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Solution-Phase Structure of an Artificial Foldamer: X-ray Scattering Study

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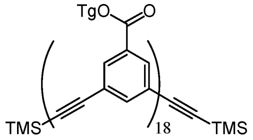
Foldamers are synthetic oligomers that adopt ordered conformations in solution due to noncovalent interactions. They often possess unique functionality resulting from their folded structures, similar to biological macromolecules.[1−5] Foldamers also provide important insights into the fundamentals of noncovalent folding, which is of primary importance for understanding biological systems and developing novel self-assembling materials.[2] The structure of artificial foldamers in solution has been studied using a variety of indirect spectroscopic techniques and theoretical methods.[2,6−8] X-ray scattering using a high flux synchrotron source has been recently shown to provide a powerful means of studying small organic[9] and biological[10] arrays that are formed due to noncovalent self-assembly in solution. Therefore, this methodology appears particularly suitable for artificial foldamers. To the best of our knowledge X-ray scattering has not been applied to structural studies of artificial foldamers in solution. Herein we present small-angle X-ray scattering (SAXS) studies on *m*-phenylene ethynylene oligomer (*m*PE) **1** in acetonitrile, providing for the first time direct structural data on a *m*PE foldamer in solution.



Tg = -$(CH_2CH_2O)_3CH_3$

1

The synthesis and characterization of oligomer **1** is described in the Supporting Information. UV−vis spectra (Figure S1) indicate that **1** is largely folded in acetonitrile solution.[11] SAXS measurements were performed on 10^{-3}−10^{-4} M acetonitrile solutions of **1** using a high-flux synchrotron source (Advanced Photon Source at Argonne National Laboratory). SAXS measurements on unfolded oligomers were precluded due to absorption of X-rays by the chlorinated solvents required to unfold the structures. The X-ray wavelength was set at $\lambda = 0.69$ Å and the sample to detector distance was adjusted to achieve scattering measured across the $0.001 < q < 1.5$ Å^{-1} region, where $q = (4\pi/\lambda)\sin\theta$, λ is the X-ray scattering wavelength, and 2θ is the scattering angle.

In the low-resolution region ($q < 0.1$ Å^{-1}), the scattering follows the Guinier relationship, $I(q) = I(0)\exp(-q^2R_g^2/3)$, which is parametrized in terms of the forward scattering amplitude, $I(0)$, and the radius of gyration, R_g.[12,13] The linearity of the Guinier plot is a measure of the monodispersity.[14] Oligomer **1** shows a linear Guinier plot over the range $0.002 < q^2 < 0.010$ Å^{-2}, indicating that the samples consist of monodisperse structures, with radii of gyration of 14.7 Å, see Figure 1.

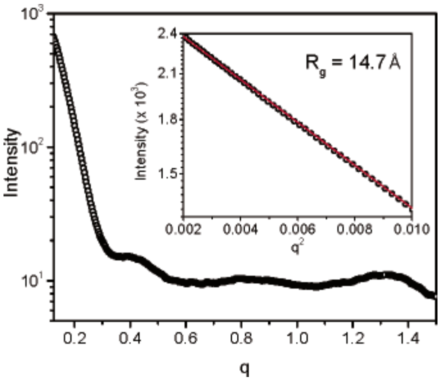


Figure 1. Experimental scattering intensity $I(q)$ versus scattering length vector q data for 1 in MeCN (5×10^{-4} M) solution (0.125 Å$^{-1} < q < 1.5$ Å^{-1} region). Inset: I(q) versus q^2 for the same sample ($0.002 < q < 0.01$ Å^{-2} region). Guinier fit to the data is also shown.

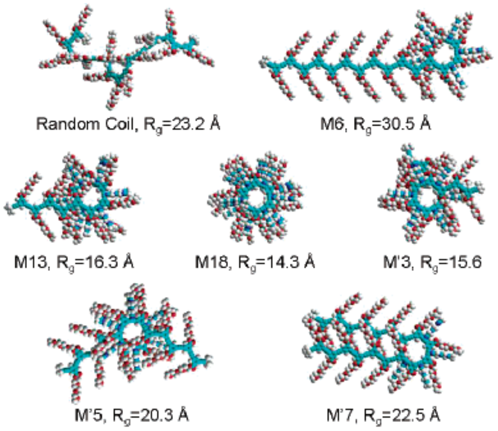


Figure 2. Representative models used to simulate the structure of **1** in acetonitrile solution

The monodisperse character of oligomer **1** in acetonitrile solution allows examination of the solution-phase structure through atomic pair distribution function (PDF) analysis.[15] A direct comparison between the reciprocal-space scattering pattern and real-space molecular models (Figures 2 and S2) can be made by comparing their PDFs.[14] The PDF derived from the scattering data of **1** in MeCN, along with those from the models, are presented in Figure 3 and Figure S4.

The models of oligomer **1** were created using the Hyperchem program.[16] Starting with a fully unfolded structure, M1, folded models (Figure 2) were generated by rotating the oligomer around sequential ethynyl bonds until **1** adopted a fully folded conforma-

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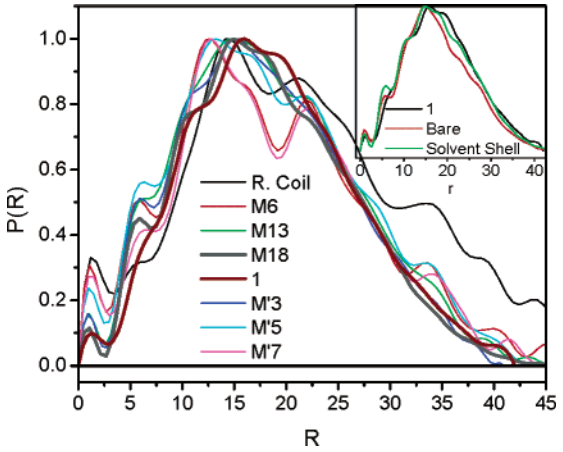

Figure 3. Atomic pair distribution functions (PDFs) for **1** and representative folded models in MeCN obtained using the program GNOM. The same *q* region was used in the calculation of PDFs of both **1** and the models. The inset shows PDFs for the model foldamer with and without solvation shells. The PDF of **1** is also shown.

tion, M18. Additional models were generated by simultaneously unfolding M18 from both ends, M′1−M′8, and a random coil model was generated to more accurately depict the fully unfolded structure. Coordinate-based scattering data (Figure S3) and theoretical values of R_g (Table S1) were generated for each of these models.[17] The coordinate-based scattering data was converted into PDFs using the same methodology employed for the experimentally obtained scattering data.[15] Comparison of the values of R_g and the PDFs show that the folded structures M15−M18 and M′1−M′2 provide the best fits to the experimental data. Notably, the gradual smoothing of sharp PDF peaks at ca. 12 and 23 Å upon folding (Figure 3) appears to be a characteristic feature that can be used to estimate the extent of folding, indicating that **1** is completely folded (or nearly so) in acetonitrile solution. The fully folded, helical model M18 has a radius of 7.3 Å, a monomer-to-monomer distance of 7.6 Å, and a pitch of 4.1 Å. These dimensions are in good agreement with those previously reported for a similar theoretical model of a folded *m*-phenylene ethynylene oligomer,[7] the overall deviation being about 9%.

To reproduce the difference in solvation of the side groups versus the folded core, we inserted three acetonitrile molecules per Tg group around the folded part of the oligomer models. This improved the fit to the experimental PDF, although the influence of the solvent shell on the smoothing of PDF peaks upon folding was found to be insignificant (Figure 3 inset and Figure S6). Extended conformations of Tg groups fit best the experimental PDF and radius of gyration.

To corroborate the PDF analysis, a direct reconstruction of the aggregate shape from the experimental scattering data was performed using the ab initio simulated annealing procedure.[18] Ten separate simulations were constrained to cylindrical, 6-fold symmetry and averaged to reveal the final simulated structure (Figures 4 and S6). This structure correlates with the core structure of a hollow, helical foldamer with outer dimensions of 18 Å × 12 Å and an inner diameter (i.d.) of 11 Å. These values are nearly identical to those obtained for the fully folded model M18 (18 Å × 11 Å, i.d. 10 Å). The absence of Tg side groups in the calculated structure is the result of the partially random conformations of Tg atoms in the individual simulated models, that is, the averaging procedure retains only atoms that are consistent between all models.

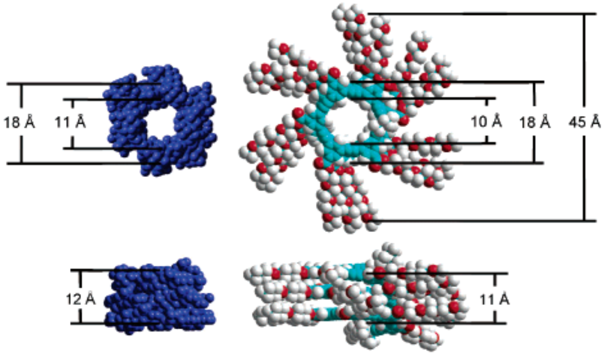

Figure 4. Top and side views of the structure reconstructed from SAXS data (left) and the foldamer model (right). The dimensions of the two models are also shown and are nearly identical.

We obtained the first direct insight into a solution-phase structure of an artificial foldamer using SAXS. We believe that X-ray scattering can be employed as a general methodology for direct structural studies of foldamers in solution.

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Supporting Information Available: Experimental details, including synthesis and characterization, and additional models, scattering data, and PDFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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