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Stretching Single Polymer Chains of Donor−Acceptor Foldamers: Toward the Quantitative Study on the Extent of Folding

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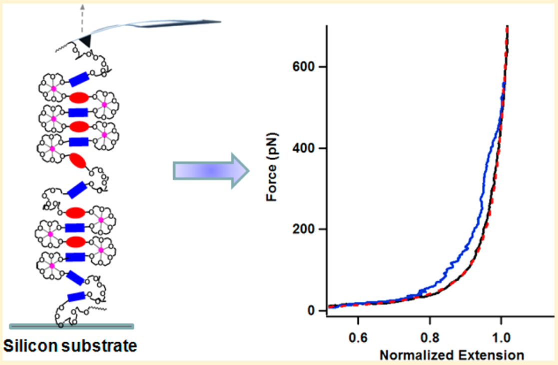
Supporting Information

ABSTRACT: Single-molecule force spectroscopy has proven to be an efficient tool for the quantitative characterization of flexible foldamers on the single-molecule level in this study. The extent of folding has been estimated quantitatively for the first time to the best of our knowledge, which is crucial for a better understanding of the "folding-process" on single-molecule level. Therefore, this study may provide a guidance to regulate folding for realizing rational control over the functions of bulk materials.



■ INTRODUCTION

The term "foldamer" is used to describe synthetic polymers that can be made to adopt well-defined conformations in solution by inclusion of specific intrachain interactions.[1−6] The family of "foldamers" has ranged from the rigid folamers with relatively stiff chains, which have limited conformational degrees of freedom as a result of steric and/or bond-angle constraints along the backbone,[7−12] to flexible systems that need to include specific intrachain intersegment interactions.[13−22] Compared with the rigid foldamers, the flexible foldamers have attracted more attention because of their much larger and dynamic conformational freedom, for which they are wildly employed as biomimetic soft materials.[23−25] In particular, 3D-polymeric materials constructed by flexible foldamers can absorb mechanical energy and exhibit a combination of high modulus, high toughness, and adaptive properties in one material,[23−25] mimicking the excellent mechanical properties of muscles. However, the flexible foldamer chains cannot completely fold because of the tendency to maximize entropy of the flexible polymer backbone, and the mechanical performances of the foldamers-based materials are closely related to the extent of folding. A quantitative estimation of the extent of folding is crucial for a better understanding of the "folding-process" and to provide a guidance to regulate folding, thus realizing rational control over the functions of bulk materials. Recently, oligomeric π-stacked foldamers (containing three stacking units) were extensively studied by Li et al.[26] In their study, single-molecule unfolding behavior of the foldamers helped to quantify the nonequilibrium doubly folded, singly folded, and unfolded states. Also, single molecule fluorescence spectroscopy has been employed by the same group to study the unfolding and refolding behaviors of foldamers containing exactly two or four stacking units, which were induced by photoabsorption and excitation.[22] However, the real quantitative detail about folding efficiency and the magnitude of the quantitative values still remains a difficult parameter to be experimentally measured, especially for polymeric foldamers, because of the limitation of the traditional characterizing methods, such as UV/vis, NMR, etc., which can only give qualitative but not quantitative assessment of folding, as the relationship between the output signal and folding is usually far from simply cumulative.[1−6]

We wonder if it is possible to address this important issue by the technique of AFM-based single-molecule force spectroscopy (SMFS). AFM-based SMFS has been employed to manipulate single polymer chains, to measure tiny forces on the molecular scale, and to record exceptionally small distances simultaneously.[26−44] The curves of force signals versus extension can be obtained, thus providing valuable information about intramolecular and intermolecular interactions of polymeric and supramolecular systems on the single-chain level.[45−54]

Herein, by combining SMFS and theoretical calculations, we are able to reveal the structure of the flexible foldamer at single-molecule level. In addition, for the first time to the best of our

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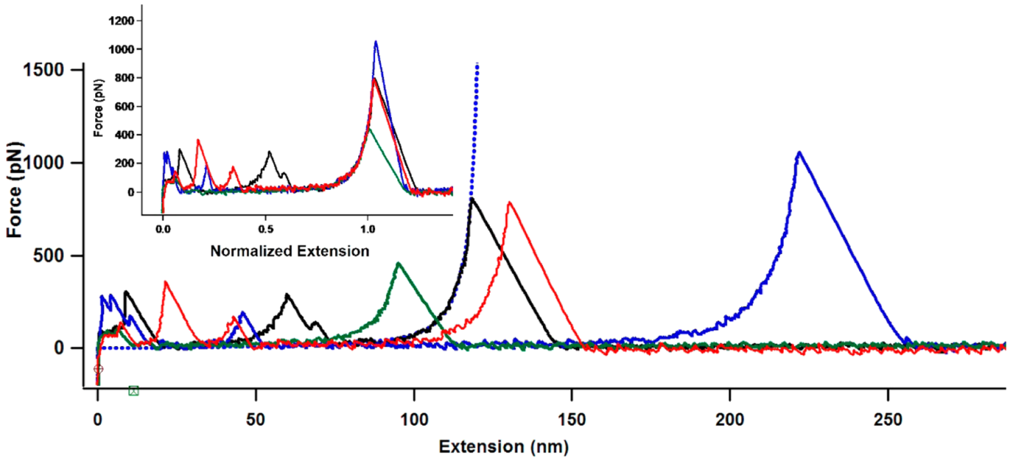


Figure 1. Typical force curves of DA foldamers obtained in DMSO, in which negligible folding exist in the polymer. The blue dotted line is the fitting curve using the WLC model with a parameter of L_c = 125.5 nm and l_p = 3.7 Å. The inset is the force curves after normalization. The curves were normalized at 400 pN. Different colors were used to distinguish each curve.

knowledge, some quantitative and important information, i.e., the extent of folding has been successfully obtained. As a proof-of-concept study, the flexible foldamer based on aromatic donor (D)−acceptor (A) interactions (DA foldamer) was investigated by SMFS. The foldamer investigated here could be coerced into folding utilizing three different effects in tandem; the charge-transfer interaction between adjacent donor and acceptor units, the solvophobic effect due to the relatively hydrophilic hexa(ethylene oxide) linking segment and the complexation of the flexible oligoethylene oxide segment with alkali-metal ions that restricts the conformational freedom of the linking segment and in turn assists the formation of the charge-transfer complex.[17−19] However, it should be noted that, the polymer chain of the DA foldamer cannot completely fold due to the highly flexible backbone (large entropy reduce for folding) and the weak and dynamic nature of the noncovalent interactions (there is an equilibrium between the folded and unfolded state).[17,26] In addition, the polymer sample investigated here contains some randomly placed additional acceptors along the polymer backbone (about 11 mol %, "stack-breaker"),[21] which also limits the maximum attainable DA stack length. The objective of this study is to quantify the length of the folded domain along one single chain using SMFS, thus leading to the quantitative characterization on the extent of folding for DA foldamers.

■ EXPERIMENT SECTION

SMFS Sample Preparation. A stock solution was prepared by dissolving the DA foldamer in a KSCN saturated solution (dry methanol/dry chloroform = 1:1, *v*/*v*), in brief, KSCN solution (concentration of KSCN: ∼70 mg/mL), with a concentration of 5×10^{-3} mg/mL. Silicon wafers were treated with hot piranha solution (70:30 v/v, 98% H_2SO_4/30% H_2O_2) for 1 h, sonicated in large amounts of deionized water several times, rinsed with ethanol, and dried in a steam of nitrogen. (*Caution! Piranha solution is very corrosive and can react violently with organics, so security measures should be taken*). A clean silicon wafer was immersed in the stock solution overnight, and then the silicon wafer was flushed thoroughly with the KSCN solution. After being dried in a steam of nitrogen, the silicon wafer was used as a substrate in the SMFS experiment. For the SMFS in chloroform, dry chloroform is used instead of the KSCN solution.

SMFS Setup. Commercially available V-shaped Si_3N_4 AFM cantilevers (Bruker, Santa Barbara, CA) with a sharp tip (radius of curvature 50 nm) at the end of a soft cantilever and a spring constant of 0.010−0.040 N/m were utilized in the experiment. The SMFS experiments were carried out at room temperature using the KSCN solution as buffer. For the SMFS in chloroform, dry chloroform was used instead of the KSCN solution. The SMFS experiments were carried out by utilizing a commercially available DI multimode picoforce (Bruker, Santa Barbara, CA) with a stretching velocity of 2 μm/s unless specified. Details of the SMFS experiment have been described elsewhere.[26−44] In brief, when an AFM tip was brought into contact with a polymer that had been physical adsorbed on the substrate, the polymer could adsorb onto the AFM tip as well as on the substrate, thus forming the so-called polymer bridge between the tip and the substrate. With the tip separated from the substrate, the polymer bridge was elongated, resulting in the bending of the cantilever toward the substrate. The deflection of the cantilever and the extension were recorded and converted to force−extension curves (in brief, force curves).

Fitting of the Force Curves. The force curves of DA polymer in freely coiled state (force curves obtained in DMSO, Figure 1) were fitted by WLC model using the least-squares method. For details, please refer to the Supporting Information, SI.

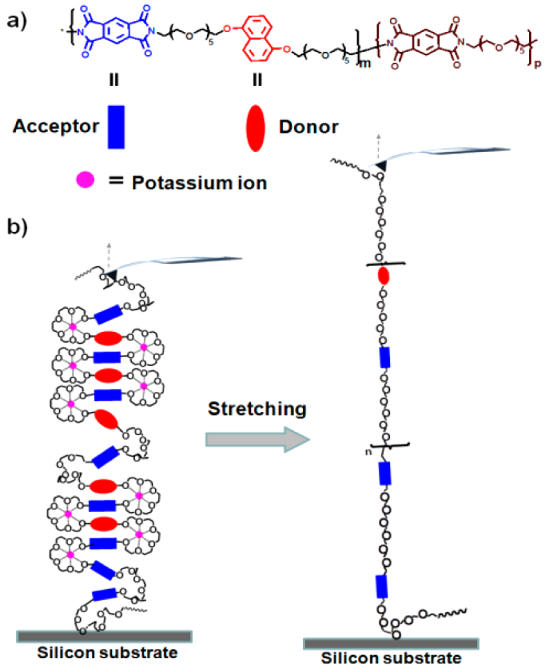
Synthesis and Characterizations of the DA Polymer. The synthetic procedure and characterizations of the donor (dialkoxynaphthalene)−acceptor (pyromellitic dianhydride) foldamers has been reported elsewhere.[21]

■ RESULTS AND DISCUSSION

The experimental setup for this kind of study is shown in Scheme 1. The folded polymer was mounted between the AFM tip and the substrate by physical adsorptions. Upon retraction of the AFM tip, the folded domains in the polymer chain were unfolded gradually, leading to the gain of the end-to-end distance of the DA foldamer. At the same time, the unfolding force would deflect the cantilever, leading to a force signal output. The gain of the length of the whole polymer chain during unfolding could be a reflection of the extent of folding.

The elastic behavior of the DA foldamer with a freely coiled state with negligible folding was first studied. The SMFS experiment of the DA foldamer was performed in DMSO, in which minimum folding exists along the polymer chain. The polymer shows a freely coiled state that is typical for flexible polymer chains,[26−44] because DMSO is a good solvent for the DA foldamer and poor solvent for stabilizing charge-transfer complex (see the SI).[20,21] As shown in Figure 1, all of the force curves exhibit similar deformational characteristics: a sharp monotonically rising force with increasing extension and a rapid

Scheme 1. (a) Molecular Formula of the DA Foldamer, *p* = 0.11, *m* = 0.89. (b) Setup for the Single-Molecule Force Spectroscopy Experiment on DA Foldamer



force dropping to zero upon rupture of a polymer bridge from the tip or substrate. In addition, all of the normalized force curves obtained can be overlapped well (the inset of Figure 1). This suggests that each force curve is representative for the elastic behavior of single DA polymer chains.

The force curves can be fitted using a wormlike chain (WLC) model, which describes a polymer chain as a homogeneous string with a constant bending rigidity, and treats the molecule as a continuous entity with persistence length l_p.[48] The force−extension relationship is given by the following formula:

$$F(x) = \frac{k_B T}{l_p}\left[\frac{1}{4}\left(1 - \frac{x}{L_c}\right)^{-2} - \frac{1}{4} + \frac{x}{L_c}\right]$$

Here, F is the external force acting on the polymer chain, l_p is the persistence length that reflects the flexibility of polymer chain, x is the extension of the polymer chain (end-to-end distance), L_c is the contour length of the polymer chain, k_B is the Boltzmann constant, and T is the temperature in Kelvin. The force curves were then fitted using the WLC model, and one representative fitting curve is shown by the dotted line in Figure 1. All of the force curves can be well fitted using the fitting parameters of l_p = 3.7 ± 0.18 Å, which is a robust proof of the fact that a single polymer or the same kind of polymer being pulled each time and each force curve is representative for the elastic behavior of single DA polymer chains without any supramolecular structures.

The SMFS experiments were then performed in a KSCN saturated solution (chloroform/methanol = 1:1, *v*/*v*), wherein the DA foldamers would be expected to be folded because of the solvophobic interaction and potassium ion complexation with the flexible hexa(ethylene oxide) segment. According to the previous studies, the folding of the DA polymer in the presence of K^+ was clearly demonstrated to be a regular folding process, i.e., adjacent DA pairs folded and stacked together,[17−20] as shown in Scheme 1 (see the SI for detailed illustration). To further confirm this point, in this study, we have also employed molecular dynamics simulation to study the stability of the adjacent DA pairs folded polymer. With the aid of potassium ion-complexation, the model compound adopted an adjacent folded state, which has the lowest energy compared with the nonadjacent folded confomers (see the SI). Even after 10 ns MD simulation starting from adjacent DA folded polymer in the present of potassium ion, the polymer still exists in a completely folded state, and the corresponding structure of the DA foldamer is shown in Figure S2 of the SI. This further supports the expected regular adjacent DA folding, as the model structure shown in Scheme 1 (see the SI for more details). The representative force curves for the unfolding of DA foldamers are shown in Figure 2a. A "shoulder", i.e., force kink can be observed in each of the curves, so the attempt to fit the whole curve with WLC model were not successful because this model can only describe a semiflexible polymer chain without any conformational changes. Upon further stretching of the single chain after the appearance of force kink, the force curves show sharp monotonically rising behavior that is commonly observed for the deformation of freely coiled chains in the absence of any supramolecular structures. These indicate that a single DA foldamer chain may have been stretched for each force curve, and the force kink should correspond to the unfolding process of the folded domains.

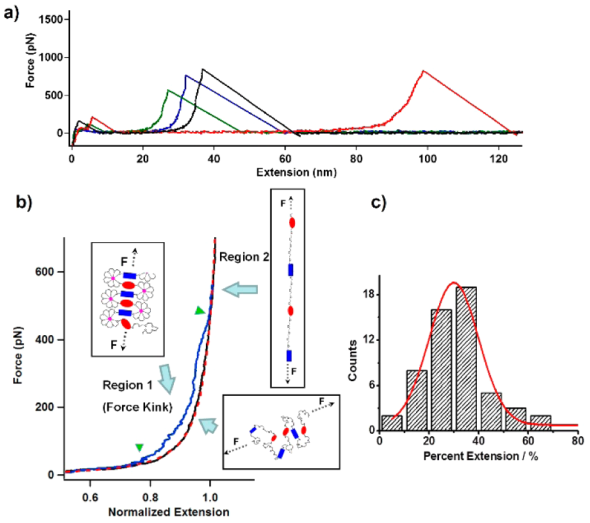


Figure 2. (a) Typical force curves of DA foldamer obtained in the KSCN saturated solution (solvent:methanol/chloroform = 1:1, *v*/*v*). Different colors were used to distinguish each curve. (b) Normalized force curves (normalization force: 500 pN) for the DA foldamer in DMSO (black color) and in KSCN saturated solution (solvent: methanol/chloroform = 1:1, *v*/*v*) (blue color). The raw force curves were smoothed using the "average smoothing" in Origin 8.0. The red dotted line is the fitting curve of the freely coiled chains, using the WLC model with a parameter of l_p = 3.6 Å and L_c = 1.08 (normalized unit, where the extension at F = 500 pN is defined as "1 unit"). The start and end points of the force kink were marked out using the green triangle for clarity. (c) Distribution of relative percentage of length of the force kink to the whole length of the polymer. The red curve in (c) is the Gaussian fitting on the distribution.

To confirm the speculation above, the force curves of the DA foldamers obtained in the KSCN saturated solution (folded state), and that in DMSO (freely coiled state) along with its WLC fitting curve were normalized at the force value of 600 pN and were put together for comparison (Figure 2b). As expected, a clear deviation occurs at the force kink region (Region 1); however, the force curves can be overlapped well in the high force region after the force kink, i.e., above ~500 pN (Region 2). It can be visualized that, before stretching to the extended state of the single DA foldamer chain, the folded domains of the foldamer have to be dismantled first by the AFM tip. Thus, compared with stretching of freely coiled chains, extra energy is needed for the dismantling of the folded domains, leading to the appearance of the force kink in the force curve (Region 1), as shown in Figure 2b. However, when the applied force is above 500 pN, the force curves can be overlapped well with that of the single freely coiled chain without any supramolecular structures (force curves obtained in DMSO). This indicates that all the folded domains on the single chain have been completely unfolded under a force of 500 pN and upon further stretching, the DA foldamer shows typical deformation behaviors for elastic single chains without any supramolecular structures. Thus, the force kink should be related to the unfolding process of the folded supramolecular structures.

It should be noted that every single chain exhibits different folding behaviors, as indicated by the variations of the "percent extension", i.e., length of the force kink divided by the whole length of the polymer. A statistical analysis on the "percent extension" of the force kink was carried out, as shown in Figure 2c. The Gaussian analysis on the distribution produces a unimodal distribution with a most probable value of 30%.

The length of the force kink should be equal to the gain of the end-to-end distance of the polymer resulting from the dismantling of the folded domains. However, to correlate the SMFS results with the extent of folding, which is a true reflection of the folding ability of the DA foldamer, eq 2 is evolved as follows. The folded domain can be regarded as the tandemly linkage of the repeat units, i.e., one donor, one acceptor and the connecting hexa(ethylene oxide) segment; the gain of the end-to-end length of the whole polymer (ΔL) upon stretching is the sum of that for the folded repeat units ($\Delta d = d^* - d$), as shown in Figure 3a. Then a mathematical equation describing the unfolding process of the DA foldamer can be roughly estimated as follows:

$$\omega = \frac{\Delta L}{L_c} = \frac{\Delta d \times n}{\alpha \times d^* \times m} \tag{1}$$

where the ω is the "percent extension", i.e., the ratio of the length of the force kink (ΔL) to the end-to-end distance of the extended polymer chain (contour length of the extended polymer chain, L_c), $\Delta d = d^* - d$ represents the increase in length per repeat unit upon stretching, n is the number of the repeat units that are folded in the DA foldamer, α is a correction factor arising from the presence of stack-breaker (see the SI), d^* is the extended length of the repeat unit, m is the total number of the repeat units in the polymer chain. With the help of molecular dynamics simulation and quantum chemistry computation (see the SI for details), d and d^* were obtained (Figure 3b,c). The mathematical equations for assessing the extent of folding (η) can be simplified as eq 2.

$$\eta = \frac{n}{m} = \frac{\alpha \times d^*}{\Delta d} \times \omega = 1.213 \times \omega \tag{2}$$

In terms of the eq 2, the extent of folding for the current foldamer is estimated to be ~36% in the KSCN saturated solution. Therefore, the folding ability of the flexible foldamer can be quantitatively estimated directly at the single-molecule level, which cannot be obtained by traditional methods.

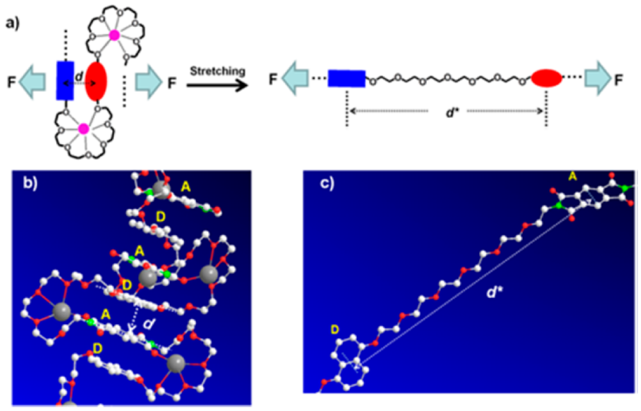


Figure 3. (a) Schematic illustration of the model for unfolding the DA foldamer. (b) The folded state of the DA foldamer in the KSCN saturated solution (solvent/methanol/chloroform = 1:1, v/v) from molecular dynamics simulation. (c) The extended state of the DA foldamer from quantum chemistry computation. The average distance between adjacent donor and acceptor pair in the folded state was measured to be d = 0.336 nm, and that for the extended state was measured to be d* = 2.68 nm. The solvent molecules and hydrogen atoms are not shown for clarity. Carbon atoms are represented by white spheres, oxygen atoms are represented by red spheres, nitrogen atoms by green spheres, and potassium ions by gray spheres.

The quantitative result obtained here indicates that, from the point view of the single polymer chain, the folding of the flexible DA foldamer is far from perfect, and there is substantial room for further enhancing the extent of folding in these systems. A better understanding on the interplay between different noncovalent interactions should be helpful to regulate folding.[19] To find out the reason for the imperfection, the complexation process of the DA foldamer in the presence of potassium ion was further analyzed by molecular dynamics simulation and quantum chemistry computation. As indicated by Figure S4a of the SI, the hexa(ethylene oxide) linking segments is forced to adopt a distorted conformation upon potassium ion complexation, for the steric hindrance arising from the charge-transfer interactions between the adjacent DA pairs. The average distance between the potassium ion and the surrounding oxygen atoms (d_{K^+-O}) is measured to be 3.34 Å. However, the conformation of the structural analogues, i.e., 2-, 5-, 8-, 11-, 14-, and 17-hexaoxaoctadecane (Figure S4b,c of the SI) and 18-crown-6 (Figure S4d,e of the SI) in the presence of potassium ion are much more regular, with the d_{K^+-O} values of 2.83 Å and 2.81 Å, respectively. All of the above indicate that the folding elements in the DA foldamer are not well-balanced, and a negative cooperative effect exists. In other words, the charge-transfer interactions between the adjacent donor and acceptor have weakened the strength of the coordination bonds of potassium ion with the hexa(ethylene oxide) linking segments, and thus could lead to a lowering of the extent of folding of the DA foldamer. Thus, delicate molecular design should be focused more on well-balancing the folding elements to create a positive cooperative effect among them. The development of flexible foldamers is far from finished since there is still much room for further improvement, based on the quantitative result obtained here.

Moreover, in SMFS experiment, we have found that the unfolding process of the DA foldamer is pulling speed independent in our experiments (Figure S5 of the SI), indicating that these transitions are reversible on the time scale of our experiments. This indicates that the folding and unfolding process of the polymeric foldamer based on noncovalent interactions is highly dynamic.

In contrast, SMFS studies of the DA polymer in the solvent without potassium ion (either in pure chloroform or the solvent mixture, i.e., methanol/chloroform = 1:1, v/v) clearly confirms that the extent of folding is negligible (Figure S7 of the SI). The force curves obtained in these solvents can be overlapped with those in DMSO, which confirms that charge-transfer interactions alone are not adequate to effect folding. In addition, SMFS experiments were also performed in a NaSCN saturated solution. Force curves with smaller force kinks can be observed (Figure S8 of the SI), and the extent of folding was roughly estimated to be ~8% according to eq 2 mentioned above, which is much smaller compared with that in the KSCN solution. The great contrast helps us to verify that the force kinks observed in Figure 2a,b are indeed due to the unfolding process of the folded domains, rather than other less specific interactions or effects of salts. Moreover, the ionic size-dependent complexation ability of the hexa(ethylene oxide) loop further supports the hypothesis that the folded domains are indeed formed by the aromatic charge-transfer interactions between adjacent D and A units along the polymer chain.

■ CONCLUSIONS

Single-molecule force spectroscopy has proven to be an efficient tool for the quantitative characterization of flexible foldamers directly on the single-molecule level. As indicated by SMFS, the folding of the flexible DA foldamer is far from perfect. By a combination with molecular dynamics simulation, the negative cooperative effect between the folding elements was found to be responsible for the folding imperfection, which may shed light on the design of foldamers toward improved folding and functions. It is greatly anticipated that the technique of SMFS may become a general tool to examine other supramolecular dynamic structures and provide useful information directly at the single-molecular level, thus guiding the rational fabrication of functional materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

UV−vis spectroscopy; methods; UV−vis spectra of the DA polymer solution (Figure S1); folding of the DA polymer as a regular folding process; energy and structure of each DA folded conformer (Figure S2); SMD simulation on the pulling process (Figure S3); calculations for the value of correction factor "α" and "percent extension" (ω); distorted conformation of the hexa(ethylene oxide) segment in the foldamer; snapshot of the folded DA foldamer by SMD (Figure S4 and AVI movie file); independence of the pulling speed in the pulling process; histograms of the height of the force kink obtained under four different stretching speeds (Figure S5); free energy of folding calculated from single molecule force spectroscopy; statistical analysis of the free energy change of each repeating unit upon unfolding (Figure S6); force curves of DA foldamers in chloroform (Figure S7) and NaSCN solution (Figure S8); and additional references. 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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