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Two-Step Folding of Donor−Acceptor Foldamers

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ABSTRACT: In a series of polymers containing alternately placed electron-rich dialkoxynaphthalene (DAN) donors and electron-deficient pyromellitic diimide (PDI) acceptors linked by hexa(oxyethylene) (OE-6) segments, the ability to form a folded D-A stack was intentionally disrupted by random inclusion of varying amounts of a comonomer that is devoid of DAN donor units. NMR spectroscopic studies of folding in these copolymers, induced by NH_4SCN that coordinates with the OE-6 segments and facilitates the charge-transfer (C-T) induced D-A stacking, clearly reveals the presence of PDI units that are isolated and those that are located at the ends of $(D\text{-}A)_n$ stacks. Similar conclusions regarding the presence of stacked and unstacked regions along the polymer chain were also inferred from UV−vis spectroscopic studies that probe the evolution of charge-transfer band. One fascinating aspect of these copolymers was their ability to undergo a two-step folding: first, short $(D\text{-}A)_n$ stacks are formed by the interaction of the NH_4^+ ion with some specific regions of the polymer chain, and subsequently these stacks are further stacked via a two-point interaction with a suitably designed external folding agent that carries a DAN unit and an ammonium group. In the second step, the interaction first occurs by the coordination of the ammonium group of the folding agent with the OE-6 segment, which in turn facilitates the C-T interaction of the DAN unit with the adjacent uncomplexed PDI units along the polymer chain, leading to an increase in the stacking. Variations of several spectral features, during both UV−vis and NMR spectroscopic titrations, clearly reveal this novel two-step folding process.

Introduction

Controlling the solution conformation of long chain polymers through intrachain noncovalent interactions is at the heart of biomacromolecular structure and function. Mimicking the structure and function of biomacromolecules in synthetic systems has engaged chemists for several decades now. Recent years have seen a surge of activity in this area leading to the coining of several new terms, such as peptidomimics, foldamers, etc., that reflect different approaches for the conformational control of long chain molecules.[1] Many of the approaches rely on restricting the conformational degrees of freedom of the polymer backbone by imposing specific constraints, such as bond angle or conformational constraint, which in turn decreases the entropic penalty for attaining a particular folded structure. Examples of such efforts include the works of Hamilton,[2,3] Huc,[4−7] Moore,[8−12] Lehn,[13,14] Hecht,[15,16] Gellman,[17−22] Iverson,[23−26] and several others.[27−32] When dealing with truly flexible polymers, alternate approaches have been developed wherein the conformational flexibility is reduced by specific interactions of backbone segments with external agents, such as metal ions. These interactions in turn facilitate other weak interactions, such as π-stacking, donor−acceptor charge-transfer interactions, etc., to set in and stabilize the targeted folded form.[33] Interaction of alkali-metal ions with oligo(oxyethylene) segments has been extensively used to reinforce π-stacking and charge-transfer (C-T) interactions in varying contexts.[34,35] Similarly, solvophobic interactions in suitably designed oligomers and polymers have also been utilized to enhance the folding process by spatially colocating specific backbone segments that could then interact by π-stacking and/or charge-transfer interactions.[33,36−39] In a recent example, we demonstrated the reinforcement of the zigzag folded conformation of specially designed ionenes through solvophobic and donor−acceptor C-T interactions.[40]

Charge-transfer interaction is a particularly attractive design element as the strength of their interactions can be readily tuned both by varying the π-surface area and the electron densities on the donor and acceptor units. Moreover, it provides a convenient spectroscopic signal arising from the charge-transfer transition for its monitoring. In a series of detailed papers, Iverson and co-workers[23−25,41] have examined the folding of several oligomeric systems that carry alternately placed donor (D) and acceptor (A) units linked via relatively flexible spacers. They nicely elucidated the role of several structural parameters, such as donor (acceptor) strength, π-surface area, spacer length, and flexibility, etc., on the structure and stability of the folded state. Instead of an alternating placement, Zhao et al. designed systems wherein the donors and acceptors are included as pendant units and are clustered together in two separate blocks, and this causes the polymer backbone to turn around in a loop to form charge-transfer stabilized folded structures.[42] Simple π-stacking interactions between large aromatic rings, such as perylene, assisted by solvophobic interactions have also been used to generated pleated structures.[43] Some years ago, we designed D-A polymers carrying oligo(oxyethylene) spacers that were shown to fold under the combined influence of alkali-metal ion complexation, solvophobic effects, and C-T interactions.[44,45] The importance of various factors, such as the length of the OE-*n* spacer, solvent polarity, size of the alkali-metal ion, and temperature, on the folding were elucidated. Later, we also reported an alternate design wherein a polymer bearing only pyromellitic dimide (PDI) acceptors linked by OE-*n* spacers was made to fold via a two-point interaction with a small molecule carrying a dialkoxynaphthalene (DAN) donor linked to an ammonium group[46] or a potassium carboxylate unit.[47] In all these systems the extent of folding, i.e., the stack length, remained a difficult parameter to study and modulate.

In this paper, we describe a simple way to disrupt the folding and generate truncated D-A stacks in polymers prepared by

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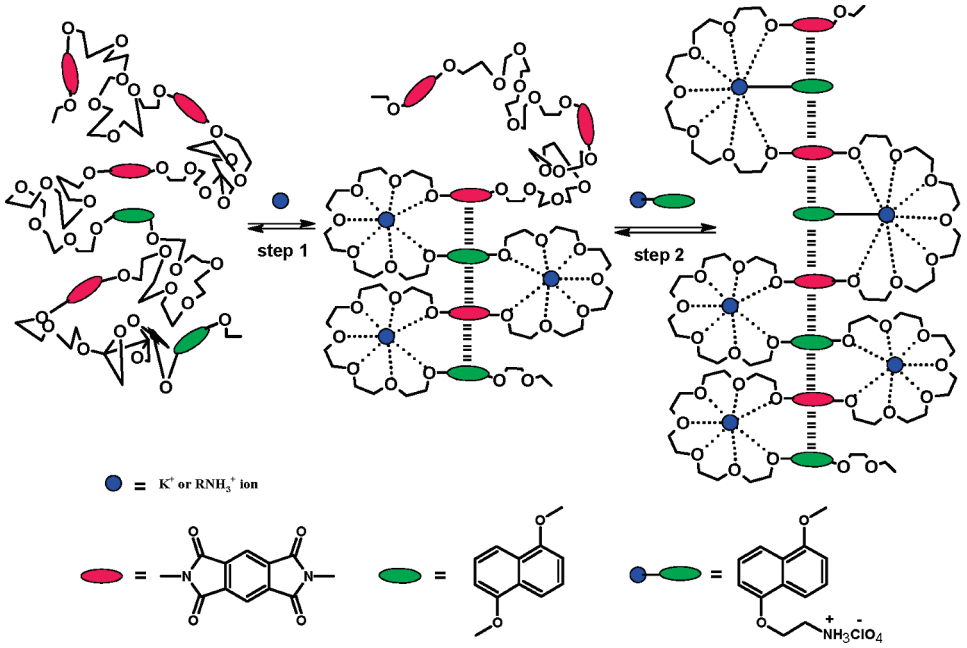
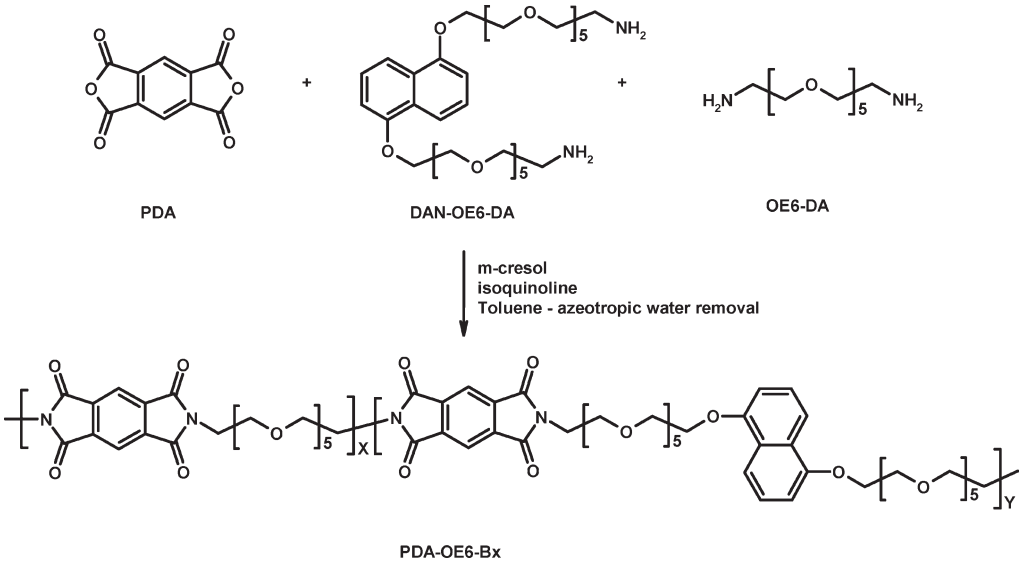
Scheme 1. Schematic Depiction of the Two-Stage Folding Process in PDA-OE6-B*x* Foldamers



Scheme 2. Synthesis and Structures of PDA-OE6-B*x* Copolymers



copolymerization of a DAN containing diamine and pyromellitic anhydride in the presence of varying amounts of a second diamine, namely α,ω-diaminohexa(oxyethylene), which serves as a stack-breaker. We also demonstrate that the stack length can be extended in a second step using the folding agent, DAN-C2-NH_3^+, that interacts with the remaining OE-6 spacers and brings the adjacent PDI acceptor units to form an extended D-A stack, as depicted in Scheme 1, making this the first example of a polymer that undergoes folding in two discrete steps.

Results and Discussion

The PDA-OE*n* type foldamers are typically prepared by the polycondensation of a DAN bearing diamine (DAN-OE6-DA) with pyromellitic dianhydride (PDA) under standard polyimide synthesis conditions (Scheme 2).[48] Use of an OE-diamine comonomer, such as OE6-DA which does not carry a DAN unit, leads to the formation of a copolymer wherein occasionally two acceptor units lie adjacent to each other along the polymer backbone. As depicted in Scheme 1, this will lead to the disruption in stacking under the usual folding conditions, such as in the presence of a suitable alkali metal or ammonium ion (step 1). Such a disruption occurs because metal ion complexation with the OE-6 loop alone is inadequate to form the pleated structure; the additional C-T interactions are essential to stabilize it. Thus, depending upon the extent of stack-breaker incorporation, the maximum attainable stack length can be regulated.

The donor−acceptor copolymers bearing stack-breakers were synthesized as per Scheme 2. Considering that the reactivity of the amine groups in both DAN-OE6-DA and OE6-DA would be the same, one could expect that the two comonomers will be incorporated in a statistically random fashion. Three copolymers were prepared using different mole ratios of the two diamine monomers in order to affect low, medium, and high level of stack disruption. The aromatic regions of the proton NMR spectra of the three copolymers (PDA-OE6-B*x*, where *x* represents the mole

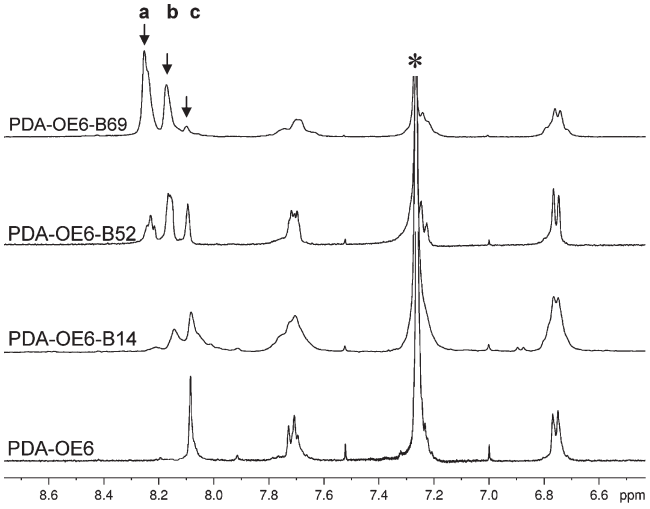


Figure 1. Aromatic region of the ^{1}H NMR spectra of the homopolymer PDA-OE6 and the copolymers (PDA-OE6-B*x*) in $CDCl_3$ (peak marked by an asterisk is due to residual solvent).

fraction of stack-breaker incorporated), along with that of the pure homopolymer, PDA-OE6, are shown in Figure 1.

The composition of the copolymers was calculated from the relative intensities of the peaks belonging to the PDI unit and those belonging to the DAN unit. Thus, the total intensity of the peaks between 8.0 and 8.2 ppm (due to the 2 protons of PDI) can be directly compared to intensity of the peak at ca. 7.7 ppm (due to two of the protons of the DAN unit).[49] For the pure homopolymer, PDA-OE6, these two peaks are of equal intensity, but for the copolymers the relative intensity of the DAN peak would be lower; the relative extent of this lowering can be used to calculate the exact copolymer composition. Using this approach, the extent of stack-breaker incorporated in the three copolymers was found to be 14, 52, and 69 mol %. This is in slight variance with the expected values based on the comonomer feed compositions of 25, 50, and 75 mol %; a possible reason for this could be the loss of some low-molecular-weight OE6-rich fraction during purification by reprecipitation.

One interesting feature in the copolymer spectra is that, whereas the homopolymer exhibits a single peak for the acceptor ring protons, the copolymers exhibit three peaks corresponding to the PDI ring protons. To rationalize this, it is important to recall that C-T interaction between the donor and acceptor units causes the aromatic peaks of both the D and A units to move upfield.[23,45,50] Furthermore, the extent of this shift strongly depends on whether a given acceptor unit interacts with a single donor or two donor units. On the basis of these observations, the most upfield peak (peak **c**) can be assigned to a PDI unit that lies between two donors (DAD), whereas the most downfield peak (peak **a**) is due an isolated PDI unit, and the intermediate one (peak **b**) is due to a PDI unit that lies at the end of a DA sequence (A[DA]$_n$), meaning that it can interact with a donor unit only on one side but not the other. The relative intensities of these three peaks are a reflection of the mole fraction the various types of units, and as expected, they are seen to vary with amount of stack-breaker incorporated in the copolymer. At high levels of stack-breaker (PDA-OE6-B69), the most intense peak is due to isolated PDI units (peak **a**), whereas the reverse is true in the case of PDA-OE6-B14, wherein the most intense peak is the one due to the sandwichable PDI unit (peak **c**).

To study the folding process, the copolymers were first titrated with ammonium thiocyanate. In Figure 2 (left panel), the spectral variation of a representative NMR titration experiment of PDA-OE6-B52 with NH_4SCN (in $CDCl_3/CH_3CN$, 1:1, v/v) is presented. It is evident that the extents of shift experienced by the

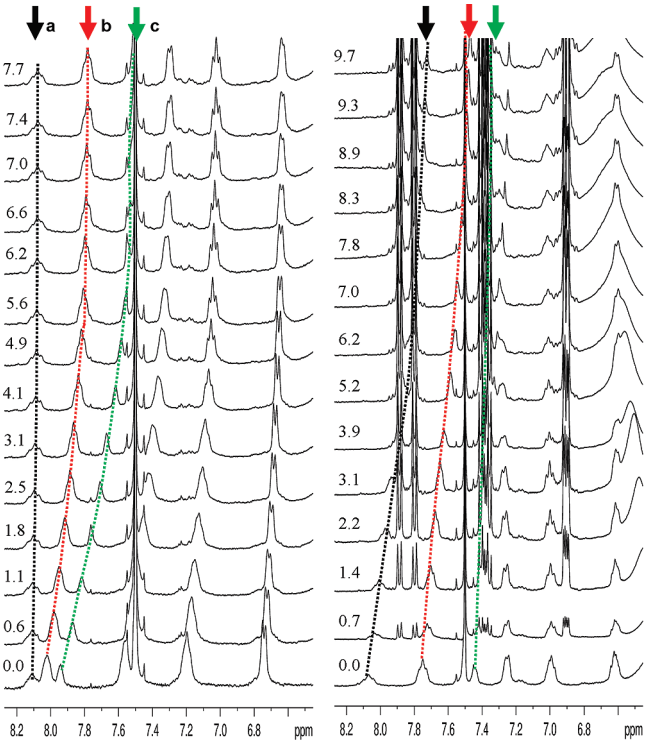


Figure 2. ^{1}H NMR titration of PDA-OE6-B52 (in $CDCl_3/CD_3CN$, 1:1 v/v), depicting the two-step folding process: left panel depicts the titration with NH_4SCN (step 1), and the right panel depicts subsequent titration with DAN-C2-NH_3^+ (step 2). Peaks due to isolated, half-sandwiched, and fully sandwiched PDI protons are marked by black, red, and green arrows, respectively. The ratio of folding aid to the appropriate repeat unit in the polymer is given against each spectrum.

three PDI peaks are distinctly different—the most upfield peak (peak **c**) is seen to vary the most, followed by the second most upfield one (peak **b**), whereas the most downfield peak (peak **a**) is almost invariant. In accordance with our earlier peak assignment, this may be explained as follows: the isolated PDI units cannot stack under these conditions and therefore the peak shifts very little, while PDI units that lie at the end of a DA stack has a donor unit only on one side and hence the corresponding peak experiences an intermediate shift. The peak due to the PDI units that have donor units on either side (peak **c**) experiences the maximum shift as it becomes sandwiched between two donor units. These observations are also in accordance with the behavior of various DA, DAD, and ADA type model compounds that were studied by us earlier.[45] These studies suggest that NH_4SCN induces a partial folding of the polymer, leading to DA stacks in only those regions of the polymer that have an alternating placement of D and A units along the polymer chain. The polymer chain remains unstructured in regions wherein isolated A units are present, as postulated in Scheme 1. The extent of the stack formation depends on the mole fraction of the stack-breaker; the smaller the mole fraction of stack-breaker, the larger is the extent of stack formation. Similar titration experiments that were carried out with PDA-OE6-B14 and PDA-OE6-B69 confirm these observations (Figures S1 and S2 in the Supporting Information).

A particularly interesting feature about these copolymers is that the unstructured regions of the partially folded polymer chain can also be folded using an external folding agent that engages with the chain via a two-point interaction. The folding agent DAN-C2-NH_3^+ (with ClO_4^- counterion) induces the second step of the folding process, during which the OE-6 spacers coordinates with the ammonium unit and brings the DAN donor between two adjacent PDI acceptor units to enable a

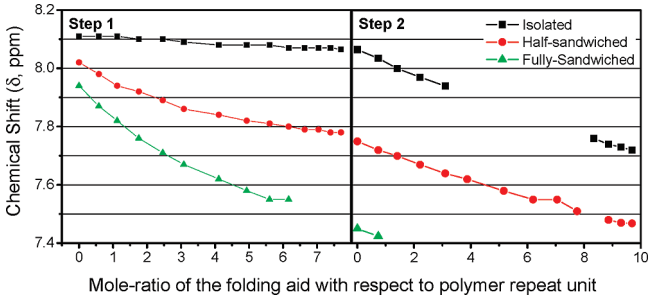


Figure 3. Plot of the chemical shift variation of the three different PDI protons as a function of NH_4SCN or DAN-C2-NH_3^+ in the case of polymer PDA-OE6-B52. Missing points are due to peak overlap with some intense peak due to solvent or folding agent. The mole ratios are with respect to the mole fraction of DAN ($1 - x$) in the copolymer in the case of NH_4SCN and with respect to mole fraction of OE6-DA (x) in the copolymer in the case of DAN-C2-NH_3^+. The experiments were done in $CDCl_3$–acetonitrile (1:1 v/v) using a polymer concentration of 1.7 mg/mL.

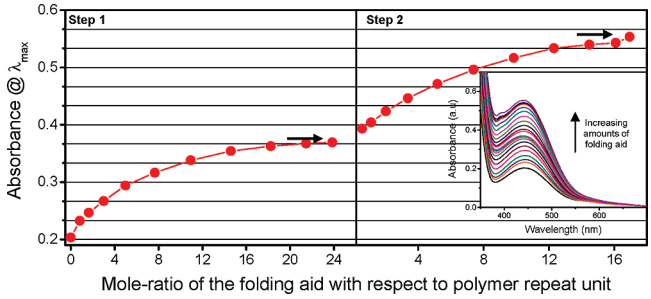


Figure 4. Variation of absorbance (at λ_{max}) of PDA-OE6-B52 as a function of folding aid mole ratio. Inset shows the evolution of charge-transfer band with increasing amounts of folding aid: NH_4SCN in the first step (left panel) and DAN-C2-NH_3^+ (right panel). The mole ratios are with respect to the mole fraction of DAN ($1 - x$) in the copolymer for NH_4SCN and with respect to mole fraction of OE6-DA (x) in the copolymer for DAN-C2-NH_3^+. The experiments were done in DCM–acetonitrile (1:1 v/v) using a polymer concentration of 0.9 mg/mL.

C-T complex formation and consequent folding.[46] The NMR spectral variation during the titration with DAN-C2-NH_3^+ is shown in Figure 2 (right panel), wherein it is evident that peak **a**, due to isolated PDI units, experiences a considerable upfield shift. For this second step of the titration, the solution of PDA-OE6-B52 is taken along with excess NH_4SCN (1:12 mole ratio with respect to DAN unit in the copolymer) and titrated with a solution of DAN-C2-NH_3^+. In Figure 3, the variation of the chemical shifts of the three different acceptor proton peaks (**a**, **b**, and **c**) are plotted as a function of mole ratio of NH_4SCN (during the first step) and the folding agent DAN-C2-NH_3^+ (during the second step).[51] The mole ratios in the first step are calculated with respect to the mole fraction of DAN units in the copolymer, while it is calculated with respect to the mole fraction of OE6-DA incorporated in the copolymer (i.e., the x-value) for the second step. This is done to reflect the fact that the binding of NH_4SCN and DAN-C2-NH_3^+ is expected to occur at **D**-OE6-**A** and **A**-OE6-**A** segments, respectively.

As evident from the left panel (Figure 3), peaks **b** and **c** exhibit large variations during the first step, and they begin to saturate. However, upon addition of DAN-C2-NH_3^+ (right panel), peak **a** corresponding to the isolated PDI units experiences the largest shift followed by peak **b**, whereas peak **a** shifts very little. Although the δ-values of peaks **b** and **c**, belonging to the terminal and sandwiched PDI units, respectively, become comparable at the end of the titration, peak **a** due to isolated PDI units remains slightly downfield even after saturation during the second step. This could be a reflection of the difference in the exact geometry of the intramolecularly folded and intermolecularly folded C-T complexes, which is known to affect the chemical shift.[23,52] The saturation of the chemical shifts during the first step of the titration followed by another decrease of selected peaks during the second step is clear evidence for the two-step folding process as envisaged in Scheme 1. A similar variation is seen in the NMR titrations of other two copolymers as well (Figures S4 and S5), the main difference being the relative intensities of the various peaks. One interesting question would be whether the order of addition of NH_4SCN and DAN-C2-NH_3^+ could be reversed. However, because of the increasing intensity of the DAN peaks (aromatic) in the region upfield to the PDI peaks, the reverse titration experiments would be difficult to perform cleanly. The PDI peaks would move upfield during the titration and would soon get buried under the DAN peaks. From previous studies,[46] we know that NH_4SCN would not affect the folding the acceptor-rich regions of the polymer. However, to address the question of whether DAN-C2-NH_3^+ would interact with the D–A regions of the polymer, we carried out a control experiment wherein the D–A homopolymer was titrated with DAN-C2-NH_3^+. Much to our surprise, we found that the PDI peaks move substantially upfield, suggesting that DAN-C2-NH_3^+ is not selective to the acceptor-rich regions alone (see Figure S3). Hence, the stepwise folding by reverse addition does not appear to be feasible. Further studies to understand and explain this unexpected observation is currently underway.[53]

The evolution of the folding process can be similarly examined by monitoring the C-T band in the UV–vis spectra. In the first step, a solution of PDA-OE6-B52 in DCM–acetonitrile (1:1, v/v) is titrated with increasing amounts of NH_4SCN, leading to a steady increase in the intensity of the C-T band followed by a saturation, as evident from Figure 4. In the second step the polymer solution saturated with NH_4SCN (1:12 mole ratio with respect to DAN unit in the copolymer) is titrated with DAN-C2-NH_3^+, which causes a further increase in the C-T band intensity. The second increase is due to the intercalation of the DAN units of the external folding agent between two adjacent PDI units within the unstructured sections of the polymer chain. As mentioned earlier, this C-T interaction occurs due to a cooperative two-point interaction—first the ammonium groups coordinate with the OE6 unit, which brings the DAN units in an appropriate position to facilitate the formation of a C-T complex with the adjacent PDI units. Here again, the relative absorbance values at which the saturation occurs after the first and second steps of the folding process are a reflection of the relative extents of stacking at each step. As expected, this value is seen to vary from 1.65 in PDA-OE6-B69 to 1.35 in the case of PDA-OE6-B14 (Figures S6 and S7). The higher ratios of folding agent to polymer in the UV–vis studies is because of the significantly lower concentrations at which these experiments were done when compared to the NMR titrations, which were carried out at nearly twice the polymer concentration.

Conclusions

We have shown that the extent of folding in a donor–acceptor type polymer bearing hexa(oxyethylene) spacers can be regulated by using a simple copolymerization strategy, wherein the use of OE6-diamine comonomer leads to randomly distributed segments along the backbone that possess only PDI acceptor units. Such copolymers exhibit a unique stepwise folding process: titrating with NH_4SCN causes the regions of the chain that carry alternatingly placed D and A units to fold due to interaction of the ammonium group with the OE-6 segments, which brings adjacent D and A units to form a C-T complex. At this stage a pleated structure is formed in some sections of the polymer chain whereas other regions remain unstructured. In the second step, the use of an external folding agent, namely DAN-C2-NH_3^+,

leads to the formation of a similar pleated D-A structure in the remaining regions of the chain—this time induced by a two-point interaction of the folding agent with the OE-6 segments and the adjacent PDI units. Although the present study of a stepwise folding process leads to a simple extension of the pleated stack in the second step, the idea of generating structured segments in a macromolecule which can then be further organized in a second step is reminiscent of the secondary and tertiary structures seen in proteins. One shortcoming of the present design is that the strength of the intrachain noncovalent interactions that induce folding is not very high, thereby leading to fairly dynamic structures. Therefore, the logical steps forward would be (a) to develop designs that lead to more stable secondary structures and (b) to provide distinctly different type of binding motif for the second step of the folding process that will enable a more purposeful control of the tertiary structure—similar to those seen in proteins.

Experimental Section

Materials and Methods. Triethylene glycol, 10 wt % Pd/C, *p*-toluenesulfonyl chloride, and 1,5-dihydroxynaphthalene were purchased from Sigma-Aldrich Chemical Co. and used without further purifications. Pyromellitic dianhydride (1,2,4,5-benzenetetracarboxylic dianhydride) was recrystallized from freshly distilled acetic anhydride (1 g in 10 mL). The monomers DAN-OE6-DA and OE6-DA either were prepared using previously reported procedures[39,42,43] or were slightly modified to improve yields or simplify purification procedures (see Supporting Information for details). Common organic solvents and reagents were procured from Ranbaxy, Spectrochem, or Nice chemicals. Solvents were distilled prior to use and, if necessary, were dried following the standard procedures. ^{1}H NMR spectra were recorded using a Bruker 400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as internal reference, unless otherwise mentioned. The absorption spectra were recorded using Cary UV−vis spectrophotometer. Dry distilled solvents were used for all the experiments.

Typical Polymerization: PDA-OE6-B14. In a typical polymerization, DAN-EO6-DA (1.42 g, 2 mmol) and OE6-DA (0.193 g, 0.7 mmol) were taken in 3 mL of freshly distilled *m*-cresol. The contents were stirred for 30 min under nitrogen purge. Freshly recrystallized pyromellitic dianhydride (0.6 g, 2.7 mmol) was then added, and the contents were stirred at 80 °C under nitrogen for 4 h. After cooling, 2 mL of *m*-cresol, 3 mL of toluene, and a few drops of freshly distilled isoquinoline as a catalyst were added. The contents were then heated to 180 °C; the water formed during this step was azeotropically removed using a Dean−Stark apparatus. After 8 h, the contents were cooled and concentrated using a high-vacuum pump. The residue was dissolved in 5 mL of chloroform and reprecipitated into methanol to afford a fibrous red polymer in 69% yield. For PDA-6OEG-52 and PDA-6OEG-69, the yields were 72 and 70%, respectively.

Folding Studies. Solutions for NMR studies were prepared in 1:1 (v/v) mixture of dry acetonitrile and dry $CDCl_3$. The concentration of the polymer solution was kept constant at around 1.7 mg/mL for all the experiments. Three stock solutions were prepared, namely **A**, **B**, and **C**. Solution **A** is the stock solution of the polymer at a concentration of 1.7 mg/mL. Solution **B** was prepared by dissolving the required amount of NH_4SCN in solution **A**, such that the final concentration of NH_4SCN is 20 mM. Solution **C** was similarly prepared by dissolving the required amount of DAN-C2-NH_3^+ (compound **17**) in solution **B**, such that the final concentration of DAN-C2-NH_3^+ is 20 mM.

The first step of the NMR titration was carried out by stepwise addition of the required quantity (30−100 μL) of solution **A** to 600 μL of solution **B**. This ensured that the polymer concentration was kept constant, whereas the concentration of NH_4SCN is reduced with each step of the addition. Similarly for the second step of the titration, 600 μL of solution **C** was sequentially diluted using 30−100 μL of solution **B**. This process ensured that the concentrations of both the polymer and NH_4SCN is kept constant, whereas only the concentration of DAN-C2-NH_3^+ is varied.

UV−vis spectroscopic measurements were done using a 1:1 (v/v) ratio of dichloromethane:acetonitrile. Three stock solutions (**A**, **B**, and **C**) were similarly prepared, the only difference being that the concentrations of all of them were reduced. Solution **A** had a polymer concentration of 0.9 mg/mL, while both solutions **B** and **C** had concentrations of NH_4SCN and DAN-C2-NH_3^+ of 16 mM, respectively. As in the case of NMR measurements, titrations were carried out by stepwise addition of the required amounts of solution **A** to solution **B** for the first step and similarly by stepwise addition of the required amounts solutions **B** to solution **C** for the second step.

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Supporting Information Available: Detailed synthetic procedures, spectral data, and NMR and UV−vis titrations of all the polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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