Folding and aggregation of backbone-rigidified oligo(*m*-phenylene ethynylenes) in polar and nonpolar media

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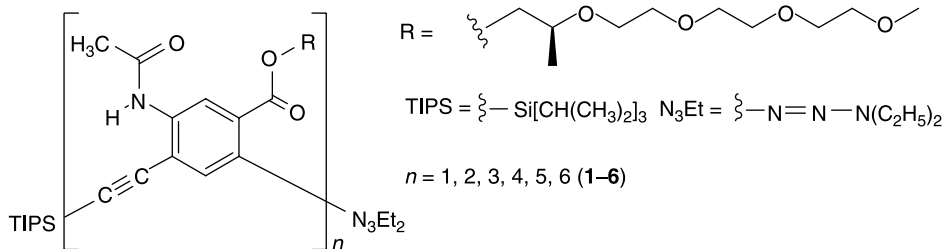*Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, NY, USA*

The folding and chiral aggregation of backbone-rigidified oligo(*m*-phenylene ethynylenes) were examined using NMR, UV, circular dichromism (CD) and dynamic light scattering (DLS) in methanol and chloroform. Evidence from 2D NMR suggests that backbone-rigidifying intramolecular H-bonds persist in chloroform and methanol, suggesting that these molecules are stably folded in both nonpolar and polar solvents. Results from CD studies further confirmed that longer oligomers (pentamer and hexamer) adopted chiral (helical) conformations. DLS indicated that, in chloroform, the oligomers are fully solvated and exhibited no aggregation; in methanol, these molecules show a size-dependent aggregation, in which a pentamer and a hexamer formed large assemblies while a smaller tetramer showed no detectable aggregation.

Keywords: hydrogen bond; folding; helical structure; aggregation

Unnatural oligomers that fold into well-defined secondary structures, i.e. foldamers (*1–11*), have attracted intense interest in recent years. The study of foldamers may provide additional insights into the folding of biomacromolecules and may also lead to biomimetic structures that exhibit new properties and functions. By introducing localised intramolecular hydrogen bonds that limit rotational freedom of backbones, we (*12–16*) and others (*17–23*) reported backbone-rigidified aromatic oligoamides that are enforced into well-defined helical conformations. The helical aromatic

oligoamides developed by us consist of *meta*- or *metal/para*-linked benzene rings and contain large hydrophilic interior cavities. A system of helical aromatic oligomers containing a hydrophobic cavity was described by Moore *et al.* (*24–30*), which was based on the folding of oligo(*m*-phenylene ethynylenes) (oligo(*m*-PE)). By attaching polar side chains, the resultant oligomers were found to adopt a helical conformation in polar solvents. For these *m*-PE oligomers, folding was achieved by the solvophobicity of the *m*-PE backbone and the solvophilicity of the polar side chains.

Thus, in nonpolar solvents such as chloroform, these oligomers adopt random coils. In addition, foldamers based on *o*-PE oligomers have also been reported (*31–35*).

By incorporating backbone-rigidifying intramolecular H-bonds, we (*36, 37*) demonstrated the enforced folding of short *m*-PE oligomers (*38*). Compared with the solvent-driven folding of *m*-PEs, which require a minimum chain length of about 10 PE residues (*30*), the backbone-rigidified *m*-PE oligomers we designed adopt length-independent, stably folded conformations in chloroform.

It is not clear whether these *m*-PE oligomers can still adopt similar H-bond-rigidified conformations in polar solvents. *m*-PE oligomers that are stably folded in both nonpolar and polar media represent an interesting class of porous molecules with well-defined cavities. Herein, we described the folding and assembly of *m*-PE oligomers **2–6** carrying polar chiral side chains and backbone-rigidifying intramolecular H-bonds. Molecular modelling (see Supplementary Materials for details, available online) shows that tetramer **4** and its

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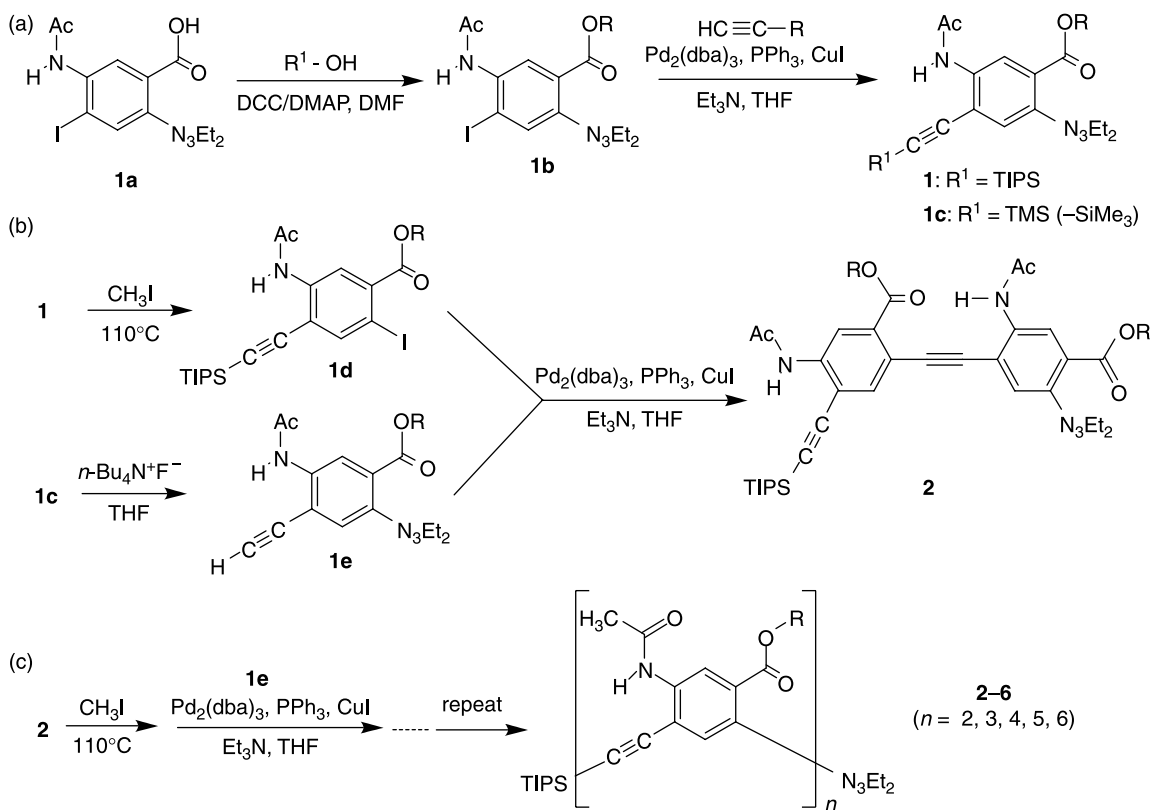
Scheme 1. Synthesis of backbone-rigidified *m*-PE oligomers.

shorter homologues are too short to adopt a helical conformation. Oligomers **5** and **6**, with their TIPS and diethyltriazenyl groups, are able to fold into helical conformations but are too short to take advantage of the

solvent-driven mechanism (*30*) due to the lack of the intramolecular overlap between their aromatic residues.

The synthesis of oligomers **2–6** is shown in Scheme 1. Compounds **1** and **1c** were prepared from **1a**, which was
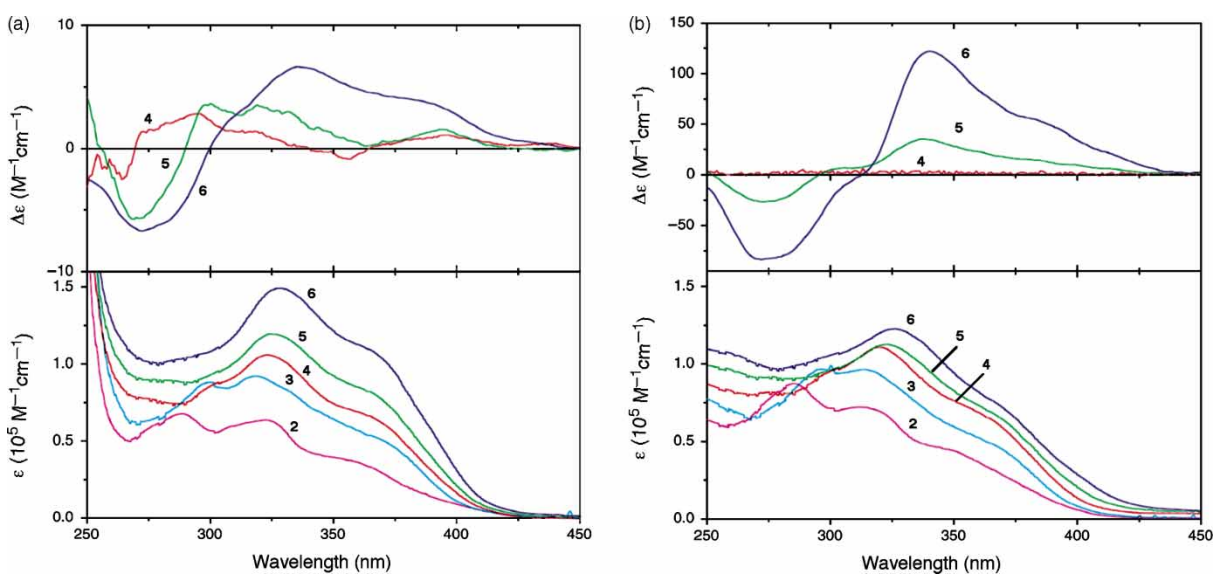

Figure 1. (a) CD (top, for **4–6**, 12 μM) and UV (bottom, for **2–6**, 2 μM) spectra recorded in chloroform. (b) CD (top, for oligomers **4–6**, 2 μM) and UV (bottom, for **2–6**, 2 μM) spectra recorded in methanol.
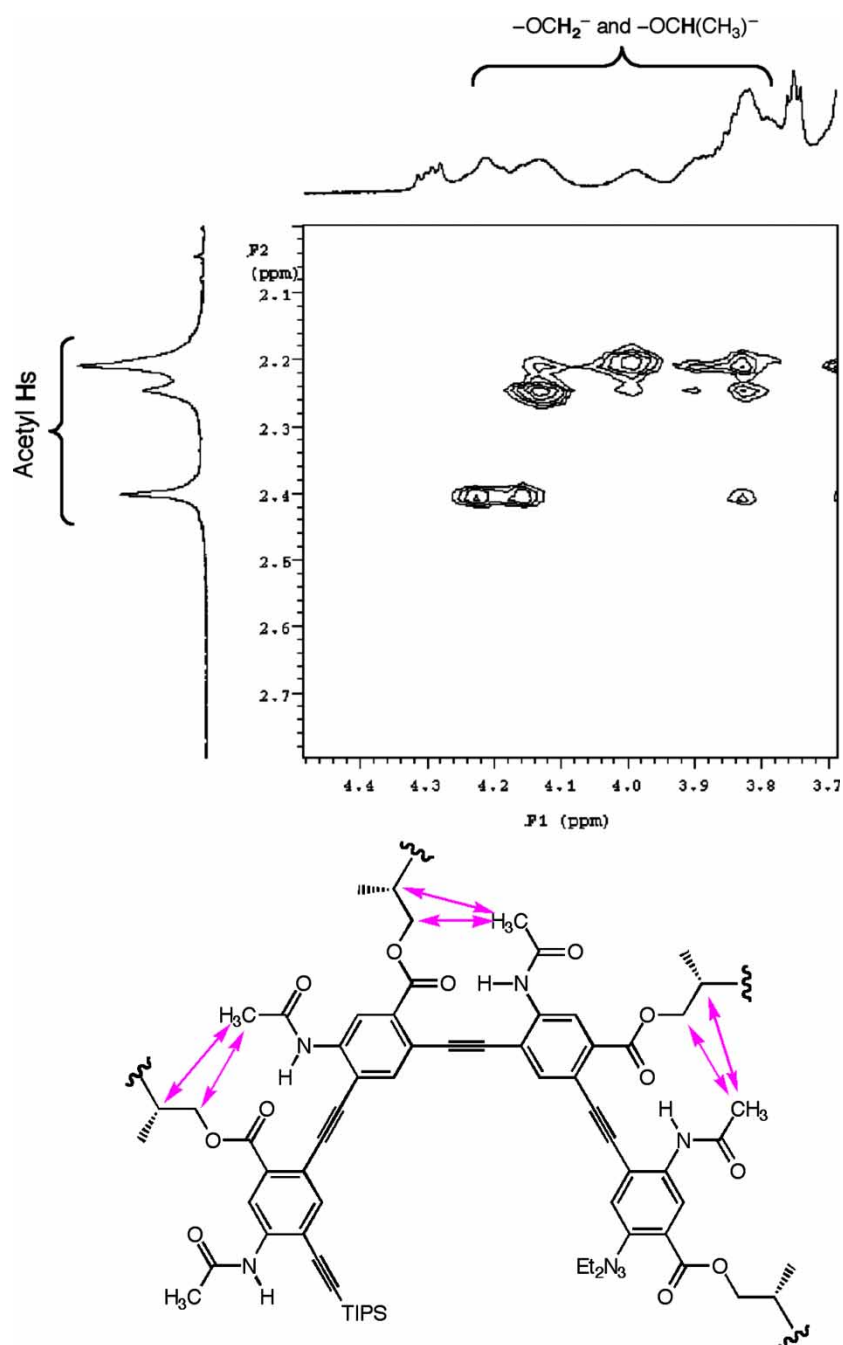
Figure 2. Partial NOESY spectrum of **4** in CD₃OD (4 mM, 293 K, 500 MHz, mixing time: 0.3 s). Strong NOEs corresponding to contacts between the acetamido protons and the methylene and methine protons are detected.

made based on the procedures we reported (*36*, *37*). Compound **1** was converted to **1d** by treating with methyl iodide. Removing the TMS group of **1c** led to **1e**. Sonogashira coupling (*39*) of **1d** with **1e** gave **2**, which was converted to the corresponding dimer iodide using methyl iodide. Repeating the coupling steps led to trimer **3** and oligomers **4–6**.

Oligomers **4–6** were first examined using circular dichroism (CD) spectroscopy in chloroform (Figure 1(a),

top) at room temperature. As expected, tetramer **4**, which is too short to adopt a helical conformation, showed no obvious Cotton effect in either chloroform or methanol. Consistent with a twist sense bias of its H-bond-rigidified helical backbone, hexamer **6** showed an obvious Cotton effect from its backbone chromophore. The CD spectrum of pentamer **5** contains weak but discernible maxima that are consistent with its UV spectrum. In methanol, the CD spectra of **5** and **6** show strong Cotton effects
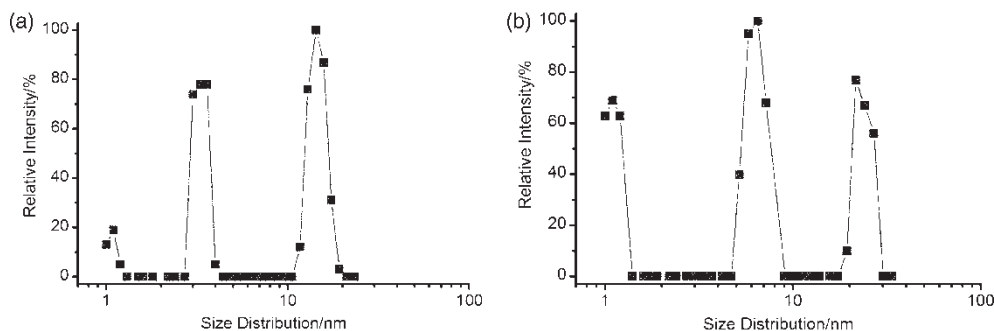
Figure 3. Results of DLS measurements of (a) oligomer **5** (0.29 mM) and (b) oligomer **6** (0.25 mM), in methanol at room temperature.

(Figure 1(b), top). By contrast, previously reported CD studies on short (<10 residues) *m*-PE oligomers with flexible backbones and polar chiral side chains revealed no Cotton effect in either chloroform or acetonitrile (*25*, *30*). Thus, the observed Cotton effects of **5** and **6** in chloroform should be due to their H-bond-enforced helical conformations.

The 1D and 2D (NOESY) ^{1}H NMR spectra of **4** and **6** in CDCl$_3$ show the same feature as we reported before (*36*, *37*), indicating the presence of intramolecular H-bonds between the ester and acetamido side chains, which were consistent with the H-bond-rigidified conformations of these oligomers. The ^{1}H NMR of **6** in CDCl$_3$ shows well-resolved peaks but looks slightly broader than those of the shorter oligomers, which could be due to limited aggregation and exchange of the molecules of **6**. The aggregates formed by **6** may not have sufficient size and stability to be directly detected. In methanol-d_4, strong NOEs corresponding to contacts between adjacent side chains were also observed for tetramer **4** by NOESY (Figure 2), suggesting that the intramolecular H-bonds enforcing the folding of **4** were not interrupted in this polar solvent. Attempts to record the 2D NMR spectra of **5** and **6** in methanol-d_4 were not successful due to serious line broadening (see Supplementary Materials for details). Nevertheless, based on the NOESY spectrum of **4**, the backbone-rigidifying H-bonds of **5** and **6**, which are the same as those in **4**, should also persist in methanol, and should lead to enforced folding. Such a conclusion is fully consistent with the Cotton effect observed for these two oligomers in methanol. Therefore, the intramolecular H-bonds in these *m*-PE oligomers are effective in enforcing the folded conformations in not only nonpolar media, but also in a polar solvent.

The observed line broadening of the ^{1}H resonances, and the significantly enhanced Cotton effect, of **5** and **6** in methanol suggests that these two oligomers underwent aggregation in this polar solvent.

The aggregation of **5** and **6** in methanol was confirmed by dynamic light scattering (DLS) experiments. Results from DLS studies demonstrated that, in

methanol, both oligomers formed aggregates with bimodal size distributions of 3.3 and 14.3 nm for **5** (Figure 3(a)) and 6.5 and 21.6 nm for **6** (Figure 3(b)), which may reflect two different groups of aggregates or an aggregate with irregular (non-spherical) shape formed by **5** or **6**. In methylene chloride, on the other hand, no aggregate with size larger than that of the constituent molecules could be detected for either **5** or **6** (see Supplementary Materials for details), suggesting that these molecules did not form aggregate in this nonpolar solvent. In methanol, the aggregates formed by **6** were larger than those from **5**, which was probably due to the

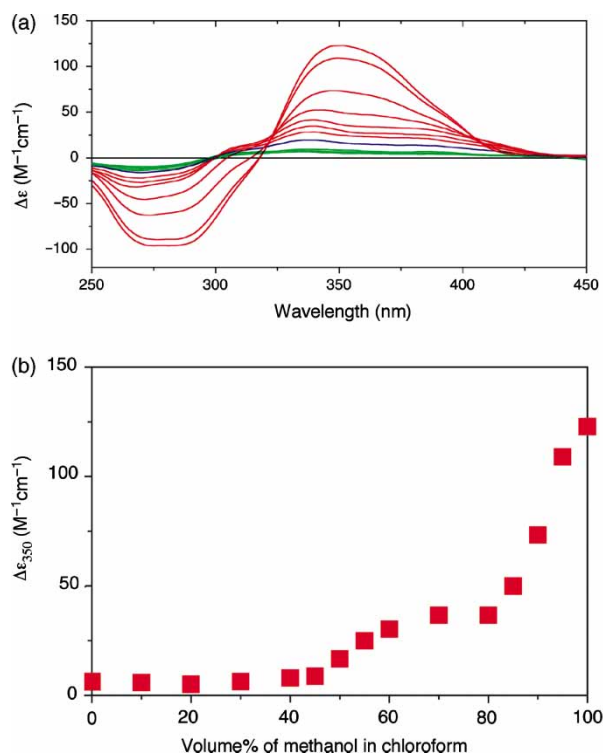Figure 4. (a) CD spectra of hexamer **6** (2 µM) in solvent mixtures with different contents of methanol in chloroform (v/v): green (0–45%), blue (50%) and red (55–100%). (b) Plot of the CD signals at 350 nm vs. per cent of methanol in chloroform.

stronger intermolecular aromatic stacking of the molecules of **6** because of the larger aromatic surface of the former. By contrast, tetramer **4** showed no aggregation in either methylene chloride or methanol (see Supplementary Materials for details, available online.).

The effect of solvent polarity on aggregation was probed by recording the CD spectra of **6** in mixed solvents containing different ratios of methanol and chloroform. As shown in Figure 4, as the content of methanol increases from 0 to 100% (v/v), the Cotton effect observed for **6** also increases. An isodichroic point at 322 nm is observed only for the CD spectra (Figure 4(a)) recorded in solvent mixtures with greater than 70% methanol. In solvent mixtures containing 0–60% methanol, the CD spectra showed no isodichroic point. Given the H-bond-enforced, helical conformation of **6**, the observed changes of the CD spectra and Cotton effect as the content of methanol increased were most likely a reflection of the aggregation states of the molecules than the result of a drastic conformational change.

Plotting the CD signals at 350 nm vs. content of methanol revealed a nonlinear increase of the Cotton effect (Figure 4(b)). The molecules of **6** seem to undergo a two-stage aggregation. In solvent mixtures with 40% or less methanol, the Cotton effect remained similar to that in pure chloroform, corresponding to little or no aggregation. When the methanol content is increased from 45 to 80%, the Cotton effect first increased and then plateaued, suggesting the formation of the first aggregation state. Such aggregates may involve helical columns consisting of stacked molecules of **6** (*26*). In solvent mixtures with higher than 80% methanol, the Cotton effect shows a steep increase, which indicates further aggregation involving either the formation of longer columns or, more likely, the association of the initially formed aggregates into higher-order assemblies.

In summary, we have demonstrated that short *m*-PE oligomers with H-bond-rigidified backbones adopt folded conformations in polar as well as nonpolar solvents. Results from ^{1}H NMR experiments suggested that the backbone-rigidifying H-bonds were persistent in both chloroform and methanol. The effectiveness of the intramolecular H-bonds in enforcing the helical conformations of pentamer **5** and hexamer **6** was further confirmed by CD studies. In methanol, results from NMR, UV, CD and DLS studies showed that **5** and **6** formed large chiral aggregates, while the smaller tetramer **4** failed to show any aggregation. By contrast, flexible *m*-PE oligomers of the same lengths cannot fold and form chiral assemblies in either nonpolar or polar solvents. These shape-persistent foldamers provide a class of porous chiral molecules with stable conformations. The observed size-dependent aggregation should guide future design of supramolecular assemblies based on the stacking of molecules with flat, aromatic surfaces.

Supplementary materials

Experimental procedures, analytical data and molecular models are available as Supplementary Materials, available online.

Acknowledgements

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