

Synthesis, Tubular Scaffolding, and Photocontrolling the Helix-Coil Transition in Phenylene Ethynylene Foldamers

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INTRODUCTION

Natural polymers such as proteins and RNA perform a variety of complicated functions based on their ability to adopt specifically folded conformations. Inspired by this structure-property relationship many artificial backbones capable of adopting well-defined secondary structures, particularly of the helix type, have been designed during the last few years. The helix-coil transition of these foldamers¹ can be utilized to generate tubular architectures² of defined length and functionality. Moreover, the dynamic nature of the folding reaction enables the design of stimuli-responsive materials.

Here, we present an extensive investigation of designing a diverse set of macromolecular architectures based on phenylene ethynylene foldamers.³ A novel method to obtain defect-free and lengthy poly(phenylene ethynylene)s (PPEs) has been developed and utilized to create organic nanotubes, a new foldamer family, sensory polymers, and the first photoresponsive foldamer.

RESULTS AND DISCUSSION

Our attention has been particularly focused on the folding properties of oligo(*meta*-phenylene ethynylene)s (*Om*PEs)³ and poly(*meta*-phenylene ethynylene)s (*Pm*PEs) in order to generate tubular structures of defined dimensions and functionality and to utilize the reversible helix-coil transition of these foldamers for the design of stimuli-responsive materials. Our approach (Figure 1) to organic nanotubes involves synthesis of a functional monomer containing folding-promoting features as well as cross-linking units. Polymerization of such monomer thus leads to a folding backbone in which reactive groups are oriented in close proximity to each other. Subsequent crosslinking of these moieties then result in covalently stabilized nanotubular objects.⁴

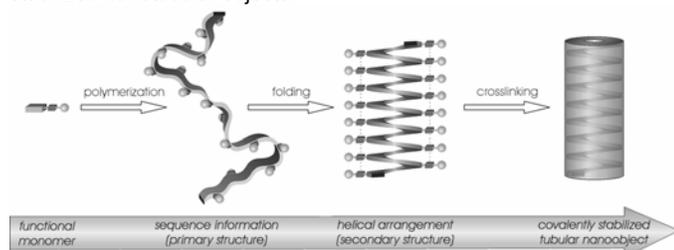


Figure 1. Organic nanotubes via intramolecular crosslinking of helical folds.

For this purpose amphiphilic *Pm*PEs³ have been chosen as the folding scaffold due to several advantageous features of this helical backbone. However, synthesis of high-molecular weight and defect-free *Pm*PEs still remains difficult.⁵ Thus, we developed a new method to obtain such lengthy and defect-free *Pm*PE structures.⁶ Our method involves a rate-limiting *in-situ* deprotection of trimethylsilyl-protected acetylene monomer/oligomer to minimize the concentration of free acetylene in the reaction mixture and therefore suppress competing side reaction such as bimolecular diyne defect formation. The polycondensation reactions could be accelerated by using microwave irradiation thus rendering the protocol highly efficient and practical. The synthetic utility of this newly developed polycondensation protocol was further demonstrated by synthesizing site-isolated, defect-free, and water-soluble conjugated poly(*para*-phenylene ethynylene)s (*Pp*PEs).⁷ This *Pp*PE derivative displays the highest recorded quantum yield for a conjugated polymer in water ($\Phi_f = 0.43$) and is a potential candidate for ultrasensitive biosensing applications. The *in-situ* activation/coupling protocol was then applied to prepare cinnamate-

based *Pm*PE (Figure 2) with respectable degree of polymerization (DP ~ 60). Solvent denaturation experiments using UV/vis spectroscopy to monitor the population of random-coiled and helical conformations reveal a typical sigmoidal curve indicative of cooperative folding behavior (Figure 3). Fluorescence spectroscopy independently yields a similar solvent titration curve with a slightly shifted transition point.^{3b} With respect to shorter oligomers of similar structure, indicating a more stable helix as predicted by the helix-coil model. Irradiation of polymer **3** under high dilution conditions to perform intramolecular [2+2] photodimerization reaction in the folding promoting solvent acetonitrile affords crosslinked polymer **4**.

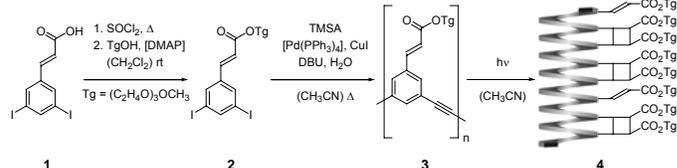


Figure 2. Synthesis of monomer **2**, polymer **3**, and crosslinked polymer **4**.

Solvent denaturation experiments were performed on polymer **4**. With increasing amount of the denaturant chloroform, no significant spectral changes were observed clearly demonstrating the locked helical conformation. These results were further supported by NMR and fluorescence spectroscopy.⁴

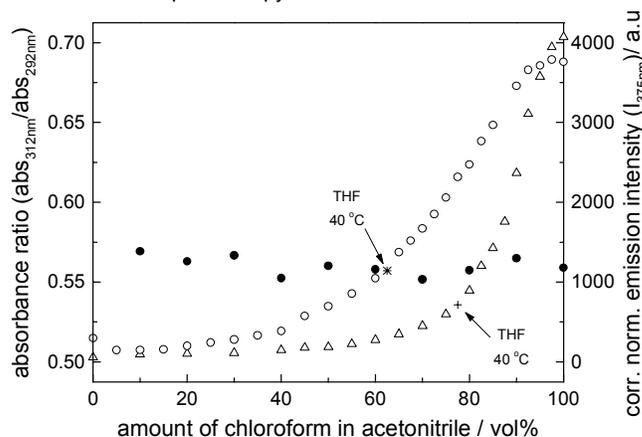


Figure 3. Solvent denaturation curves for polymer **3** before (**3**) and after (**4**) irradiation: plot of UV/vis absorbance ratio (A_{312nm}/A_{292nm}) and corrected normalized fluorescence intensity (I_{375nm}), respectively, as a function of the volume percent chloroform in acetonitrile (25 °C). UV/vis of **3** (○), fluorescence of **3** (△), UV/vis of **4** (●).

Identification of new folding backbones is crucial to the rapid development of the emerging field of foldamers. In this context, we have synthesized defect free poly(*ortho*-phenylene ethynylene)s (*Po*PEs)⁸ by using our *in-situ* deprotection/coupling protocol. Folding properties of this backbone were still not established experimentally and hence presented an attractive opportunity to study the secondary structure of this foldamer family. UV/vis and fluorescence spectroscopies were used to study the conformational behavior of these *Po*PEs in two different solvents i.e chloroform and cyclohexane. These studies suggest that the polymer backbone adopts helical conformation in cyclohexane while remains random coil in chloroform.

The reversible helix-coil transition and the tubular cavity of the *Om*PE foldamers present an ideal opportunity for the development of stimuli responsive smart materials. However, the stimuli employed so far, such as solvent composition³ and metal complexation,⁹ to control the helix-coil transition in these *Om*PE foldamers are practically difficult and result in formation of waste byproducts. Light is perhaps the ideal and the most practical stimulus in this regard as timing, location and intensity of incident light can be controlled precisely. Further advantage of using light is the absence of waste byproducts. Hence, we become

interested in using light as an external stimulus to control the helix-coil transition in synthetic foldamers.

Our approach is based on incorporation of photochromic molecule into the folding backbone such that the photoisomerization either disrupts or creates the kinked connection leading to either denaturation or helix formation.¹⁰

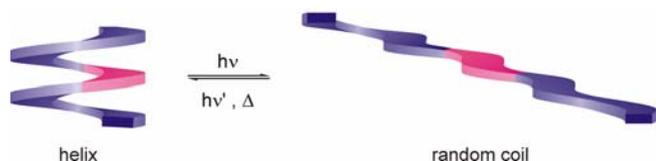


Figure 4. Photocontrol of the helix-coil transition in helical foldamers.

For this purpose, we have synthesized an azobenzene-core oligomer **5** after several design iterations.¹¹ The photoresponsive core in oligomer **5** is attached to two hexameric backbone segments such that the entire strand is long enough and capable of folding in polar environment while irradiation causes a significant change in the molecular geometry of the photochromic molecule leading to the disruption of the helical conformation since each individual segment is incapable of adopting a helical structure.

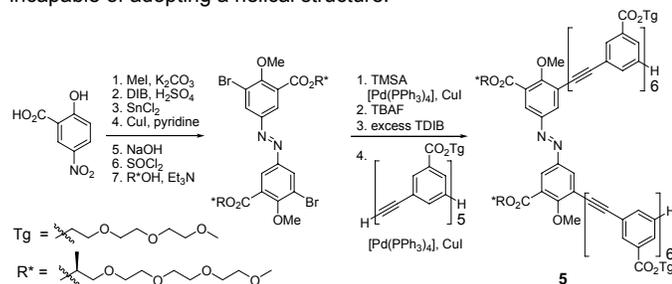
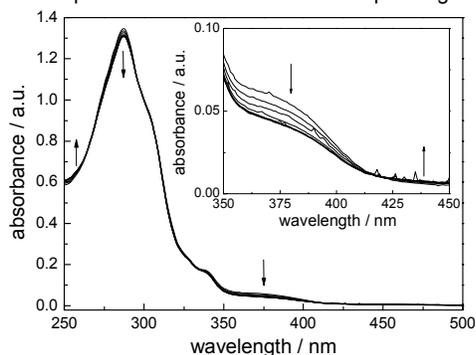


Figure 5. Synthesis of azobenzene core oligomer **5**.

The folding process of the oligomer **5** was investigated by typical solvent denaturation experiments using UV/vis spectroscopy. The sigmoidal shape of the titration curve indicates the cooperative nature of the folding process. Irradiation of the oligomer **5** using 365 nm light resulted in rapid conversion to the corresponding *cis*-isomer as



monitored by UV/vis spectroscopy.

Figure 6. UV-visible absorption spectra obtained during photochemical *trans*→*cis* isomerization of **5** caused by 365 nm irradiation in acetonitrile.

The conformational changes of the backbone during the forward and backward isomerization process were monitored by CD spectroscopy. In denaturing solvent i.e. chloroform, no CD signal has been detected while a strong CD signal is observed in folding promoting solvent aqueous acetonitrile. Irradiation of helically folded oligomer **5** leads to a rapid decrease in the CD signal indicating depopulation of the helical conformation while thermal reversion leads to complete recovery of the CD signal and indicates complete refolding of the backbone (Figure 7).

Such light triggered systems can provide fundamental insight into mechanisms of folding/unfolding by enabling time-resolved measurements and promise applications in smart delivery devices based on photoresponsive dynamic receptors.

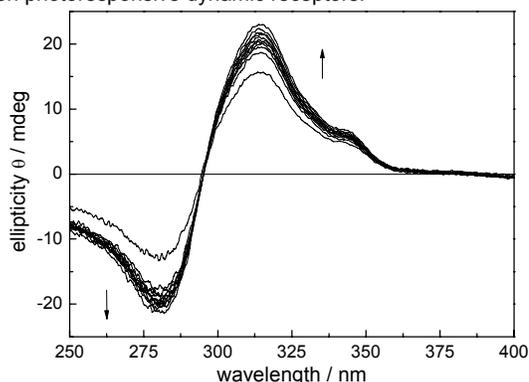


Figure 7. CD spectra obtained during thermal *cis*→*trans* isomerization of **5** in 60 vol% H₂O in CH₃CN.

CONCLUSIONS

In summary, we have designed and synthesized various macromolecular nanoarchitectures based on phenylene ethynylene foldamers. Development of a practical and efficient polycondensation method led to the synthesis of first covalently stabilized nanotubular architecture, a new foldamer family and sensing polymers while quest to control the conformational transition in phenylene ethynylene foldamers by using light as an external stimulus led to the successful design and synthesis of the first prototype of a photoswitchable foldamer.

ACKNOWLEDGMENT

Generous support by the Sofja Kovalevskaja Award of the Alexander von Humboldt Foundation (AvH), the Max Planck Society (MPG) and the German Research Foundation (DFG) is gratefully acknowledged.

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- A detailed account will appear in: Khan, A.; Hecht, S. *Chem. Eur. J.* in press.