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Synthesis of Miktoarm Branched Conjugated Copolymers by ROMP In and Out

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Abstract

Architecture represents an underutilized yet promising control element in polymer design due to the challenging synthesis of compositionally varied branched copolymers. We report the one-pot synthesis of miktoarm branched polymers by ring-opening metathesis polymerization. In this work, we graft to and from telechelic poly(3-hexylthiophene), which is end-capped by oxime click chemistry, using various norbornene monomers. The self-assembly of the resulting miktoarm H-shaped conjugated polymers is studied in solution and in the solid state. A dual stimuli-responsive miktoarm polymer is prepared which displays pH-switchable lower critical solution temperature and fluorescence.

To address challenges in fields ranging from healthcare to engineering, polymer chemists are designing increasingly complex, tailored macromolecules that present programmed responses to external stimuli. This complexity is achieved through the combination of monomers with desirable roles (solubility, targeting, payload release, fluorescence) into copolymers. Controlled polymerization enables regulation of the connectivity and quantity of these diverse building blocks in the synthesis of block copolymers, which translates to nanoscale self-assembly. Ring-opening metathesis polymerization (ROMP), a robust living polymerization strategy, has been shown to deliver highly functionalized block copolymers that serve as sensors,¹ imaging agents,² drug delivery vehicles,³ photonic crystals,⁴ organic resistive memory devices,⁵ and membranes.⁶

In addition to control of composition, control of polymer architecture can be used to tune desired material properties. Branched polymers are known to exhibit lower solution viscosity compared to linear polymers of the same molecular weight due to reduced entanglement. Bulk properties of branched polymers are also distinct from their linear counterparts: densely grafted bottlebrush polymers have been shown to act as supersoft elastomers,⁷ and asymmetric miktoarm block copolymers (from the Greek word meaning “mixed”) have been used to access unique self-assembled structures.⁸ Creating a junction between three or more chemically distinct polymers, however, presents a considerable

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ASSOCIATED CONTENT

Supporting Information. Detailed synthetic procedures and sample preparation, SEC traces, NMR spectra, oxime decomposition studies, and control experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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synthetic challenge. Achieving such a linkage requires highly efficient and mild coupling reactions between macromolecules, as well as orthogonal chain extension chemistries (Scheme 1a). The rapid adoption of “click” chemistries⁹ by polymer chemists has greatly expanded access to block copolymers with complex architectures. Even with these new selective chemistries, miktoarm star polymers have primarily been limited to poly(ethylene oxide), poly(lactic acid), and/or polystyrene¹⁰ and rarely incorporate conjugated polymers.¹¹

Alternatively, we envisioned that three-arm branched miktoarm architectures could be accessed in one pot by an “in–out” grafting strategy. Two of these arms would be created by ROMP, allowing versatile functionalization, and the third would be installed as a norbornene end-capped macromonomer.

The “in–out” method has been previously applied to the synthesis of miktoarm star polymers. For “in–out” atom transfer radical polymerization (ATRP), the crosslinked intermediate must be isolated prior to grafting from. Gao and Matyjaszewski found that reinitiation efficiency is not quantitative because of steric congestion.¹² In contrast, Nomura and coworkers have prepared star polymers by ROMP in a facile one-pot, three-step procedure; the aldehyde used to terminate the polymerization is the primary source of structural and functional diversity (Scheme 1b).¹³ By using an end-capped polymer in the second step rather than a crosslinking agent, we can introduce additional chemical diversity into the copolymer (Scheme 1c). Moreover, we hoped to study the properties and self-assembly of the resulting well-defined branched miktoarm block copolymers. This strategy is termed “ROMPing in and out.”

In this study, we targeted branched macromolecular architectures containing a conjugated polymer segment. Using a telechelic norbornene end-capped conjugated polymer, the desired product is a miktoarm H-shaped polymer¹⁴ of the form ABCBA, wherein the central C block is the conjugated polymer. While miktoarm H-shaped polymers have been prepared using dimerization of branched triblock polymers,¹⁵ click chemistry,¹⁶ and noncovalent interactions,¹⁷ conjugated polymers have not been incorporated into this architecture. The Swager lab has previously developed fluorescent nanoparticle sensors^{1,18} and imaging agents² based on linear multiblock copolymers with conjugated central blocks. Furthermore, the self-assembly of linear rod-coil block copolymers has attracted much experimental and theoretical interest.¹⁹ We anticipated that ROMPing in and out would allow us to study the effect of chain architecture on the properties and assembly of this class of materials leading to the development of enhanced sensors and devices with active organic layers (OPV, OLED, etc.).

For the central conjugated block in the proposed H-shaped polymer, we selected poly(3-hexylthiophene) (P3HT). This choice was motivated by the significant body of literature characterizing polythiophenes and their utility in organic electronics²⁰ and chemoresistive sensory materials.²¹ Furthermore, P3HT can be prepared by controlled polymerization.²² We synthesized **P3HT1** using Kumada catalyst-transfer polycondensation (KCTP) and installed aldehyde end groups using Vilsmeier-Haack conditions developed by McCullough and coworkers (**P3HT1a**).²³ 5-Norbornene-2-endo-O-methylhydroxylamine (**1**) was then conjugated to **P3HT1a** by an oxime “click” reaction under mild acid-catalyzed conditions

(Figure 1a). Conversion of the aldehyde end group to an oxime could be established by ^1H NMR of **P3HT1o** (SI, Figure S8). Functionalization was further confirmed by MALDI-TOF. The molecular weight determined by SEC (M_n 4.32 kDa, PDI 1.15) based on calibration with polystyrene standards is higher than the average molecular weights calculated by MALDI-TOF ($\text{DP}_{\text{major}} = 10$, see SI) and ^1H NMR end-group analysis ($\text{DP}_{\text{average}} = 18$, 3.30 kDa), as expected for a rod-type polymer. For many applications of conjugated polymers, molecular weight is known to significantly affect crystallinity and thus charge-carrier mobility. Therefore, we prepared higher molecular weight **P3HT2** and subjected it to the same synthetic sequence. The oxime click reaction provided **P3HT2o** (M_n 17.3 kDa, PDI 1.32; SI, Figure S6); however, end-capping does not occur quantitatively (*vide infra*).

In contrast to the synthesis of star polymers, we needed to avoid crosslinking during the addition of the end-capped conjugated polymer; therefore, an excess of initiator and norbornene monomers was required relative to the conjugated polymer.

ROMP in and out was performed with **P3HT1o** using 5 equivalents of Grubbs' third generation catalyst (**GIII**) per end group (based on the molecular weight of **P3HT1o** determined by ^1H NMR) (Figure 1b). Importantly, the living nature of ROMP enables each step to be run to full conversion of the monomer or macromonomer.²⁴ For initial studies, the same norbornene monomer (**2**) was employed in both grafting-to and -from steps. Reaction aliquots could be removed after each step, quenched by ethyl vinyl ether, and analyzed by SEC to evaluate the reaction progress (Figure 1c). Conveniently, copolymers containing P3HT may be detected by diode array detection at 450 nm, while polynorbornenes lacking P3HT incorporation are only observed by refractive index detection. A 25:1 ratio of [**2**]: [**GIII**] provided homopolymer with M_n 13.5 kDa and PDI 1.04. Analysis of peak molecular weights following addition and reaction of **P3HT1o** revealed that the major product was the desired two-armed product. However, a lower molecular weight one-arm byproduct and a higher molecular weight P3HT oligomer were also formed. The one-arm product is a result of either incomplete grafting to, or singly-functionalized P3HT. Analysis of the reaction mixture following the second addition ("grafting from") and consumption of **2** revealed a shift in retention time of the polymer indicating formation of the branched polymer **P1**.

Because excess initiator and norbornene are used to disfavor oligomerization, a significant amount of homopolymer is also produced in the reaction. In the case of **P1**, the reaction mixture may be purified by centrifugal filtration from water with a regenerated cellulose membrane (100 kDa molecular weight cutoff) to remove homopolymer, providing 57% yield of copolymers.²⁵ The 4-arm species may be further purified from incompletely grafted copolymers by preparative SEC (M_n 49.2 kDa, PDI 1.13).²⁶

Oxime formation has gained popularity in click chemistry due to their improved stability under aqueous conditions relative to other aldehyde-derived functional groups, including hydrazones.^{27,28} Accordingly, **P1** is stable under neutral aqueous and anhydrous acidic conditions, but the oxime linkage is dynamic in the presence of acid and excess aminoxy or ketone, as described by Sumerlin and coworkers²⁹ (SI, Figure S24).

We prepared a variety of miktoarm H-shaped polymers that highlight the flexibility of ROMP in and out and access functional materials (Table 1). To study the self-assembly of amphiphilic H-shaped polymers containing P3HT in bulk and thin films, we subjected **P3HT1o** and **P3HT2o**³⁰ to ROMP in and out using monomers **3** and **4** to provide H-shaped polymers **P2-*t*Bu** and **P3-*t*Bu**. Deprotection of the *t*-butyl esters by TFA provided amphiphilic polymers **P2-OH** and **P3-OH**. Trimmel and coworkers demonstrated that symmetrical diblock polynorbornenes derived from **3** and *endo,exo*-**4** cast from THF, a nonselective solvent, form lamellar nanostructures.³¹ In our system, however, the grafting-from step is inefficient with *endo,exo*-**4** (SI, Figure S26), so we employed *exo,exo*-**4**.³² It is well known that the crystallization of P3HT interferes with block copolymer self-assembly, resulting in nanofibrillar structures.³³ To discourage crystallization-driven self-assembly, we solvent-annealed **P2-OH** and **P3-OH** as blends with the corresponding polynorbornene diblocks. Indeed, we observed scattering peaks in a 1:2 ratio consistent with lamellar structures by small-angle X-ray scattering (SAXS); lamellae were also observed in solvent-annealed thin films by atomic force microscopy (AFM) (Figure 2). The d-spacing observed by SAXS (41 nm for **P2-OH** and 35 nm for **P3-OH**) is consistent with AFM observations, and greater than the spacing for the diblock alone (29 nm).³¹

Chemically distinct norbornene monomers may be employed to prepare miktoarm H-shaped polymers with tunable solubility. Specifically, materials with fluororous solubility are attractive due to the orthogonality of the fluororous phase to traditional organic and aqueous solvents, enabling the preparation of stable nanoemulsions³⁴ and complex emulsions.³⁵ Fluororous monomer **5** and hydrophilic monomer **6** represent extremes of chemical incompatibility while maintaining solubility in CHCl₃ during polymerization. The resulting amphiphilic polymer **P4** is obtained as a mixture of 3- and 4-armed P3HT, contaminated by diblock poly(**5-*b*-6**) (see SI for details). This material, due to the distinct solubilities of the P3HT, fluororous, and hydrophilic blocks, is fully soluble in THF and CHCl₃ but forms stable nanoparticles in DCM, water, and methyl nonafluorobutyl ether. The particle sizes were determined by dynamic light scattering (DLS) and the morphologies examined by transmission electron microscopy (TEM) to reveal bimodal distributions of spherical particles (Figure 3). We hypothesize that the smaller particles correspond to aggregates of poly(**5-*b*-6**), while the larger particles correspond to **P4** or a mixture of both species. While the particles formed in DCM and water display uniform contrast, the particles formed in the fluororous solvent contain a small region that appears lighter under bright field TEM and darker under low-angle annular diffraction (LAADF-STEM, SI, Figure S25). Based on previous work demonstrating that polymers with higher density have bright contrast by LAADF³⁶ and the characteristically high density of perfluorinated compounds, we propose that the larger region of the asymmetric particle corresponds to fluororous polymer.

Finally, dual-responsive fluorescent nanoparticles were prepared to highlight the potential utility of this architecture for sensing and delivery applications. **P5-*t*Bu** may be prepared from monomers **3** and **7** and deprotected by TFA to provide **P5-OH**, which bears pH-responsive and thermoresponsive arms. Poly-**7** is a known thermoresponsive polymer displaying a lower critical solution temperature (LCST) at 25 °C.³⁷ Polyelectrolyte block copolymers derived from **3** have been shown to form pH- and ionic strength-responsive

micelles, which undergo a transition in size between pH 5 and 6.³⁸ Neutral aqueous solutions of **P5-OH** may be purified from the polynorbornene diblock by centrifuge filtration. At pH 3, **P5-OH** forms 45 ± 11 nm particles displaying a LCST at 20.5 °C, as determined by DLS and transmission measurements (Figure 4). At pH 7, however, the polymer forms 147 ± 45 nm particles that do not exhibit a LCST up to 100 °C. Additionally, **P5-OH** is fluorescent at pH 7 but nonemissive at pH 3 (Figure S35). Taken together, these data suggest that when the carboxylic acids are deprotonated, electrostatic repulsion and favorable hydration provide larger particles of **P5-OH** with loosely aggregated P3HT; due to the polyanionic arms, the characteristic coil–globule transition of poly-**7** is prevented.

In contrast, the branched homo-arm and linear pentablock analogues of **P5-OH** do not display pH-dependent LCST behavior (see SI for details). A H-shaped polymer with poly-**7** arms displays a LCST at 20.5 °C at pH 3 and 7. More intriguingly, linear analogue poly(**7-b-3-b-P3HT-b-3-b-7**), after deprotection, forms nonemissive 79 ± 24 nm particles and displays a LCST of 20 °C at both pH values. The interplay of pH, temperature, and fluorescence response is unique to the miktoarm H-shaped polymer and suggests that this branched architecture could be relevant to the design of aqueous conjugated polymer sensors.

In conclusion, we have demonstrated that grafting to- and from- a norbornene end-capped telechelic polymer may be performed in one pot and provides access to miktoarm H-shaped polymers with minimal crosslinking. While a variety of telechelic polymers can be envisioned as the central block, we employed end-capped P3HT prepared by oxime click chemistry. The oxime linkage is robust under aqueous conditions, but can be cleaved by acidic aqueous oxime exchange. As a result of the functional group tolerance of catalyst **GIII**, a variety of functionalized arms may be installed by ROMPing in and out. Using this strategy, we have synthesized several miktoarm polymers with targeted responsive and self-assembly behaviors. We anticipate that ROMPing in and out will significantly expand synthetic access to complex branched polymers with controlled sequence and architecture.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Synthesis of norbornene end-capped **P3HT1o** by an oxime click reaction. (b) ROMP in and out. (c) SEC traces (450 nm detection) for **P3HTo** (magenta) and reaction progress for ROMP in (blue), and ROMP in and out (green). (d) SEC traces (RI detection) before (dashed) and after (solid) purification of **P1**.

Figure 2. Self-assembly of **P2-OH** and **P3-OH** blends as characterized (a) in bulk by SAXS and (b,c) in thin films by AFM (phase contrast, scale bar: 500 nm).

Figure 3. TEM images of **P4** in (a) DCM, (b) water, and (c) methyl nonafluorobutyl ether. Scale bars: 200 nm (a,b), 1 μm (c). Insets: effective diameters determined by DLS.

Figure 4. Effective diameter (error bars are polydispersity) at pH 3 (blue squares) and pH 7 (red triangles) for (a) **P5-OH**, (b) a homo-arm analog, and (c) a linear pentablock analog. Inset: photographs of **P5-OH** below (left) and above (right) 21 °C.

(a) Previous approaches to miktoarm branched polymers: **(b)** Star polymer synthesis by "in-out" ROMP (ref. 13): **(c)** This work:

Scheme 1. Synthetic approaches to miktoarm branched polymers

Table 1
Synthesis of miktoarm branched P3HT polymers

name	1 st monomer <i>a</i>	P3HT	2 nd monomer <i>b</i>	M_n^b	<i>b</i>
P2-<i>t</i>Bu	3 (100)	P3HT1o	4 (100)	124	1.07
P3-<i>t</i>Bu	3 (100)	P3HT2o	4 (100)	129	1.05
P4	5 (50)	P3HT2o	6 (50)	54.5	1.21
P5-<i>t</i>Bu	3 (10)	P3HT1o	7 (90)	232	1.05

^aEquivalents relative to **GIII** shown in parentheses.

^bSamples were purified by preparative SEC, and molecular weights determined by SEC relative to polystyrene standards in THF. See SI for details.