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Helical Pitch of *m*-Phenylene Ethynylene Foldamers by Double Spin Labeling

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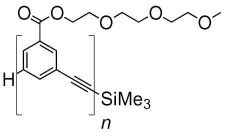
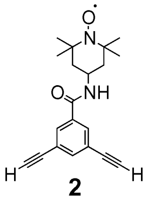
Foldamers are chain molecules that adopt a specific conformational state in solution, the structures of which are stabilized by a collection of noncovalent interactions.[1] For example, the family of oligo(*m*-phenylene ethynylene)s **1** are helical in polar solvents such as acetonitrile at chain lengths greater than eight units. In contrast, these molecules exhibit random conformations in solvophilic solvents such as chloroform.[2] Foldamers are important not only as models to understand the more complex behavior of biological macromolecules, but also as promising candidates for new functional materials[3] and synthetic receptors.[4] Given that many of the commonly used spectroscopic signatures of conformational order are low resolution and generally not applicable to new abiotic backbones, a major challenge is the need to obtain reliable structural data in solution. This is especially true for *m*-phenylene ethynylene foldamers **1** where the use of NMR is precluded due to the problems of assignments and aggregation.[2b] Although X-ray powder diffraction[2c] has provided information on the solid-state packing of **1**, information on the local helical structure in solution is based on calculations[5] and still remains as an unresolved question. Herein we describe the use of spin labeling methods to probe the helical structure of the oligo(*m*-phenylene ethynylene)s in solution.



1 (*n* = 12-24)



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To obtain detailed structural information, we designed and examined a series of double spin labeled oligomers.[6] Double spin labeling is a technique that has been used to determine the solution structure of peptides,[7] proteins,[8] rodlike oligomers,[9] and dendrimers.[10] By recording the electron spin resonance (ESR) spectrum of molecules labeled with two stable organic radicals, the distance between the two radicals can be estimated. The ESR spectral shape is a function of exchange and/or dipolar interactions between the spin labels. Because both of these interactions are highly sensitive to the separation distance, ESR spectra can reveal information about the relative position of the labels.

We expected that the spin−spin interaction between two nitroxide radicals would be greatest when the labeled units were overlapped in the folded state (Figure 1). Offset π-stacking was observed in the crystal structure of monomeric unit **2**, suggesting that the TEMPO moiety would not severely disturb the helical conformation.[11] Oligomers **3**, **4**, and **5** were thus prepared. These oligomers are identical to **1** but contain two TEMPO labeled sites, which are separated by four, five, and six repeating units, respectively. To avoid the effects of fraying, the spin labels were introduced in the middle of the sequence. Monolabeled oligomer **6** was also prepared as a control to rule out intermolecular effects. A convergent oligomer growth strategy was adopted to synthesize the oligomers using Sonogashira Pd-catalyzed coupling chemistry.[12] The nitroxide radical is known to be unreactive under these conditions.[13]

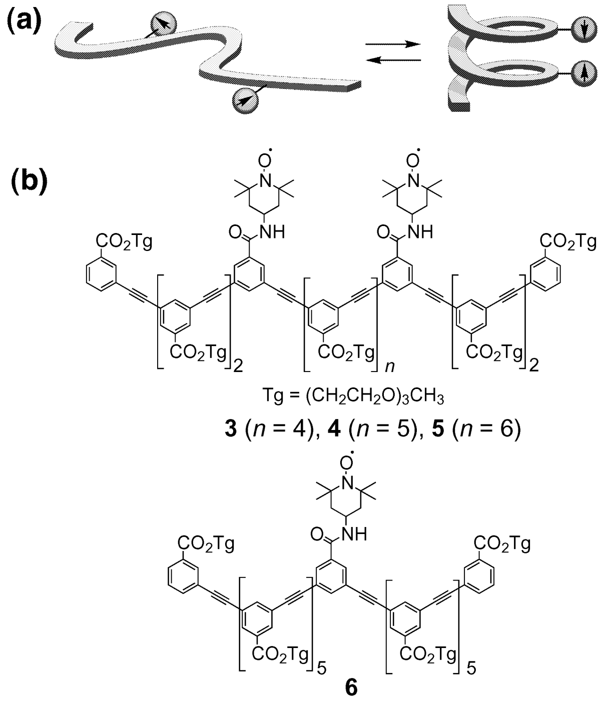

Figure 1. (a) Schematic diagram illustrating a doubly spin labeled phenylene ethynylene oligomer in the unfolded and helical conformers. (b) Chemical structures of oligomers studied.

Oligomers **3**−**6** showed solvent dependent UV−vis spectra that are characteristic of the conformational state, similar to unlabeled phenylene ethynylene oligomers **1**. In chloroform, the 305 and 289 nm $\pi-\pi^*$ bands have nearly the same relative intensity. This ratio of intensities indicates that the backbones are randomly oriented as a mixture of the *cisoid* and *transoid* states in chloroform.[2a,b] In acetonitrile, on the other hand, a decrease in the 305 nm band was observed. This indicates a conformational transition to a folded structure in which the relative orientation of adjacent aromatic rings is predominantly *cisoid*.[2a,b] In ethyl acetate, the ratio of intensities is intermediate, but still indicative of a predominantly folded state.

The ESR spectra of **3**−**6** were measured in chloroform and in ethyl acetate (Figure 2).[14] To evaluate the line broadening, the spectra were each normalized to the same double integral value. In chloroform, where the oligomers adopt a random conformation,

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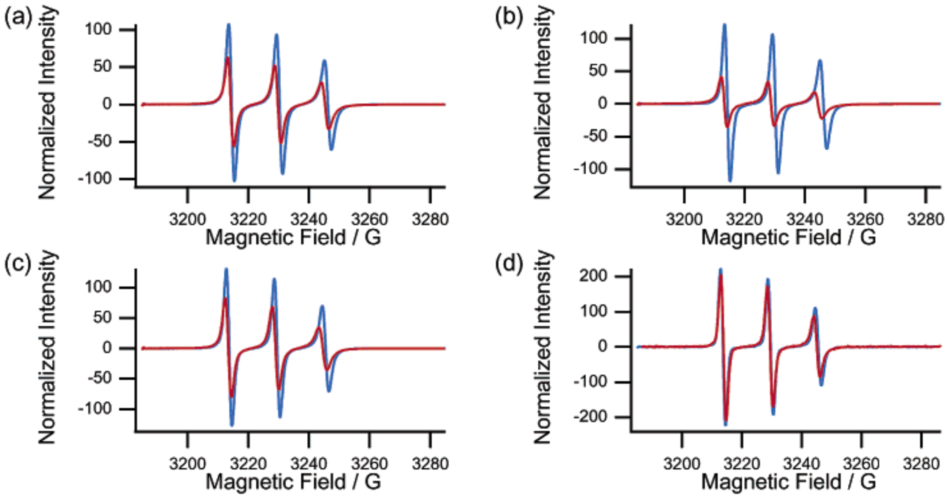

Figure 2. ESR spectra (9.07 GHz) of (a) **3**, (b) **4**, (c) **5**, and (d) **6** in chloroform (blue) and ethyl acetate (red). The spectra were measured at room temperature at a concentration of 0.3 mM. Intensity was normalized by equating double integrated values.

the observed ESR spectra consisted of three lines centered at $g =$ 2.005−2.006, which are typical of nitroxide radicals. In ethyl acetate, line broadening was observed for **3**−**5**, indicating that spin−spin interactions were present between the two nitroxide radicals.[15] This interaction is assumed to originate from the close proximity of the spin labels within the folded chains. The degree of the broadening was the largest for oligomer **4**, in which there are five repeating units between spin labels. Line broadening was not observed in singly labeled oligomer **6**. This excludes the possibility of intermolecular aggregation or any effect of folding as being responsible for the broadening.

These results indicate that the spin labels are spatially closer in the folded structure of **4**, as compared to the oligomers **3** or **5**. The experimental findings can be explained by considering that six repeating units make one helical turn.[16] Because the oligomers are *meta*-connected phenylene groups, a hexagonal helical structure made of six repeating units should have a maximum intramolecular overlap with the least amount of bond angle and torsion strain.

In conclusion, we have designed and synthesized phenylene ethynylene oligomers which were selectively spin labeled at two sites. The measurement and analysis of the ESR spectra revealed that one helical turn, within the folded structure, consists of six repeating units. The use of spin labeling methods provides a powerful way to answer fundamental questions about the conformational structure of chain molecules in solution. Attempts to gain more detailed quantitative information are currently underway.

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Supporting Information Available: Experimental procedure of the syntheses of **2**−**6**, UV−vis spectra of **3**−**6**, ESR integrated spectra of **3**−**6**, and crystallographic data of **2** (PDF). Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We used ethyl acetate because acetonitrile has too high of a dielectric constant to measure the spectrum under the same conditions used with chloroform.
(15) We performed quantitative spin integration experiments using DPPH as a reference (0.1 mM in chloroform). The spin content per molecule in oligomers **3**−**5** was confirmed to be 2.0 within experimental error.
(16) Both the exchange interaction and the dipolar interaction can contribute to the line broadening. Because the two interactions are both contributing to the observed line broadening, quantitative analysis is difficult in this case.

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