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Reversible Polymerization Driven by Folding

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The design and synthesis of nonnatural, hetero-sequenced copolymers having well-defined folded structures (tyligomers)[1] and capabilities of performing functions that rival those of natural biopolymers such as proteins remains an important, unsolved challenge for chemists. The magnitude of possible sequences, even for a binary monomer pool, makes the search for tyligomers a daunting problem. The majority of random sequences from an irreversible copolymerization of an amphiphilic pair of monomers will likely either be insoluble in the reaction medium or adopt noncompact, disordered conformations in solution.[2] We hypothesize that a reversible polymerization in which chain folding or collapsing drives high-polymer formation will yield a much *smaller subset* of all possible sequences and therefore greatly streamline the search for tyligomers. As a first step to test this hypothesis, it is essential to show that in a closed system, energy gained by folding can drive a reversible polymerization toward the formation of high polymers. Here we report a polymerization that implements the concept of supramolecular-assisted, dynamic-covalent polymerization.[3,4]

Previously, our laboratory has shown that the equilibrium distribution of monoimine-functionalized *m*-phenylene ethynylene oligomers can be shifted in polar solvents to selectively favor oligomers that adopt a stable helical conformation.[5,6] On the basis of these observations, we predicted that bisimine functionalized *m*-phenylene ethynylene oligomers could be driven to high polymer under similar conditions (Figure 1). Since the equilibrium constant of imine metathesis is close to unity,[5,7] only low-molecular weight oligomers are expected for a closed system at equilibrium in the absence of a driving force such as folding.[8] In polar media, the collapse of long chains into compact conformations should increase stability as a result of intramolecular, solvophobic, and aromatic stacking interactions, consequently shifting the equilibrium in favor of longer chains. As the reaction proceeds, monomer units will continuously add onto the existing ordered structures. A distinctive characteristic of this polymerization is that a high degree of polymerization follows from noncovalent interactions, rather than from the free energy gained in covalent bond formation or the removal of byproducts, as in most step-growth polymerizations.[8,9]

To demonstrate that folding can drive a reversible polymerization, tetrameric oligomers **1** and **2**, both having bis-imino end groups, were synthesized and used as monomers for imine metathesis polymerization.[10] The reaction between **1** and **2** (1:1 equiv at 5 mM) was first carried out in two different solvents (acetonitrile and chloroform) in the presence of 0.5 mM oxalic acid as a catalyst. These two solvents were chosen because *m*-phenylene ethynylene oligomers have previously been shown to adopt an ordered helical conformation in acetonitrile and a random conformational state in chloroform.[11] The reactions were conducted in dry solvents at room temperature for 6 d to ensure that equilibrium had been achieved.[12] After the reactions were quenched with triethylamine, the product mixtures were analyzed by size-exclusion chromatography (SEC) in THF.[13] The SEC traces of the products from reactions conducted in the two solvents are shown in Figure 2. In chloroform (trace b), the major components of the reaction mixture were the starting materials ($M_n = 1.8$ kDa), their dimers ($M_n = 3.6$ kDa), and trimers, along with a small amount of higher oligomers. Such a molecular-weight distribution is in good agreement with the theoretically calculated statistical distribution of a closed-system metathesis polymerization in which the equilibrium constant is near unity.[8] In contrast, a high-molecular weight product was obtained when the equilibrium took place in acetonitrile (trace j).[14,15] These results support the hypothesis that the stabilizing energy derived from intrachain noncovalent interactions can drive the metathesis equilibrium toward high polymers.

If indeed the folding energy is the driving force for the equilibrium shifting and consequently elongation of the polymer chains, the molecular weight of the resulting poly(*m*-phenylene ethynylene imine)s should correlate with conformational stability. Our previous studies on *m*-phenylene ethynylene oligomers have illustrated a nearly linear relationship between helix stability and chloroform composition in chloroform/acetonitrile binary mixtures.[11b] The folding propensity of the oligomers diminishes as the *m*-phenylene ethynylene backbone becomes better solvated from the increase in the amount of chloroform in the solvent mixture. Hence, increasing the chloroform composition in the cosolvent should correspondingly lead to a lower degree of polymerization. Imine metathesis between **1** and **2** was then conducted in a series of acetonitrile/chloroform solvent mixtures (Figure 2). SEC analyses of the polymerization products equilibrated in these solvents revealed a good correlation between the molecular weight of the products and the solvent composition (Figure 3). Taking into account the nonlinear relationship between the degree of polymerization and the reaction conversion,[8] the molecular weight corresponds well with the folding energy. This correlation between molecular weight and conformational stability was also manifested by examining reactions conducted in a series of solvents in which the *m*-phenylene ethynylene oligomers exhibited intermediate helix stabilities between chloroform and acetonitrile.[16] Varied molecular weight was obtained from these solutions, consistent with the expected conformational stability. These results further support the conclusion that folding energy is the driving force for the equilibrium shifting and polymerization.

If the metathesis of the imine bonds is truly reversible, polymer formation should be dynamic, and the molecular weight of the products should respond to environmental changes that perturb the folded structure. The reversibility of the polymerization was tested by monitoring changes in the product's molecular weight following both solvent and temperature changes (Figure 4). Increasing the reaction temperature, or adding the denaturing solvent chloroform, displaced the equilibrium from a high-molecular weight position

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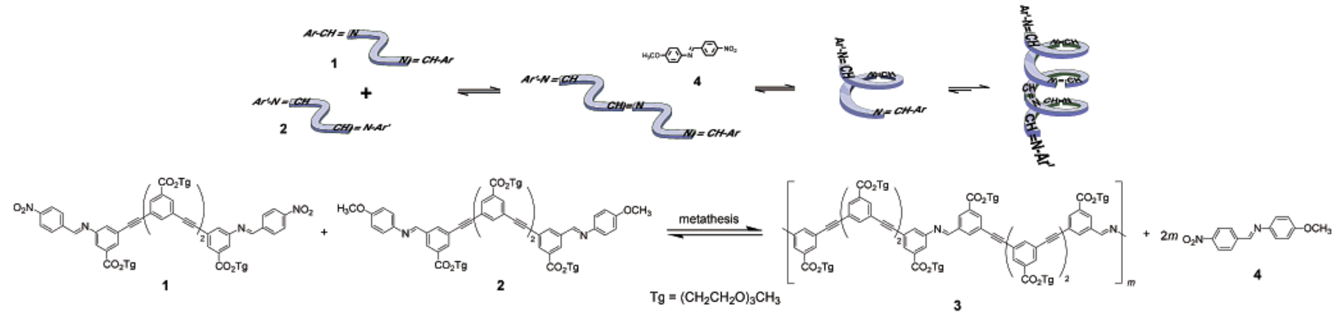

Figure 1. Imine metathesis polymerization between bis-imino *m*-phenylene ethynylene oligomers **1** and **2** (metathesis conditions: 1:1 equiv of the reactants equilibrated in dry solvent at 5 mM in the presence of 0.1 equiv of oxalic acid for 6 d).

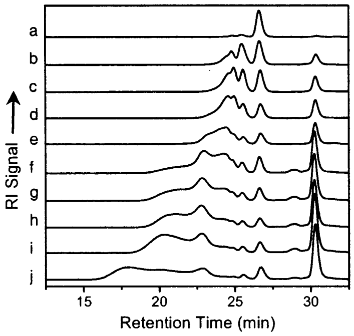

Figure 2. SEC traces of metathesis reactants **1** and **2** (a) and products equilibrated for 6 d at 5 mM rt in $CHCl_3$ (b), $CHCl_3/CH_3CN$ (vol % of $CHCl_3$: (c) 75%; (d) 50%; (e) 25%; (f) 20%; (g) 15%; (h) 10%; (i) 5%); and CH_3CN (j) solutions (the traces eluted at ca. 30 min are from the byproduct **4**).

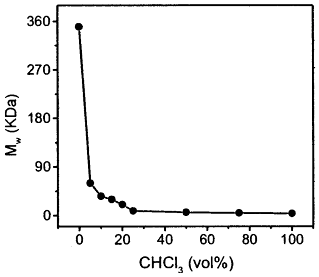

Figure 3. Molecular weight M_w of the products from metatheses between **1** and **2** in $CHCl_3/CH_3CN$ under the same condition as in Figure 2.

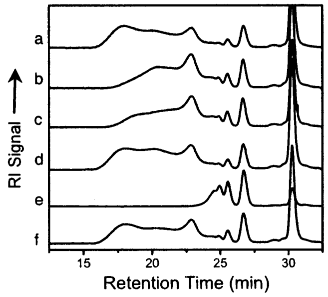

Figure 4. SEC traces of metathesis products from **1** and **2** in CH_3CN at 5 mM rt for 6 d (a); reaction mixture from (a) was then heated at 40 °C for another 6 d (b); **1** and **2** equilibrated at 40 °C in CH_3CN at 5 mM for 6 d (c); reaction mixture from (c) was then cooled to rt and equilibrated for another 6 d (d); reaction mixture from (a) was diluted with $CHCl_3$ (e) or CH_3CN (f) to 2.5 mM and equilibrated at rt for another 6 d.

toward a lower degree of polymerization; the molecular weight was independent of the pathway followed and only depended on the equilibration conditions. These results fully support the notion that the polymerization is reversible and that molecular weight adjusts in response to environmental changes.

In conclusion, high-molecular weight poly(*m*-phenylene ethynylene imine)s were synthesized via a reversible metathesis reaction. The data support the postulate that the folding energy is the driving force for shifting the equilibrium to generate high polymers. The degree of polymerization has been shown to correlate to the stability of the corresponding oligomers in their helical conformation and may be controlled by tuning the reaction conditions that determine folding stability. Furthermore, the system exhibited adaptability toward solvent and temperature changes by reversibly adjusting the product's molecular weight. Extension of these studies to heterosequenced copolymers will be carried out soon.

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Supporting Information Available: Molecular weight data and syntheses of **1** and **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Besides **1** and **2**, a pair of trimeric bisimino-monomers having three *m*-phenylene units were also synthesized and studied under the same metathesis conditions. Interestingly, cyclization as opposed to polymerization occurred in acetonitrile, giving rise to a macrocycle containing six *m*-phenylene moieties and two imino units in nearly quantitative yield.
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(12) The reaction was allowed to proceed up to 16 d, but no significant molecular weight change was observed after 6 d.
(13) All the molecular weight data are based on SEC analysis in THF calibrated by standard polystyrene samples (actual molecular weight of **1** and **2** is ca. 1.2 kDa).
(14) Equilibrium constant of the imine metathesis was assumed not to be greatly affected by the solvent polarity (refs 5 and 6a).
(15) The reaction was also conducted at lower concentration (e.g., 0.5 mM) in acetonitrile, and polymer products of similar molecular weight were obtained, supporting the premise that folding, rather than aggregation, is the dominant driving force for the polymerization.
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