polymers without the effect of gelation. Upon hydrolysis of the ester linkers and subsequent methylation, the resultant copolymers proved to possess highly regulated methyl methacrylate–acrylate AB-alternating sequences. Because the conventional radical copolymerization of these two monomers gives totally random sequences, this result is significant, because it suggests the possibility of template-assisted sequence regulation beyond the inherent reactivity ratio. Though effective the naphthalene-based design is by definition confined to AB-alternating sequences alone and, equally serious, would be cumbersome and laborious to realize regulated sequences of hydroxyl, amino, and other functional groups, unless far more versatile and perhaps orthogonal linkers other than ester groups are designed.



Scheme 1. Sequence-regulated radical polymerizations using a Pd-templated monomer.

Table 1: Radical Polymerization of Pd-SPS.[a]

Entry	Initiator	Solvent	T [°C]	t [h]	Conv [%] (S/P)[c]	Polymerization[d]	Structural Analyses[f] M_n (M_w/M_n)[g]	CE[h]
1	V-65	DCE	40	0.25	11/9	heterogeneous	–	–
2	V-65	Ethanol	40	0.25	5/7	heterogeneous	–	–
3	V-65	HFPP	40	3	61/58	homogeneous [e]	–	–
4	V-70	HFPP	−5	48	30/30	homogeneous	28000 (3.16)	75%
5	V-70[b]	HFPP	−30	96	30/30	homogeneous	24000 (2.50)	85%
6	V-70[b]	HFPP	−30	60	58/60	homogeneous	19000 (2.14)	90%
7	V-70[b]	HFPP	−60	120	32/33	homogeneous	18000 (2.10)	95%

[a] Polymerization: $[\text{Pd-SPS}]_0 = 50$ mM; $[\text{Initiator}]_0 = 5$ (40 °C) or 20 (< −5 °C) mM. [b] The azo-initiator was irradiated at $\gamma = 375$ nm. [c] The consumption ratio of the vinyl groups was determined by ^{1}H NMR spectroscopy. [d] The appearance of the polymerization solution; heterogeneous: some precipitation was observed during the polymerization, homogeneous: the polymerization proceeded homogeneously. [e] The polymerization proceeded homogeneously, but the product after reprecipitation by adding methanol was insoluble in any solvent. [f] The structures of products were analyzed after removal of the palladium template through reaction with a bisphosphine ligand (dppp) in the presence of Et_3N and H_2O: see the Supporting Information. [g] Determined by size exclusion chromatography (SEC) with poly(methyl methacrylate) calibration (see Figure S4 in the Supporting Information). [h] Cyclization efficiency, estimated by ^{1}H NMR spectroscopy (see Figure S5 in the Supporting Information).

Herein, we thus turned our template design to metal-complex frameworks that anchor, through readily cleavable coordination bonds, more than two monomeric units carrying different functional groups (Scheme 1B). This approach is particularly advantageous in anchoring various functional monomers in a well-defined geometry that ensures a selective intramolecular propagation into an ABA, ABC, and other triple-unit alternating sequences. For example, we designed a palladium-templated structure (Pd-SPS), in which two styrene (S) and one 4-vinylpiridine (P) units are programmed to align through tridentate 2,6-dicarboxyamido-pyridine and monodentate pyridine.[5] The strategy is to achieve selective, intramolecular, and directional double cyclopolymerization (S→P→S) at the Pd template to form ABA-alternating copolymers. Upon removal of Pd and hydrolysis of the amide groups, we receive polymers of repetitive sequences of ABA functionalities of two amine (A) and one pyridine (B) units.

Crucial in the template design is the π–π-stacking interaction between aromatic groups of the three monomeric units to align an array of the three vinyl groups at the Pd scaffold. The alignment effect contributes to restraints on unfavorable propagations, for example, the S→S propagation skipping the central P unit and the predominant attack of a growing radical onto P skipping the periphery S units, both leaving dangling alkene units that in turn result in crosslinking and/or irregular sequences.

The stacking interaction in Pd-SPS was indeed confirmed by ^{1}H NMR spectroscopy (see Figure S1 in the Supporting Information): The aromatic proton peaks from the S units clearly shifted to upper field, when the acetonitrile ligand in the precursor was replaced with a P unit. Molecular mechanics analysis (MM2) demonstrated a π-stacked structure and a reachable distance (around 0.37 nm) between the neighboring vinyl groups (see Figure S2 in the Supporting Information).[6]

Despite the seemingly rational design of the Pd-SPS structure, achieving the double cyclopolymerization was not straightforward.[7] For example, a diluted free-radical polymerization from Pd-SPS (50 mM) with an azo-initiator [2,2′-azobis(2,4-dimethylvaleronitrile), V-65, 10 h half-life decomposition temperature $T_{1/2} = 51$ °C] at 40 °C in common solvents [dichloroethane (DCE), ethanol, etc.], soon gave insoluble precipitates even at earlier reaction stages (Table 1, Entries 1 and 2). The free rotation of the methylene spacer in the outer S unit probably swings away its vinyl group from the central P part, and the dangling unsaturated vinyl group thus led to crosslinking (Figure 1A).

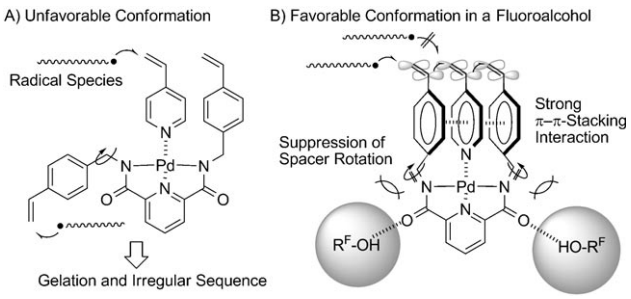


Figure 1. Proposed conformations of the Pd-SPS monomer.

This problem was circumvented by employing a bulky fluoroalcohol (1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol; HFPP) solvent in which the strong affinity of the electron-deficient hydroxyl moiety to the amide groups of the template was expected to suppress the rotation of the spacers and thereby to "fix" the triple vinyl alignment (Figure 1B).[8] Consequently, the polymerization in HFPP proceeded without any precipitation, and the three vinyl groups almost equally reacted (conversion after 3 h: S: 61%; P: 58%; Table 1 Entry 3). The interaction of HFPP with the amide groups was confirmed by ^{1}H and ^{13}C NMR spectroscopy (see Figure S3 in the Supporting Information). In the presence of HFPP (20 v% in $CDCl_3$), the ^{13}C NMR carbonyl peak of Pd-SPS shifted to downfield ($\delta = 171.1$ ppm from $\delta = 171.8$ ppm in pure $CDCl_3$). Furthermore, the styrene aromatic protons clearly shifted on the addition of HFPP. These observations support the favorable stacked conformation predominant through the carbonyl interaction in HFPP.

Although the polymerization homogeneously proceeded in HFFP at 40 °C, the resultant polymers were no longer soluble after reprecipitation into methanol (Table 1, Entry 3).

This suggests that crosslinking was not perfectly eliminated even in HFPP. Thus, to suppress the molecular mobility within the monomer (flipping a vinyl group into a unsuitable position), polymerization was performed below −5 °C with a low-temperature radical initiator [2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), V-70, $T_{1/2} = 30$ °C] and/or under UV irradiation (Table 1, Entries 4–7). Even at −60 °C, the polymerization smoothly proceeded, and both styrenic and pyridinyl vinyl groups were consumed in parallel, indicating the intramolecularly propagating double cyclopolymerization on the template.

The isolated polymers were now soluble after reprecipitation, whereas the low mobility of the repeat units, bound to the metal-complex framework, hampered ^{1}H NMR structural analyses. Therefore, the Pd template was removed by ligand exchange with a bisphosphine [1,3-bis(diphenylphosphino)-propane; dppp] (see Scheme S1 in the Supporting Information).[9] The products exhibited now well-resolved ^{1}H NMR spectra indicative of the expected ABA structure (see Figure S5 in the Supporting Information): the main chain protons (*a*, *b*, *i*, and *j*; 1–2 ppm, 9 H), the pendent aromatic protons of the P units [*c*, *d*, and *k*; $\delta = 6.0$–7.3 ppm, 10 H (obd, 9.5 H)], and other protons (*g*, *h*, and *l*; $\delta = 8.0$–8.5 ppm, 5 H). Though minor olefinic signals (*a*′) were observed at $\delta = 5.6$ and 5.1 ppm, derived from the unreacted styrene, the relative intensity of the major signals indicated a high efficiency of cyclization[10] that increased at lower temperature to reach as high as over 95 % at −60 °C.

The Pd-free polymers were subsequently subjected to acidic hydrolysis to remove the tridentate ligand. A sample (vinyl conversion around 60 %; Table 1, Entry 6) was heated with concentrated hydrochloric acid for 36 h, followed by reprecipitation into an aqueous sodium hydroxide solution. The ^{1}H NMR spectrum of the ligand-free polymer was quite similar to that of statistically random copolymers of 4-aminomethylstyrene (S) and 4-vinylpyridine (P) with a similar composition (see Figure S6 in the Supporting Information). The S/P ratio was 69:31 and agreed well with that (67:33 or 2:1) of the original product of the Pd-SPS monomer. These results further support a fair control of the repetitive sequential propagation (S→P→S) along with clean and quantitative removal of the template, and the final product is nominally an S-P-S alternating terpolymer obtaind by template-assisted regulation of the polymer sequence.

Finally, the sequence of repeat units was analyzed by ^{13}C NMR spectroscopy.[11] Figure 2 A shows the aromatic region of a ^{13}C NMR spectrum ($\delta = 138$–146 ppm) of the product after template cleavage. For comparison, a series of statistically random copolymers as well as homopolymers of S and P with varying compositions were separately prepared and analyzed similarly [Figure 2 B–F; S/P = 100/0 (B), 83/17 (C), 50/50 (D), 17/83 (E), and 0/100 (F)]. The copolymerization reactions were almost random, and thus the composition of the copolymers at low conversion was close to the initial ratio of the comonomer feed.

All the samples exhibited two sets of broad signals assignable to two aromatic carbon atoms of the 4-aminomethylstyrene unit (S): C1 adjacent to the main chain ($\delta =$ 139.9–141.8 ppm) and C4 in *para* position to C1 ($\delta = 141.8$–149.9 ppm). The peak broadening is known to result from the sequence and tacticity of the main chain.[11] As shown by comparison of the positions and the shapes of these peaks, the broad and multiple aromatic peaks were assigned in terms of triad sequences of the main chain: the large peak of C1 for the homopolymer of 4-aminomethylstyrene (S; $\delta = 140.5$ ppm, Figure 2 B) of course was attributed to the homotriad S-S-S. As the relative amount of P increased, the major C1 signals shifted downfield (Figure 2 C–E), and the large peak for the P-richest copolymer ($\delta = 141.7$ ppm; Figure 2 E) came from the P-S-P triad. Accordingly, the C1 peaks of the S-centered triad appear downfield as a function of the increasing P content in the order: S-S-S > S-S-P (or P-S-S) > P-S-P. The intermediate peak in Figure 2 C may therefore result from a mixture of S-S-S and S-S-P sequences, and that in Figure 2 D from a mixture of S-S-P and P-S-P sequences.

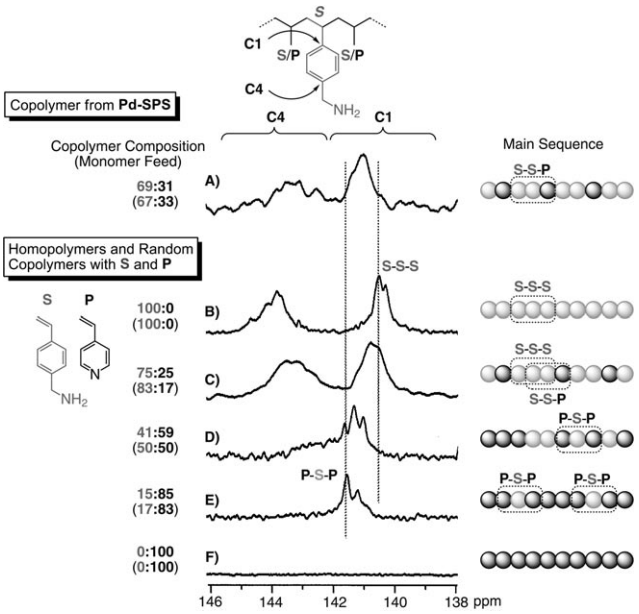


Figure 2. Sequence analyses by ^{13}C NMR spectroscopy: A) copolymer obtained from polymerization using the Pd-SPS monomer; B) homopolymer of 4-aminomethylstyrene (S); C–E) random copolymers of S with 4-vinylpyridine (P); F) homopolymer of P. See the Supporting Information for the conditions of the (co)polymerizations.

The copolymer obtained from the Pd-SPS monomer exhibited neither S-S-S nor P-S-P signals but a signal located between them ($\delta \approx 140.9$ ppm; Figure 2 A), which was, however, different from the similar intermediate peak for the S-rich random copolymer with mixed S-S-S and S-S-P sequences (Figure 2 C); note that the nominal S/P compositions are rather similar in the Pd-SPS product (69:31) and this S-rich copolymer (75:25).

On the basis of these arguments, the large C1 NMR peak of the Pd-SPS product is most likely assigned to predominant S-S-P triads (or S-P-S for P-centered triads; namely, …-S-P-S-S-P-S-S-P-S-…). A comparison of the C4 NMR peaks appears to support the periodic sequence. This in turn shows that the sequence of the main chain in the Pd-SPS homopolymer is an ABA (S-P-S) alternating terpolymer, as targeted and built by the tridentate palladium template. These repetitive regular

sequences of functional groups, such as the amine–pyridine–amine sequence obtained from the Pd-SPS monomer, possibly lead to specific functions, and these results will be presented in future.

In summary, repetitive ABA sequences were achieved with a palladium-templated monomer, Pd-SPS. Crucial in the synthesis were the π–π-stacking interactions between the aromatic side groups to array the three vinyl groups, and the interactions were enhanced in a bulky fluoroalcohol solvent through inhibition of spacer rotation. Thus, double cyclopolymerization was achieved through radically propagating species in fluoroalcohol (CE ≈ 95 %) to give soluble polymers. Removal procedures for the template led to sequence-regulated copolymers consisting of amine–pyridine–amine sequences, which were confirmed by NMR analyses. This study opens the door to controlled sequences of functional groups in copolymers.

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