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Communication

Monodisperse Macromolecules by Self-Interrupted Living Polymerization

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ABSTRACT: Biological macromolecules such as proteins and nucleic acids are monodisperse just as low-molar-mass organic compounds are. However, synthetic macromolecules contain mixtures of different chain lengths, the most uniform being generated by living polymerizations, which exhibit a maximum of 1−3% of chains with the desired length. Monodisperse natural and synthetic oligomers can be obtained in low quantities by tedious, multistep iterative methods. Here we report a methodology to synthesize monodisperse synthetic macromolecules by self-interrupted living polymerization. This methodology relies on a concept that combines supramolecular and macromolecular chemistry and differs from the conventional reactivity principles employed in the synthesis of polymers for over 100 years.

For 100 years,[1a−d] macromolecular synthesis has relied on the reactivity of species being independent of the degree of polymerization (DP)[1e] and produced mixtures of polymers of different chain lengths.[2] When growing species do not undergo side reactions, living polymerizations (LPs)[3−8] result. LPs produce macromolecules with predictable molecular weights (MWs) and Poisson MW distributions (M_w/M_n = 1 + 1/DP).[5] The most perfect polymers obtained by LPs contain a maximum of 1−3% of their chains having the desired MW. In contrast, biological macromolecules such as nucleic acids and proteins are perfectly monodisperse, M_w/M_n = 1.00. Monodisperse synthetic macromolecules, derived from both natural[9−12] and synthetic[13−18] repeat units, can be synthesized by multistep iterative methods and by genetic polymerization.[19,20] However, monodisperse macromolecules cannot be obtained by simple LPs, and current iterative methods to generate them are laborious, step-intensive, and limited to low molar mass and small scale.[9−18] Here we report a simple living ring-opening metathesis polymerization (ROMP) that undergoes self-interruption of its active growing chains, providing a methodology to synthesize monodisperse macromolecules (M_w/M_n = 1.00) by chain reactions. The key component of this concept is a self-interruption process in which encapsulation of the reactive chains reduces their reactivity to zero at a certain DP. This decrease in reactivity with increasing molecular size was predicted[21] and demonstrated[22,23] for the iterative synthesis of dendrimers[13] and is transplanted here to generate monodisperse macromolecules by self-interrupted living polymerization (SILP). We expect that SILP may be extended to other perfect LPs[24] and therefore may be employed to produce monodisperse synthetic macromolecules (M_w/M_n = 1.00) that can evolve into biological-like and other atomic-level[25] designed functions. This concept could initiate the development of additional methodologies toward monodisperse synthetic macromolecules.

Figure 1 compares conventional chain, step, and living polymerizations and the evolution of their most important features with those of the SILP reported here.[1−5] Substituted 7-oxanorbornene monomers **3a**, **3b**, and **3c** were subjected to living ROMP[6−8] at 23 °C with the Grubbs catalyst $RuCl_2({=}CHPh)(PCy_3)_2$ (Figures 2A and S1).[6−8] Conventional monomer **3a**,[7] tapered monomer **3b**[8] that forms a columnar polymer with growing-chain reactivity independent of the chain length, and monomers closely related to **3b**[8] undergo classic ROMP, as exemplified in Figure 1A−C, while monomer **3c** undergoes SILP, as outlined in Figures 1D−F and 2.

At higher temperature under conventional free radical polymerization, methacrylates and styrenes related to **3b** and **3c** do not undergo SILP or self-interrupted polymerization.[26,27] We envisioned that polymers jacketed with rigid conical self-assembling dendrons[26−32] would force the interruption of the LP at room temperature at an exact number of repeat units required to enclose a spherical shape. To demonstrate this hypothesis, we focused on ROMP of monomer **3c**. Regardless of its steric crowdedness, ^{1}H NMR spectroscopy proved that the initiation efficiency was close to 100% using the first-generation Grubbs catalyst (Figures 2A and S1) that was already used in the ROMP of **3a**[7] and **3b**.[8] Within the limits of ^{1}H NMR spectroscopy, the initiation step was quantitative after 1 h, as indicated by 100% addition of the catalyst to **3c** to generate the two stereoisomers of their adduct (i.e., DP = 1) (Figure S2). At longer times, a broad signal was

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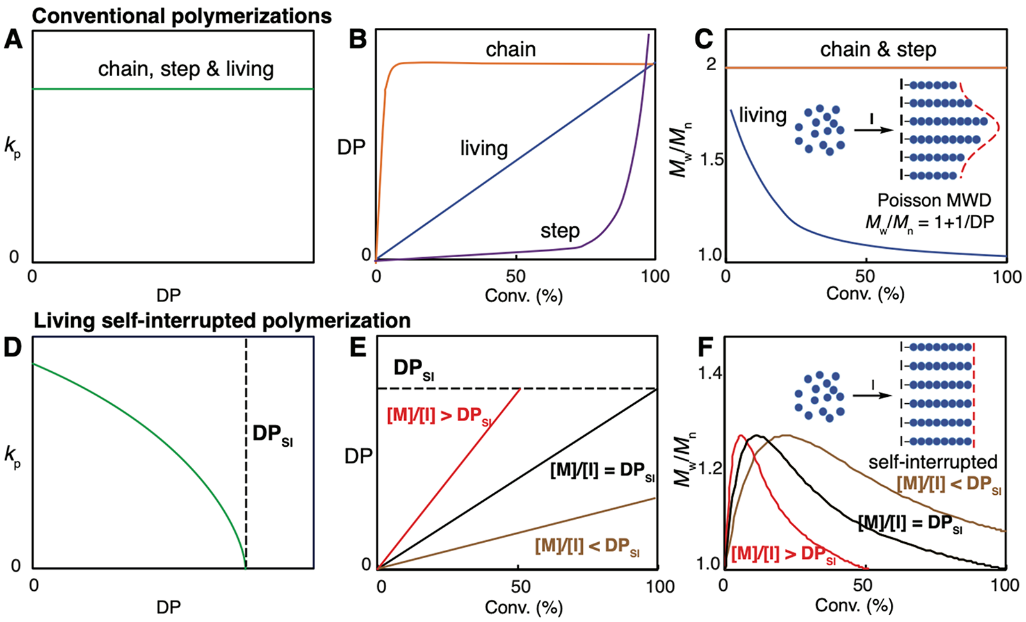

Figure 1. Comparison of conventional chain, step, and living polymerizations (top) with SILP (bottom). (A, D), k_p vs DP. DP_{SI} denotes the degree of polymerization at which polymerization self-interrupts. (B, E), Dependence of DP on monomer conversion. In (E), [M] denotes the concentration of monomer and [I] the concentration of initiator. (C, F) Dependence of the polydispersity (M_w/M_n, where M_w is the weight-average MW and M_n is the number-average MW) on the monomer conversion.

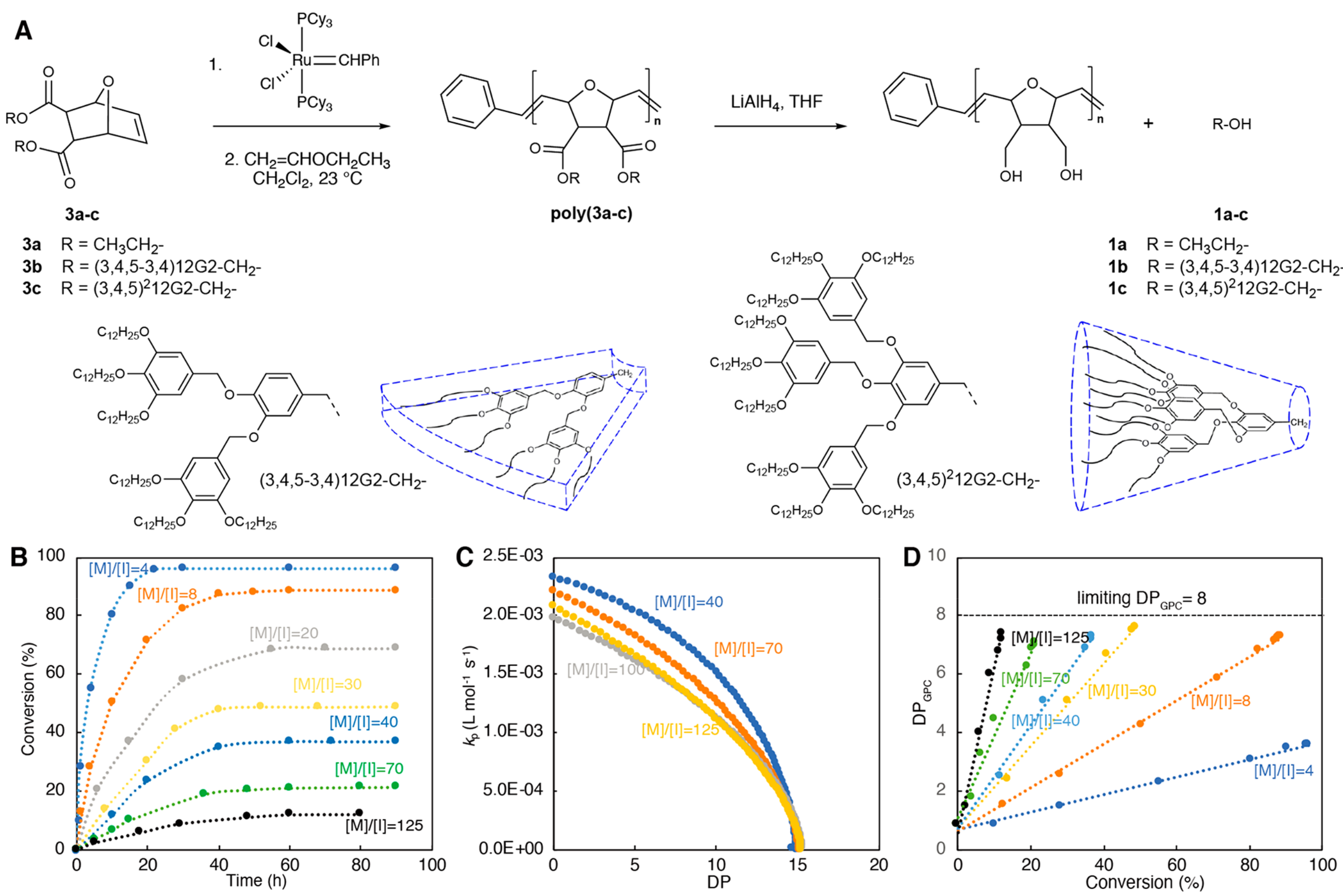

Figure 2. (A) Chemical structures of dendritic oxanorbornene monomers **3a–c** and their polymerization and cleavage. (B–D) Kinetics for SILP of **3c**: (B) monomer conversion as a function of time; (C) selected examples of k_p against DP; (D) DP determined by gel-permeation chromatography (DP_{GPC}) as a function of monomer conversion. DP_{GPC} is lower than the true DP. Dashed lines in (B) and (D) are guides for the eye.

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observed because of the more rigid polymer chains at higher DPs.

The ROMP of **3c** was investigated using different $[\mathbf{3c}]_0$:catalyst ratios (Figure 2B). In all cases, $[M]_0$ was maintained constant at 0.073 M to avoid solution self-assembly of the monomer.[27] A remarkable result is the lower limited conversion as the $[M]_0/[I]_0$ ratio increased. Although at first sight this could be due to the decrease in $[I]_0$, the rates of polymerization were much lower than predicted by eq 1,

$$x = 1 - e^{-k_p[I]_0 t} \tag{1}$$

where x is the fractional conversion and t is the reaction time (Figure S3). The experimental initial rate was identical to the predicted one at low conversions but markedly lower at high conversions. Therefore, retardation of the LP occurred at higher DPs.

Irrespective of $[M]_0/[I]_{0,}$ gel-permeation chromatography (GPC) revealed that the MW of the polymers has a limiting value of about M_n = 32 000, which corresponds approximately to DP_{GPC} = 8, with M_w/M_n = 1.04 to 1.02 (Figure 2C). The hydrodynamic volume of the polymer decreases as the polymer becomes more compact (e.g., as it becomes a sphere), and thus, the DP_{GPC} is an underestimation of the true DP limiting value, while the polydispersity is an overestimation because of GPC column broadening. In fact, the theoretical DP, calculated by multiplying $[M]_0/[I]_0$ by the conversion, has a limiting value of DP_{th} = 16. MALDI-TOF analysis of poly(**3c**) at $[M]_0/[I]_0$ = 20, 30, and 70 showed that this was the case. Regardless of $[M]_0/[I]_0$, all of the polymers had a similar MW, M_n = 68,588 (DP = 16), and M_w/M_n = 1.0002, suggesting the formation of well-defined monodisperse species (black trace in Figure 3 and Figure S4).

The shape of the MALDI-TOF MW distribution was not symmetrical (i.e., Poisson, Figure 1C and red line in Figure 3) at DP = 16, indicating that polymer chains could not grow to higher DPs. Such a limitation could be attributed only to a nonstatistical SILP, since it occurred in a narrow range of MWs and corresponded to narrow polydispersity according to GPC and MALDI-TOF.

The rate of living ROMP is governed by k_p in eq 1. The value of k_p as a function of DP (eq 4) can be calculated from the combination of eqs 2 and 3 with the assumption that propagation is first-order in monomer and initiator:

$$DP = x\frac{[M]_0}{[I]_0} \tag{2}$$

$$k_p(t) = \frac{(dx/dt)}{[I]_0(1 - x)} \tag{3}$$

$$k_p(DP) = \frac{(dx/dt)}{[I]_0\left(1 - \frac{DP[I]_0}{[M]_0}\right)} \tag{4}$$

The conversion versus time profiles in Figure 2B were fit with a third-order polynomial, and the dependence of k_p on DP is given in Figure 2C for all of the polymerizations. It can be observed that with increasing DP the value of k_p decreased, reaching a value close to zero at DP = 16. A kinetic model solving the individual stiffly coupled differential equations at each DP was used to simulate the kinetic data in Figure 2B (see Figure S5). Using a much higher rate constant of initiation (k_i = 0.03 L mol^{-1} s^{-1}) and a dependence of k_p on DP (using

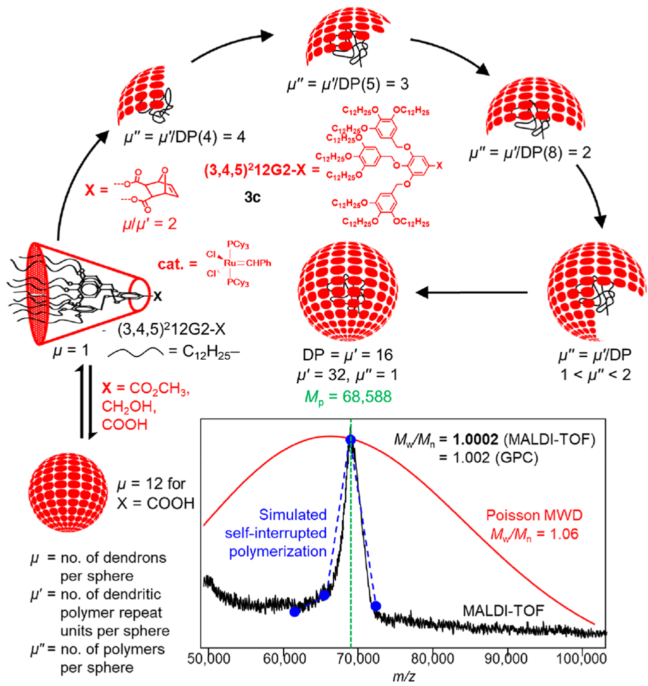

Figure 3. (top) Mechanism of SILP. Polymer chains with DP < 16 and nonpolymerizable dendrons with ester, acid, or alcohol apex groups self-assemble into spheres. A sphere can be formed from a single chain with DP = 16), at which point the active polymer chain end is sequestered inside the sphere and polymerization ceases (center). (bottom) Comparison of experimental (black), simulated (blue), and theoretical Poisson (red) MW distributions.

the rate data from $[M]_0/[I]_0$ = 70) in which k_p was set to 0 for DP > 16, we could fit the rate and polydispersity data accurately. There was a remarkable fit of the simulation (blue curve in Figure 3) to the MALDI-TOF polydispersity, confirming that self-interruption occurred at DP = 16 with M_w/M_n = 1.0002. The simulations (data not shown) further showed that at very long reaction times the polydispersity would eventually reach M_w/M_n = 1.0000, which could be lower than even that of proteins, forming perfectly uniform polymer chain lengths. A kinetic model suggested that in our system the polymerization at early DP is controlled primarily through translational diffusion, with fast segmental diffusion (Figure S6). This is in agreement with high rates of polymerization at low conversion and DPs predicted by eq 1 (Figure S3). As the DP increases, a transition from translational- to segmental-diffusion-controlled polymerization occurs because of steric restriction due to addition of monomer to a highly compact 3D structure. Consequently, k_p decreases, resulting in retardation of the polymerization (Figures 4, S5c, S6, and S7). At high DPs, the polymerization slows considerably and eventually stops because of the formation of a sphere when k_p becomes solely controlled by segmental diffusion. When a DP of 16 is reached, segmental diffusion and thus k_p decrease to zero as the large monomer is restricted from entering the sphere and reacting with the active chain end.

At this point it was tested whether the chain end of the polymer was still active when self-interruption occurred (DP = 16). A demonstration of the activity of the chain end was rendered by addition of monomer **3a** to a polymerization mixture of **3c** ($[M]_0/[I]_0$ = 40, $[M]_0$ = 0.073 M) at 37% conversion, which corresponds to the limiting conversion and DP. Rapid initiation and propagation of 70% of **3a** occurred in

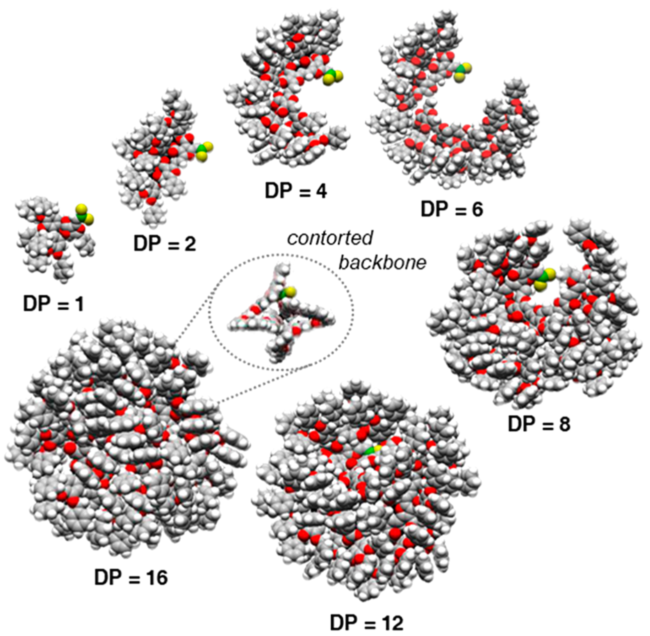

Figure 4. Development of spherical poly(**3c**) during SILP. Self-interruption occurs at DP = 16. The backbone in DP = 16 is contorted (center) to enable the polymer chain to adopt a spherical conformation. Color code: C, gray; O, red; H, white; Ru, green; Cl, yellow.

15 min, followed by copolymerization of **3a** with **3c** until both monomers were consumed (Figure S8). This analysis indicated that the polymerization of the small monomer **3a** was initiated from the existing active polymer chain end of poly(**3c**) encapsulated in the supramolecular sphere and that the propagation involved monomeric species **3c** that can escape from the sphere. At complete conversion of **3c**, approximately 96% of the active chain was involved in polymerization, while the other 4% was consumed in unidentified side reactions. Similar results were obtained using norbornylene instead of **3a**, with quantitative copolymerization in 6.5 h, yielding a polymer with M_n = 133 000 (M_w/M_n = 1.22). These experiments proved that the limited conversion is not due to the loss of activity of the growing polymer chain.

Thermal polarized optical microscopy showed that poly(**3c**) is isotropic between 20 and 180 °C. Nevertheless, there is a change in viscosity at about 83 °C upon heating, indicating a transition from isotropic to the isotropic liquid-crystalline state. Differential scanning calorimetry showed only a melting transition at −10 °C. Similar findings were observed for the polymer obtained after addition of **3a** in the **3c**:poly(**3c**) (63:37) mixture. X-ray diffraction (XRD) was performed on end-capped and separated poly(**3c**) obtained for $[M]_0/[I]_0$ = 4, 8, and 30. At 65 °C, XRD indicated that the bulk phase of the polymer with $[M]_0/[I]_0$ = 4 is a cubic *Pm*3*n* phase[26] with lattice parameter *a* = 84.9 Å (Figure S9), corresponding to 12 monomer units in the sphere. This calculation assumes that poly(**3c**) has the closest packing in the lattice, corresponding to an experimental density of 1.05 g/cm^3. Scanning force microscopy showed that poly(**3c**) with $[M]_0/[I]_0$ = 4, 8, and 30 can be visualized as spherical supramolecules, as reported previously for different backbones.[26]

In order to assess the MW and polydispersity of poly(**3c**), reductive cleavage of the dendritic groups from the backbone was performed and monitored online (Figures 2A and S10). Hydrolysis of the unreacted monomer produced compounds **1c** and **5** (Figures 2A and S11), and hydrolysis of the polymer produced compounds **1c** and **6**. Partial reduction of the unsaturated chain end furnished small quantities of compound **7**. During mass analysis, the fragmentation of **1c** to products **8** and **9** was expected since the analysis was conducted in an acidic medium (see the Supporting Information). Figure S10 presents a slice of the FTMS envelope spectrum of the cleaved mixture. Remarkably, the polymer backbone was identified only in expansion (Figure S10A) in the form of its doubly charged forms **6** and **7**. This finding confirms the MALDI-TOF and light scattering data and definitively demonstrates the monodisperse nature (M_w/M_n = 1.00) of poly(**3c**). Libraries of self-assembling conical dendrons that self-organize into quasicrystals[30] or *Pm*3*n*,[28,29,31,32] tetragonal,[33] or other globular Frank−Kasper phases are available.[32] The DP accessible by SILP is equal to the number of conical dendrons that assemble into a supramolecular sphere, which is in the range of 2 ≤ DP ≤ 250.[32] An extra requirement is that the conical dendron must be rigid under SILP conditions.[31,32] The dendritic alcohol used in SILP is regenerated and reused (Figures 1A and S1). The alternative methods to produce monodisperse macromolecules rely on flash chromatography of polymers obtained by LPs[34a] and temperature-dependent Ni-catalyzed transfer polymerization.[34b,c] Preliminary attempts to generate SILP with the methacrylate and acrylate of **3c** via ATRP, RAFT, and SET-LRP[35] were not as successful as by ROMP.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c07912.

> Synthesis of monomers and polymerization, NMR and MALDI-TOF spectra, simulation of kinetics, GPC, powder X-ray diffraction, and GPC/ESI-FTMS analysis (PDF)

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Notes

The authors declare no competing financial interest.

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