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A new strategy for folding oligo(*m*-phenylene ethynylenes)†

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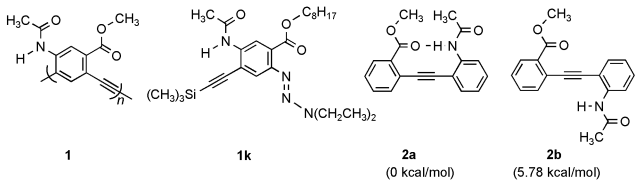
Backbone-rigidified oligo(*m*-phenylene ethynylenes) fold into crescent or helical conformations in non-polar organic solvents.

Helical structures are ubiquitously found in Nature[1] and have inspired current efforts in developing unnatural oligomers and polymers that fold into well-defined conformations.[2–18] In spite of the progress made so far, the foldamer field is still in its infancy. For example, the generation of well defined cavities, a feature usually seen at the tertiary and quaternary structural levels of biopolymers, has been realized in few unnatural foldamer systems.[6,18] Moore *et al*. have developed an elegant sytem of folding oligo(*m*-phenylene ethynylenes) (*m*-PE) in polar organic solvents based on a solvophobically driven mechanism. We describe here a different strategy for folding oligo(*m*-PEs) in non-polar organic solvents. Our strategy involves backbone-rigidification by H-bonding as shown by the general structure **1**. Depending on chain length, crescent and helical conformations are obtained.

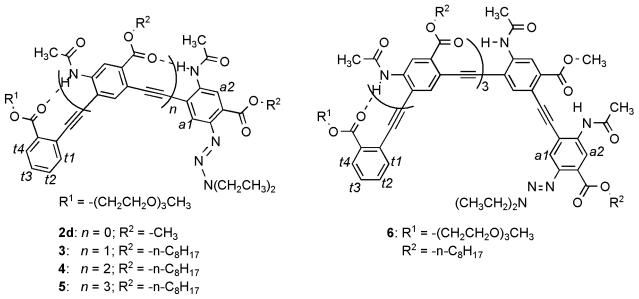


It is known that a small barrier (~0.6 kcal mol^{-1}) exists for the internal rotation of diphenylacetylene **2**.[19] The conformations of simple *o*- and *m*-PE oligomers and polymers should thus be very flexible and random. By incorporating an intramolecular H-bond into **2**, the resulting **2a** should adopt a well-defined conformation enforced by this additional non-covalent interaction. *Ab initio* molecular orbital calculations[20] indicated that **2a** adopted a completely planar conformation that was rigidified by its intramolecular H-bond. Deviation from the planar conformation of **2a** by interrupting the intramolecular H-bond led to a rapid increase in energy. A rotational barrier of 7.19 kcal mol^{-1} between conformers **2a** and **2b** was also found.

Crystals of dimer **2c** were obtained from ethyl acetate by slow cooling and the X-ray structure is shown in Fig. 1.‡[20] The intramolecular H-bond, as expected, leads to a planar conformation that is consistent with the above calculation.

If the same intramolecular H-bond is introduced into PE oligomers of various chain lengths, well-defined conformations may be enforced. Thus, oligomers **2c–d**, **3**, **4**, **5** and **6** with two, three, four, five and six benzene rings, respectively, along with monomer **1k**, were examined by ^{1}H NMR in $CDCl_3$ (500 MHz).

The chemical shift values of amide ^{1}H signals indicated the formation of intramolecular H-bonds: the spectrum of **1k** (2 mM), which can not form any intramolecular H-bond, showed an NH signal at 7.92 ppm. In contrast, one of the NH signals of dimer **2c** (2 mM) moved significantly downfield (9.22 ppm), and the other appeared at 8.03 ppm, which indicated that one was involved in intramolecular H-bonding and the other was not. For oligomers **2d** and **3**–**6** (2 mM), all NH signals appeared at significantly downfield positions (8.98 to 9.46 ppm), consistent with their involvement in intramolecular H-bonding.



Upon diluting a sample of tetramer **4** from 8 mM to 0.063 mM, the three NH signals of **4** showed minuscule shifts of 0.008, 0.016 and 0.015 ppm, confirming the existence of intramolecular H-bonding.

Variable temperature (VT) ^{1}H NMR study of the amide signals of tetramer **4** provided additional evidence for the prevalence of intramolecular H-bonds. At 2 mM and from −20 to 60 °C in $CDCl_3$, the three amide signals of **4** showed small upfield shifts (-2.3×10^{-3}, -2.2×10^{-3} and -2.2×10^{-3} ppm K^{-1}) reminiscent of intramolecular H-bonding.[17,21] Instead of moving upfield, the amide resonances of hexamer **6** (2 mM) showed very small downfield shifts ($2–4 \times 10^{-3}$ ppm K^{-1}) with increasing temperature (−20 to 60 °C in $CDCl_3$).[20] This observation, along with the fact that the amide proton signals of **6** appeared at positions upfield to those of **2d**–**5**, suggests that (1) the amide protons of **6** werer involved in intramolecular H-bonding, and (2) at 2 mM, hexamer **6** was, to certain extent, involved in stacking interaction that was disrupted at elevated temperatures.

Comparing the chemical shifts of aromatic protons *t1–t4* and *a1*,*a2* on the end residues of oligomers **2d–6** revealed an interesting trend:[20] from dimer **2d** to pentamer **5**, the chemical shifts of protons *a1*,*a2* and *t1–t4* showed very small changes. In contrast, protons *t1–t4* and *a1*,*a2* of hexamer **6** all showed obvious upfield shifts. The shifts are particularly significant (up

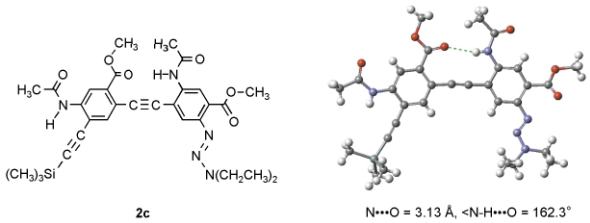


Fig. 1 The crystal structure of **2c**.

† Electronic supplementary information available: experimental data. See http://www.rsc.org/suppdata/cc/b2/b209809a/

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to 0.5 ppm) for protons *t2* and *t3*. A similar trend of upfield shifts was observed for the ethyl protons of the diethyltriazenyl group: while those of **2d–5** remained constant, those of **6** showed upfield shifts for up to 0.7 ppm. These results can only be explained by the corresponding oligomers adopting a curved backbone: while oligomers **2d**–**5** are not long enough, hexamer **6** reaches a length that allows its two termini to be brought into close proximity, which caused the observed upfield shifts.[22]

If hexamer **6** adopts a folded conformation, the chemical shifts of its end proton signals should be sensitive to change in temperature. The folded conformation will be partially interrupted with increasing temperature, which should change (increase) the distance between the two ends and should thus cause the ^{1}H NMR signals of the end protons to move downfield. This was indeed the case. The NMR signals of protons *t2* and *t3* showed obvious downfield shifts with rising temperature, protons *t1* and *t4* were less sensitive. In contrast, the corresponding protons *t2* and *t3* of tetramer **4** showed very small temperature-dependent changes in their chemical shifts.[20]

Tetramer **4** was then examined by two-dimensional (NOESY) ^{1}H NMR studies (Fig. 2). NOEs clearly indicated the side chain contacts between protons a_{Me}, b_{Me} and c_{Me} of the acetamido methyl groups and the α-CH_2 groups of the ester side chains. NOEs between the protons of the amide NH groups and the ester α-CH_2 groups were also observed. The observed NOEs were consistent with a crescent conformation enforced by the intramolecular H-bonds.

The NOESY spectrum of hexamer **6** also revealed numerous NOEs corresponding to side chain-side chain contacts.[20] One significant difference was observed between **6** and **4** (Fig. 2): the NOESy spectrum of **6** revealed NOEs between proton *t1* (7.36 ppm), and those of the two diethyltriazenyl methyl groups, *Me¹* and *Me²* (0.79 and 1.10 ppm). On the other hand, similar NOEs involving protons *t1* and *Me¹* and *Me²* were absent in the spectrum of **4**. The observed end-to-end contacts for hexamer **6**, combined with the chemical shift changes, are fully consistent with the helical conformation shown in Fig. 3. Modeling shows that such a folded helical conformation has a hydrophobic cavity of ~8 Å across.

The UV spectra of **2d**–**6**[20] revealed chain length-dependent features. All five compounds showed a very strong absorption band at ~330 nm. In chloroform (2 μM), the spectra of **2d**, **3** and **4** were very similar. However, a new band appeared for pentamer **5** at ~370 nm and much more so for hexamer **6**. The 370-nm shoulder for **5** or **6** should not be due to intermolecular aggregation because nearly identical spectra for **2d**–**6** were obtained at a higher concentration (10 μM) in chloroform.[20] In methanol/chloroform (1:1), the 370-nm bands of **5** and **6** greatly diminished, while the spectra of **2d**–**4** remained unchanged. Except for dimer **2d**, the longer oligomers were all highly fluorescent. The highest energy emission feature lay between 420 and 440 nm. New emission features appeared for pentamer **5** (525 nm, not very obvious) and hexamer **6** (530 nm, very obvious). These new bands are mostly likely due to the intramolecular exciton coupling between the two ends of **5** or **6**.

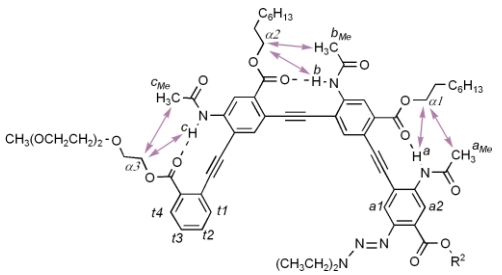

Fig. 2 NOEs between adjacent amide and ester groups of tetramer **4** as revealed by NOESY (8 mM in $CDCl_3$, 500 MHz, 263 K, mixing time: 0.3 s).[20]

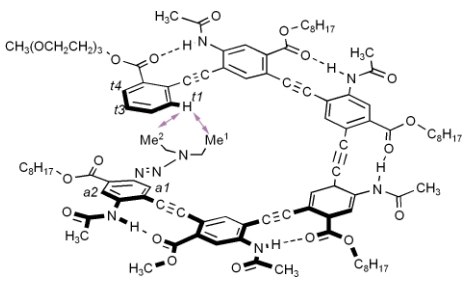

Fig. 3 End-to-end NOE contacts between proton *t1* and the methyl protons *Me¹* and *Me²* of hexamer **6** as revealed by NOESY (8 mM in $CDCl_3$, 500 MHz, 263 K, mixing time: 0.3 s).[20]

This study has demonstrated the feasibility of designing PE oligomers with stably folded conformations based on backbone-rigidification. By incorporating building blocks with the two ethynyl linkages being placed in a *para*-geometry on the same bezene ring, the curvature of the backbones can be adjusted. This, combined with the localized nature of backbone-rigidification, allows the development of PE helices with larger interior cavities.

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Notes and references

‡ *Crystal data* for **2c**: $C_{31}H_{37}N_5O_6$, M = 603.75, triclinic, space group $P\bar{1}$, a = 9.8811(19), b = 13.014(3), c = 14.189(3) Å, α = 115.143(3), β = 90.863(4), γ = 99.193(4)°, U = 1623.4(5) Å^3, Z = 2, μ(Mo-Kα) = 0.121 mm^{-1}, 7198 reflections measured (4472 unique, R_{int} = 0.0222). The final $wR(F^2)$ was 0.1907 (all data). CCDC 195111. See http://www.rsc.org/suppdata/cc/b2/b209809a/ for crystallographic data in CIF or other electronic format.

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