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Compartmentalization of Single Polymer Chains by Stepwise Intramolecular Cross-Linking of Sequence-Controlled Macromolecules

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Supporting Information

ABSTRACT: We report the intramolecular double compaction of sequence-controlled linear macromolecules into "structured" random coils. These compartmentalized single-chain objects were prepared by performing successive cross-linking reactions in an orthogonal fashion. The foldable precursors were synthesized by sequence-controlled copolymerization of styrene with N-substituted maleimides (MIs), namely pentafluorophenyl 4-maleimidobenzoate (**1**) and TIPS-protected *N*-propargyl maleimide (**2**). These two functional MIs allow intramolecular cross-linking. The activated ester pentafluorophenyl moieties of **1** were reacted with ethylenediamine, whereas the deprotected alkyne functions of **2** were self-reacted by Eglinton coupling. The compaction of model copolymers containing only one cross-linkable zone (i.e., either **1** or **2**) was first studied. ^{1}H NMR and SEC analysis indicated that these structures could be efficiently compacted into single-chain objects. Thus, more complex copolymers containing two individually addressable cross-linking zones were prepared and sequentially compacted. Detailed characterization of the folding process indicated that double-compaction occurred and that the formed single-chain particles contain distinct cross-linked subdomains.

The functions of biomacromolecules such as enzyme activity, transport, signal transduction, and recognition are directly correlated to their higher order structure.[1] Inspired by biological principles, there is in recent years a significant research activity to achieve comparable functions with synthetic materials.[2] For example, the basic secondary structures of biopolymers such as single-chain helices, double helices, and sheets have been reproduced with synthetic stereoregular polymers and foldamers.[3] It was also recently shown that atactic polymer chains, which generally adopt an amorphous random coil configuration in solution, can be "structured" into more defined objects using intramolecular interactions.[4] For instance, a number of systems have been reported wherein synthetic polymer chains are compacted into single-chain nanoparticles by covalent bond formation.[5] The earliest example was reported by Hawker et al. who exploited the random intramolecular dimerization of benzocyclobutene units to form compact polystyrene nanoparticles.[6] Other covalent chemistries such as olefin cross-metathesis, copper-catalyzed azide−alkyne cycloaddition, Glaser coupling, and Diels−Alder reaction have been used afterward to prepare such single-chain particles.[7] It was also reported that noncovalent interactions [8] and dynamic covalent bonds[9] can be exploited to form collapsed random coils. Interestingly, Meijer, Palmans et al. have shown that the directional self-assembly of supramolecular motifs can be used to guide the compaction of single polymer chains.[10] These recent advances pave the way toward more complex single-chain objects.[11]

In fact, it seems that the inner structure of single-chain nanoparticles can be more complex than it was initially thought. In recent publications, Pomposo et al. have proposed that single-chain nanoparticles are not compact globules but rather more-complex "pearl-necklace" morphologies.[12] Comparable observations were recently reported by Meijer, Palmans et al. for polymers containing chiral and achiral supramolecular moieties.[13] These authors have also recently investigated the single-chain folding of block copolymers containing two different supramolecular motifs.[14] It was found that the block sequence of the foldable precursors influences the formed morphology.[15]

These important recent developments indicate that a pseudotertiary structure (i.e., distinct compacted subdomains) can be created inside single-chain nanoparticles. However, it is still a challenge to control accurately such compaction processes. In particular, the use of randomly distributed cross-linking moieties in the foldable polymer precursors severely limits morphological control. It seems obvious that the density and chain localization of the cross-linking sites need to be more precisely controlled in order to prepare finely structured single-chain objects. Here, recently introduced sequence-controlled polymerization methods have an important role to play.[16] In a recent series of papers, we have shown that precisely positioned covalent bridges can be used to shape atactic random coils into defined cyclic topologies.[17] Here, a related approach is described to control the compartmentalization of polymer single chains.

Single-chain objects containing two distinct compacted subdomains were designed using a three-step strategy (Figure 1). First, linear precursors containing precisely positioned cross-linkable units were prepared by sequence-controlled copolymerization. A few years back, our group developed a strategy to incorporate N-substituted MI units at precise locations inside polystyrene chains.[18] The concept relies on the fact that MI units are difficult to homopolymerize but exhibit highly favored cross-propagation tendency with styrene.[19] These marked differences

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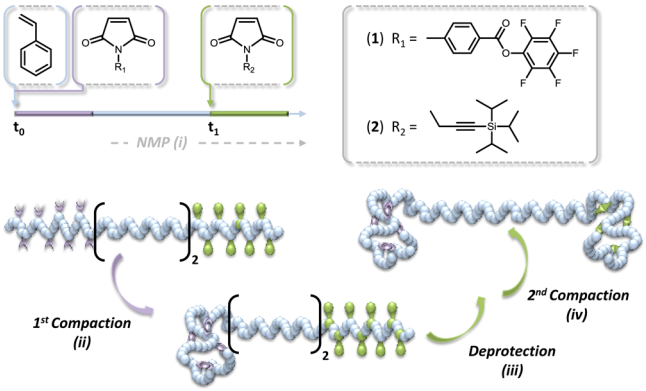

Figure 1. General concept used in the present work for preparing compartmentalized single-chain objects. A sequence-controlled precursor was first prepared by NMP of styrene with N-substituted maleimides **1** and **2** (top). Afterward this polymer was compacted in dilute conditions using a stepwise folding process (bottom). Note that the middle part of the copolymer is shown as an extended chain for clarity only. This segment is atactic and amorphous. Experimental conditions: (i) bulk, 120 °C, BlocBuilder MA; (ii) THF, RT, ethylenediamine; (iii) THF, RT, TBAF; (iv) THF, 60 °C, $Cu(OAc)_2$, piperidine.

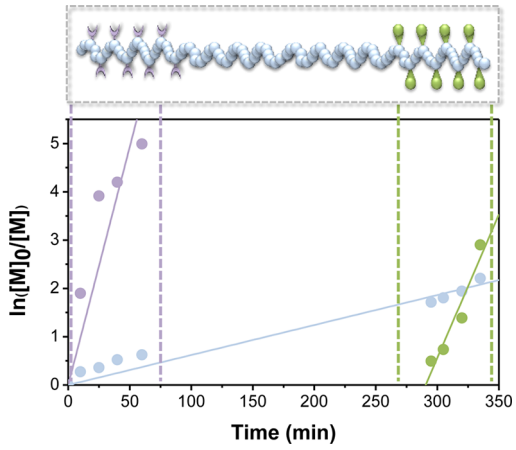

Figure 2. Semilogarithmic of monomer conversion vs time recorded for the sequence-controlled copolymerization of styrene (blue) with the N-substituted maleimides **1** (purple) and **2** (green).

in comonomer reactivity can be "written" in the polymer chains if a living polymerization mechanism is used to synthesize them,[20] e.g., a controlled radical polymerization method such as nitroxide-mediated polymerization (NMP).[21] This strategy was used in the present work to prepare copolymers containing distinct cross-linkable zones. It should be however noted that discrete amounts of MIs (i.e., 1−3 units per chain) were usually incorporated in the copolymer in previous studies. In the present case, higher amounts of MIs (i.e., ∼10 units per cross-linkable zone) were used in order to obtain an efficient chain-compaction. Two functional MIs were selected to prepare the cross-linkable precursors, namely pentafluorophenyl 4-maleimidobenzoate (**1**) and TIPS-protected *N*-propargyl maleimide (**2**). After copolymerization with styrene, the former monomer can be easily reacted with aliphatic primary amines,[22] whereas the latter can be deprotected and self-reacted by Glaser or Eglinton coupling.[23] As shown in Figure 1, these positionable reactive units were reacted intramolecularly in dilute conditions in order to form single-chain objects containing local compacted zones.

The cross-linkable sequence-controlled copolymers were prepared by NMP in bulk using the commercial alkoxyamine BlocBuilder MA (Table S1). Copolymers containing only one cross-linkable zone (i.e., using either **1** or **2**) were synthesized (Figures S1−S2). These model copolymers **P1** and **P2** were prepared in order to study individually the compaction steps (*vide infra*). In addition, a copolymer **P3** containing two cross-linkable zones (i.e., using both **1** and **2**) separated by a polystyrene spacer was synthesized. Figure 2 shows the kinetic of copolymerization recorded by ^{1}H NMR during the synthesis of **P3**. The copolymerization was started using 300 molar equiv of styrene and 12 molar equiv of **1**. As demonstrated in a previous study,[22a] **1** is copolymerizing extremely fast with styrene. Complete conversion of **1** was observed after 30 min of reaction, whereas conversion of styrene was 30% during the same time interval. This suggests that all of the **1** units were distributed in a specific region of the formed copolymer chains. It should be specified that a dense alternating zone P(S-*alt*-**1**) was not targeted in the present work since the cross-linking moieties should probably not be too close to each other for optimal compaction. Afterward the copolymerization was pursued for an additional 285 min, thus resulting in the formation of a polystyrene spacer of ∼150 units. After that, **2** was added to the reaction mixture, and the polymerization process was continued for an additional 70 min. This MI was copolymerized quickly, thus resulting in the formation of a second cross-linkable zone. These results indicate that the formed copolymers exhibit a controlled microstructure. Moreover, size exclusion chromatography (SEC) measurements indicated that well-defined copolymers with controlled chain-lengths and narrow molecular weight distribution were prepared in all cases (Table S1).

The intramolecular compaction of the sequence-controlled copolymer was investigated in dilute THF solution. The folding of model copolymers **P1** and **P2** was first studied in order to verify that the chosen MIs allow efficient intramolecular cross-linking. In the case of **P1**, ethylenediamine was used as an external cross-linker. The two primary amine functions of this molecule react readily with the pentafluorophenyl (Pfp)-activated ester functions of **1**. The compaction process was studied by ^{1}H NMR and SEC analysis. In ^{1}H NMR (Figure S3), the aromatic protons of **1** shifted from 8.2 to 7.8 ppm, thus indicating the quantitative conversion of the Pfp-activated ester moieties into substituted amides.[17b,c,22a] These results were obtained using a small excess of NH_2 functions as compared to Pfp. Indeed, when an equimolar amount NH_2/Pfp was used, incomplete Pfp conversion was observed in NMR. Of course, using NH_2 functions in slight excess may reduce the probability of cross-linking and affect intramolecular compaction. However, intramolecular cross-linking was confirmed by SEC. The compacted polymer **P1**′ eluted at higher elution volume in SEC than its parent polymer **P1** (Figure S4). This result should be interpreted with care. Indeed, two opposite effects influence the elution volume of **P1**′. As originally demonstrated by Hawker et al.,[6] the compaction of a polymer chain should result in a reduction of its hydrodynamic volume in SEC (i.e., compacted structures elute at a higher volume than their parent precursors). However, in the present case, the cross-linking reaction also results in a molecular weight reduction. When reacted with the cross-linker, two units of **1** lose two Pfp moieties (i.e., -2×183 g·mol^{-1}) and gain one ethylenediamine spacer (+60 g·mol^{-1}). This molecular weight variation should be taken into account before calculating the compaction parameter $\langle G \rangle$ (Table S2). For the compaction **P1** → **P1**′, a $\langle G \rangle$ value of ∼0.5 was found.

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This result is in good agreement with previous literature data[6] and suggests an efficient chain-compaction. Moreover, high molecular weight shoulders due to intermolecular cross-linking could not be detected in the SEC chromatogram of **P1′**. However, a broadening of polydispersity was observed after compaction. Although such a behavior is not standard when intramolecular chain collapse occurs,[24] it was already described for single-chain nanoparticles prepared using external cross-linkers.[25] It should also be noted that **P1′** is not a conventional single-chain nanoparticle but a coil−globule hybrid object composed of a soluble polystyrene segment linked to a compacted domain. Such tadpole structures often give broad SEC traces.[26] Chain compaction was also observed for polymer **P2**. The TIPS-protecting groups of **2** were first removed using TBAF, thus affording the deprotected polymer ***d*-P2**. Quantitative deprotection was observed in ^{1}H NMR with the disappearance of TIPS protons at 1 ppm (Figure S5). The resulting polymer was then cross-linked by Eglinton coupling using copper(II) acetate and piperidine in dilute THF solution. The compaction ***d*-P2** → **P2′** was confirmed by a significant decrease of the apparent hydrodynamic volume in SEC (Figure 3). Moreover, intermolecular coupling was only weakly detected

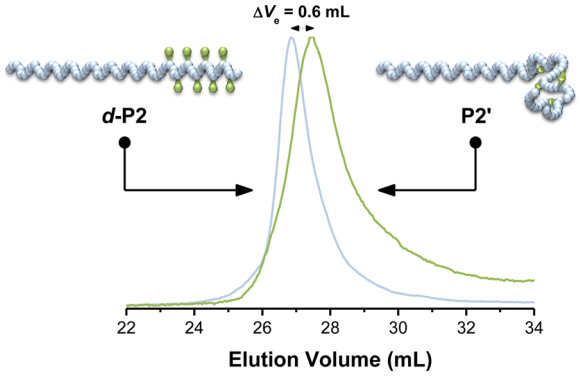

Figure 3. SEC chromatograms obtained in THF for the deprotected model copolymer ***d*-P2** before (blue) and after intramolecular compaction by Eglinton coupling into **P2′** (green).

in the chromatogram of **P2′**. All the results obtained with model copolymers **P1** and **P2** showed that the chosen cross-linking chemistries are suitable to prepare compacted single-chain objects.

The stepwise compaction of polymer **P3** was studied by ^{1}H NMR and SEC (Figures 4 and 5). As displayed in Figure 1, three individual steps are required to prepare a double-compacted structure: (i) intramolecular cross-linking of **1**, (ii) deprotection of **2**; and (iii) intramolecular cross-linking of **2**. These three steps have to be performed in that particular order since the labile PfP-activated ester units of **1** may not survive the experimental conditions used in steps (ii) and (iii). First of all, **P3** was transformed in a monocompacted species **P3′** by cross-linking the units of **1** with ethylenediamine in dilute conditions. As discussed above for **P1**, the characteristic signal of **1** at 8.2 ppm was shifted upfield of ∼0.4 ppm, thus indicating amide formation (signal a and a′ in Figure 4). It is relevant to note that the intensity of that new peak at 7.8 ppm is very weak in comparison to what we observed in earlier studies.[17b,c,22a] This behavior is probably due to the restricted motion of the cross-linked units in the compacted domain of the copolymer. This assumption is supported by the fact that the signature peaks from the non-cross-linked part (e.g., the signals due to the protons of **2**) of the

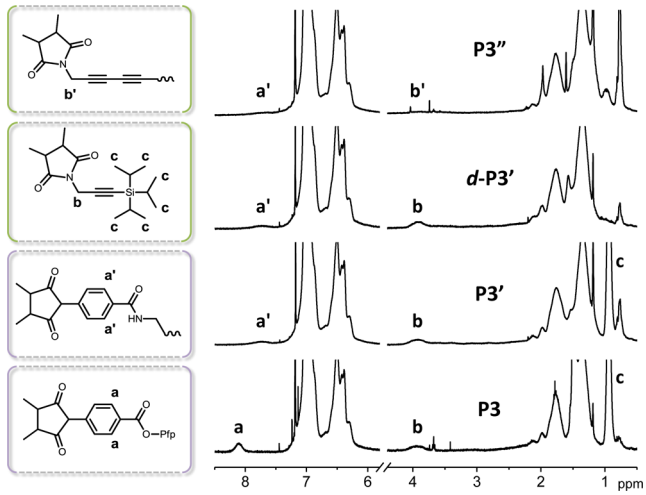

Figure 4. ^{1}H NMR spectra (regions 0.5−4.4 and 5.8−8.5 ppm) recorded in $CDCl_3$ for the sequence-controlled precursor **P3**, the monocompacted polymer **P3′**, the deprotected polymer ***d*-P3′**, and the final double-compacted copolymer **P3″**.

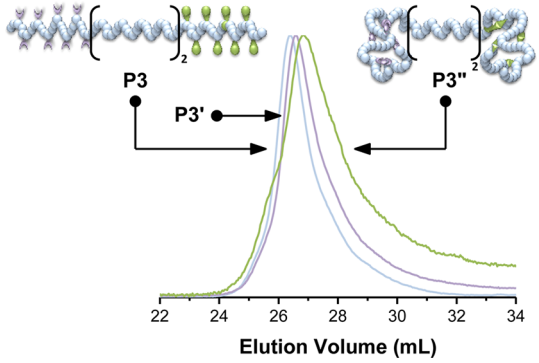

Figure 5. SEC chromatograms obtained in THF for the sequence-controlled copolymer **P3** before compaction (blue), after mono-compaction into **P3′** (purple), and after double compaction into **P3″** (green).

copolymer remain unaffected. Similar observations were reported for core cross-linked micelles and intramolecular cross-linking of a selective block in block copolymers.[27] Moreover, the intramolecular compaction **P3** → **P3′** was confirmed by a decrease of the apparent molecular weight in SEC (Figure 5 and Table S2). These differences allowed calculation of a ⟨*G*⟩ value of ∼0.9. This value is lower than the one calculated for **P1** → **P1′** since the molar fraction of **1** is lower in **P3** than in **P1**. In the next step, the TIPS-protecting groups of **2** were removed using TBAF. This step was not trivial with the partially cross-linked polymer **P3′** and had to be performed in dilute THF conditions. Indeed, at higher concentrations of **P3′** in THF, intermolecular cross-linking was observed during the deprotection step. Nevertheless, using optimal dilution, TIPS removal could be easily obtained. Quantitative deprotection was confirmed by the disappearance of the peak at 1 ppm due to the terminal methyl groups of the isopropyl functions (signal c in Figure 4). The deprotected copolymer ***d*-P3′** was then compacted by Eglinton coupling as described above for **P2**. Successful compaction was also evidenced by signal loss in NMR due to the restricted motion of the newly cross-linked sites. For instance, the peak at 3.9 ppm due to the methylene protons located between the succinimide ring and the alkyne moiety of **2**

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significantly vanished after cross-linking (signal b and b′ in Figure 4). In comparison, the compaction process did not affect the ^{1}H NMR signal shape of the polystyrene central segment. Furthermore, the SEC analysis of the double compacted polymer **P3″** indicated that intramolecular cross-linking occurred, even though a small amount of intermolecular cross-linking could be detected as well (Figure 5). Indeed, a clear decrease of apparent molecular weight of ∼5000 g·mol^{-1} was observed for ***d*-P3** → **P3″** (Table S2). These results suggest that the final copolymer **P3″** contains two distinct compacted subdomains linked together by a soluble polystyrene spacer.

In summary, complex single-chain objects containing distinct cross-linked subdomains were prepared. These folded macromolecules were obtained by stepwise intramolecular cross-linking of sequence-controlled precursors. This simple strategy is not limited to the model morphologies shown herein. Indeed, sequence-controlled copolymerizations allow almost unlimited design of tailored polymer microstructures, in which the amount and positioning of cross-linking sites can be precisely controlled. Thus, using orthogonal cross-linking chemistries, it seems that a wide variety of single-chain morphologies is attainable. Yet, it is important to remind that the physico-chemistry of complex single-chain objects is still *terra incognita*. Indeed, conventional polymer analytics are sometimes limited for characterizing small globular objects,[4a] even though significant progress has been recently made using SAXS and SANS techniques combined with MD simulations.[12,13] Nevertheless, the present results show that single-chain technology is becoming an important facet of modern polymer science.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental part, Tables S1−S2, and Figures S1−S5. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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