

NJC

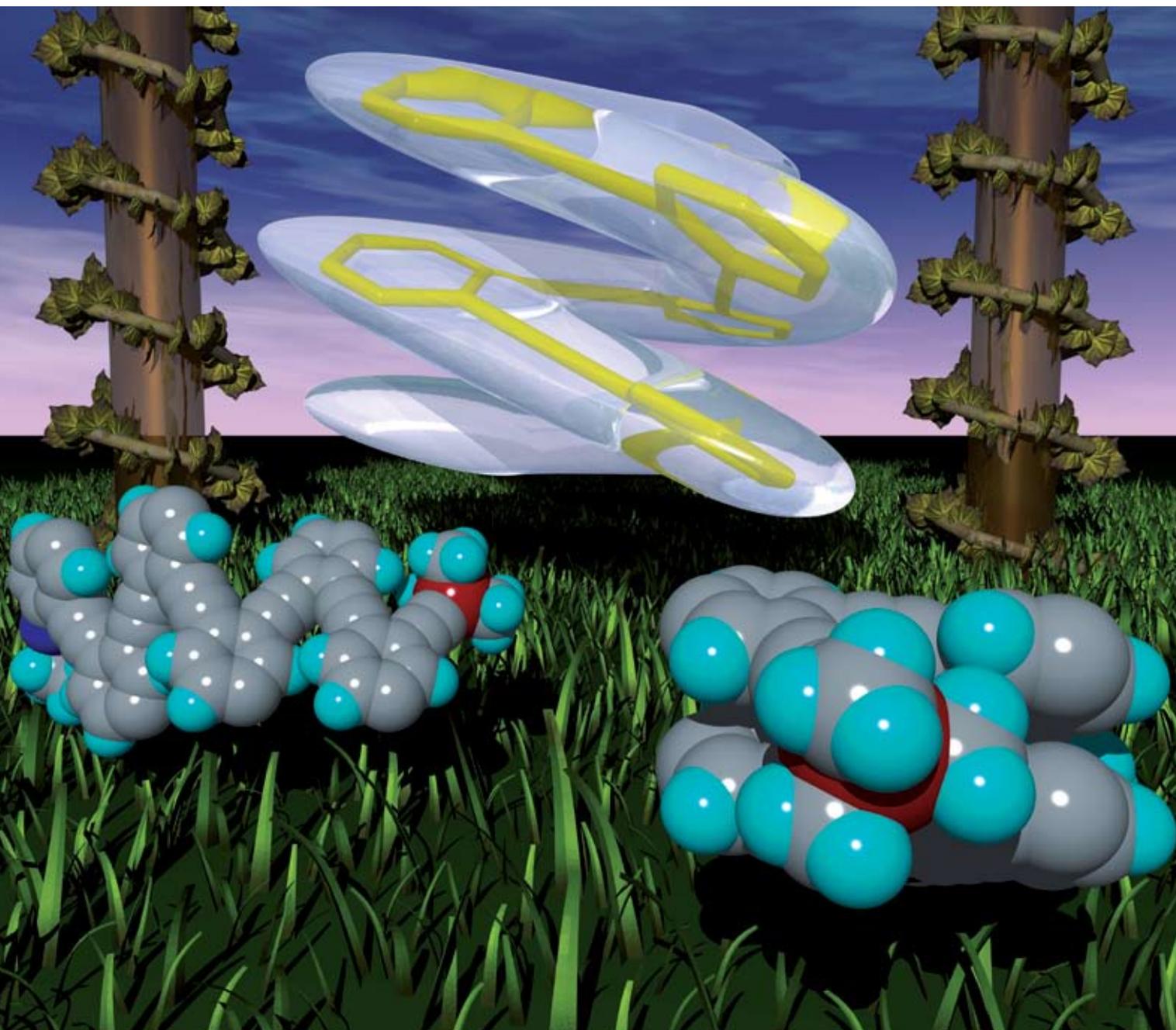
New Journal of Chemistry

An international journal of the chemical sciences

www.rsc.org/njc

Volume 32 | Number 4 | April 2008 | Pages 557–744

Published on 15 January 2008. Downloaded by TIB und Universitaetshilfenetz Hannover on 28/10/2014 11:36:58.



ISSN 1144-0546

RSC Publishing

CNRS
CENTRE NATIONAL
DE LA RECHERCHE
SCIENTIFIQUE

PAPER

Gregory N. Tew *et al.*

Extending helicity—capturing the helical character of longer *ortho*-phenylene ethynylene oligomers

Extending helicity—capturing the helical character of longer *ortho*-phenylene ethynylene oligomers†

Ticora V. Jones, Morris M. Slutsky and Gregory N. Tew*

Received (in Gainesville, FL, USA) 14th September 2007, Accepted 19th December 2007

First published as an Advance Article on the web 25th January 2008

DOI: 10.1039/b714237b

New *ortho*-phenylene ethynylene oligomers are shown to fold into helices of up to two full turns. Evidence of folding is shown by both 1D NMR, where π - π stacking is explored through both solvent and temperature titrations, as well as by 2D ROESY NMR which confirmed folding but also showed the dynamic nature of these helices through the flipping of the terminal TMS group into and out of a hydrophobic pocket created when the helix forms.

Introduction

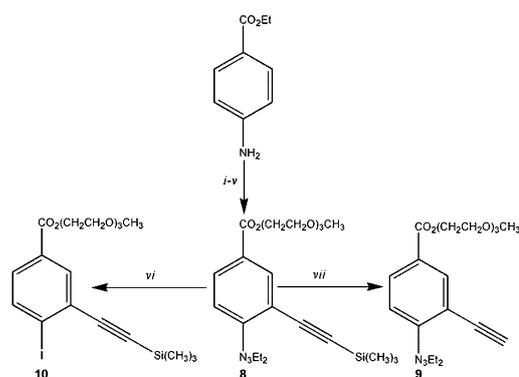
Foldamers, and their implications for deciphering the complexities of macromolecular biological systems, are of great interest.^{1–4} Extending the helicity of newly synthesized foldameric systems is essential for discovering their utility as a new class of molecular objects. Previous studies showed that short, tetrameric *ortho*-phenylene ethynylene (*o*-PE) oligomers adopted helical conformations in solution.^{2d} This was confirmed using 1D solution NMR experiments to monitor the influence of π - π stacking on the aromatic proton chemical shifts and Rotating Frame Overhauser Spectroscopy (ROESY)⁵ to determine through space interactions. In the tetrameric oligomers, only the two terminal rings would be involved in the π - π stacking of a helical conformation and solvent titration experiments confirmed the protons on these two rings shifted upfield as expected while the protons on the two remaining central rings did not.^{2d} At the same time, ROE correlations confirmed through space interactions consistent with helical conformations.

This article reports the helical conformation of two new, longer *o*-PE systems, including the hexamer, which forms a helix with two full turns. The helical conformations are examined in solution using NMR methods; two key titration studies supported helix formation. These titration results were complimented with ROESY experiments. In general, the determination of a helical secondary structure for longer *o*-PE oligomers has been more difficult to decipher compared to their *meta* PE isomers in which UV and fluorescence spectroscopy provided a convenient correlation between the cisoid (folded) and transoid (unfolded) conformations.^{3a,b} Unfortunately this correlation appears to be absent for the *o*-PE system, due to the electronic connectivity of the *ortho* vs. the *meta* series.^{2d,6} However, solution NMR techniques continue to provide clear evidence supporting helical conformations in these *o*-PE systems.

Results and discussion

Deprotected monomers **9** and **10** were synthesized starting from ethyl 4-amino benzoate as shown in Scheme 1. Oligomers **1**, **2**, and **3** were synthesized by a partially convergent strategy of TMS-acetylene deprotection and Sonogashira couplings as shown in Scheme 2. Coupling of deprotected acetylene monomer **9** with iodide **10** gave dimer **11**, which was taken on to both iodide **12** and deprotected acetylene **13**. Coupling of monomer iodide **10** with dimer **13** gave trimer **14**, which was followed by another reaction cycle to yield tetramer **1**. Pentamer **2** and hexamer **3** were produced by coupling dimer iodide **12** with the corresponding trimer or tetramer acetylene.

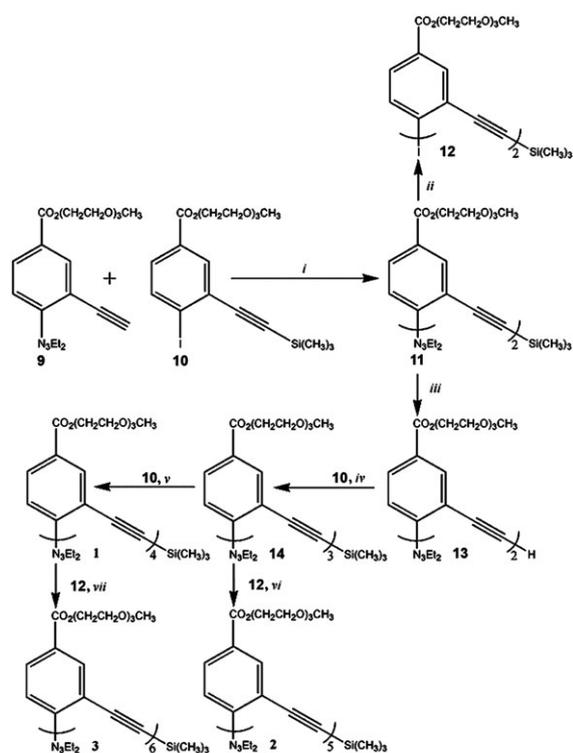
Fig. 1a shows that the three oligomers (**1–3**) studied here contain four, five, and six *o*-PE repeats. The aromatic rings of each oligomer are numbered consecutively beginning from the silyl terminus so that **1** contains R₁–R₄. As the oligomer length is extended from the tetramers, other folded conformations besides a ‘correctly’ folded helix, with $i, i + 4$ residues π - π stacking, become possible. For example, Fig. 1b highlights some possible conformers for the hexamer, **3**, starting with R₁ and R₄ folded *via* π - π stacking as was demonstrated previously in the tetramer. In this case, the other rings can all fold into a helix as shown in the boxed structure, which is referred



Scheme 1 Synthesis of pivotal monomer and deprotected derivatives. (i) I₂, Ag₂SO₄, EtOH (ii) KOH, MeOH (iii) H₂O, CH₃CN, HCl, NaNO₂, HN(Et)₂, K₂CO₃ (iv) DMAP, EDC, DCM, CH₃(OCH₂-CH₂)₃OH (v) HCCSi(CH₃)₃, PdCl₂(PPh₃)₂, CuI, TEA, THF (vi) CH₃I, I₂ (vii) TBAF, THF.

Department of Polymer Science & Engineering, University of Massachusetts, 120 Governors Drive, Amherst, MA 01003, USA.
E-mail: tew@mail.pse.umass.edu

† Electronic supplementary information (ESI) available: Synthesis for **1–3**, NMR traces for data shown in Fig. 2 and 3, and ROESY data for oligomers **1–3**. See DOI: 10.1039/b714237b



Scheme 2 Synthesis of oligomers **1**, **2**, and **3** by stepwise Sonagashira couplings and deprotection steps. (i) PdCl₂(PPh₃)₂, CuI, TEA, THF, 55 °C (ii) CH₃I, I₂, 110 °C (iii) TBAF, THF, 0 °C (iv) **10**, PdCl₂(PPh₃)₂, CuI, TEA, THF, 55 °C (v) TBAF, THF, 0 °C/**10**, PdCl₂(PPh₃)₂, CuI, TEA, THF, 55 °C (vi, vii) TBAF, THF, 0 °C/**12**, PdCl₂(PPh₃)₂, CuI, TEA, THF, 55 °C.

to as the ‘correctly’ folded helix since this structure has all six rings involved in π - π stacking. However, since this requires an entropic penalty, the ability of this hexamer to adopt less “well-folded” conformations such as those shown in Fig. 1b were considered. Three other possible structures are illustrated in which either R₅ and/or R₆ are not folded into the helical conformation. As a result of this increasingly complicated landscape, it was important to consider experimental methods that could distinguish between these partially folded structures and the ‘correctly’ folded helix shown in the box of Fig. 1b. This possibility of “misfolded” structures appeared important since computational calculations showed that while longer *o*-PE helical conformations were lower in energy, the energy difference between fully and partially folded structures was relatively small.^{6b}

Returning to the previous experimental observations that confirmed folding of **1**, in which only the terminal rings R₁ and R₄ shifted upfield in CD₃CN, it seemed reasonable that ‘correctly’ folded helical conformations of **2** and **3** would have four and six rings, respectively, that experience upfield shifts due to π - π stacking. More specifically, R_{1,2,4,5} of **2** and R₁₋₆ of **3** would shift upfield leaving only R₃ of **2** unshifted. Using multiple NMR methods (COSY and HMBC), each aromatic proton and its position in the oligomer has been assigned^{6c} allowing absolute tracking of each individual proton.

The 1D NMR results of solvent titrations (CDCl₃ to CD₃CN) for **2** and **3** are shown in Fig. 2a and b. The data was normalized, as our previous report,^{2d} so that the average ppm of the protons on each ring at the beginning of the

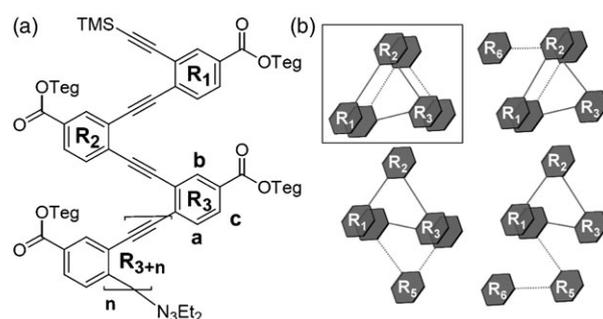


Fig. 1 (a) Tri-ethylene glycol substituted *o*-PE ester oligomers. Tetramer **1** ($n = 1$), Pentamer **2** ($n = 2$), Hexamer **3** ($n = 3$). Each ring (R_n) has three protons that are labeled respectively to their *J*-coupling and splitting pattern: a (8.4 Hz, d); b (2.1 Hz, d); and c (8.4 Hz and 2.1 Hz, dd). (b) Four of the many potential conformations of **3**. The ‘correctly’ folded helical conformer is highlighted.

titration was 0 ppm, then the change in average ppm of the protons on each ring (Δ ppm) during the titration was determined. Each point on the graph represents the average Δ ppm value for the protons of each ring. Fig. 2a shows the protons on rings R_{1,2,4,5} of **2** shift upfield as CD₃CN is added, while only R₃ remains at ~ 0 Δ ppm. Similarly, all six rings of **3** shift upfield as CD₃CN is added. These upfield shifts are in the opposite direction of the natural tendency for these protons as model compounds that cannot fold shift *downfield* when CD₃CN is added to CDCl₃.^{2h} Here, the results are consistent with π - π stacking and the *upfield* shift caused by this interaction as the oligomers adopt a helical conformation. The solvent titration results agree fully with the expectations of a ‘correctly’ folded helical conformation for both **2** and **3**. As was the case with the previously reported tetramers, these solvent titrations of **2** and **3** never flattened out as the concentration of CD₃CN approached 100% suggesting that the solution always contained an equilibrium between folded and unfolded oligomers. Since it was not possible to increase the volume percent of CD₃CN further, we decided to examine the influence of temperature on the aromatic protons’ chemical shift.

It was speculated that if an equilibrium of folded and unfolded structures coexisted in 100% CD₃CN at room temperature then cooling the solution would see an increased upfield shift of the protons as the equilibrium was shifted toward the folded structure. In contrast, heating the solution would shift the protons back downfield as the equilibrium moved toward the unfolded confirmation. As shown in Fig. 3a and b, temperature titrations (−26 to 77 °C in CD₃CN) were performed to study these oligomers and are plotted as the Δ ppm versus temperature. For oligomer **2**, these temperature titrations show that only the protons of R₃ remain unshifted as the temperature is changed by 100 °C while all the protons on R_{1,2,4,5} shift. Starting from 25 °C, as the system is cooled the protons shift upfield and as the system is heated the protons shift downfield. Similarly, for **3** the temperature study makes it very clear that *all* of the protons on R₁₋₆ shift downfield during heating from −26 to 77 °C. This change would only occur if all the aromatic rings of **3** were associated intramolecularly *via* π - π stacking of a compact helix in CD₃CN. These observations support the boxed conformation shown in Fig. 1b as the major conformer in solution and rule out the other possible

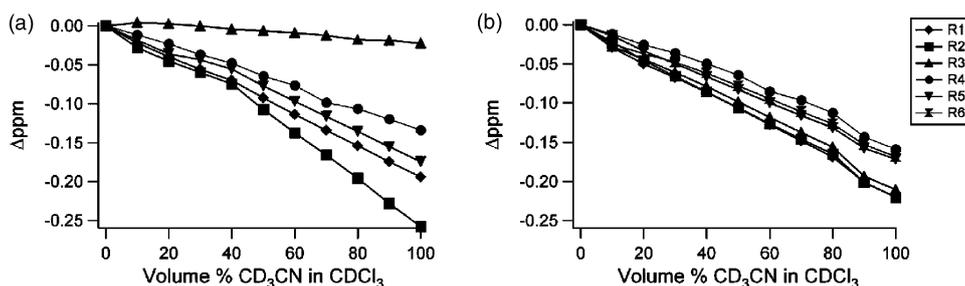


Fig. 2 Solvent titrations for oligomers **2** (a) and **3** (b) from CDCl_3 to CD_3CN (600 MHz, 1.25 mM from 0–100% CD_3CN in CDCl_3) at 298 K (**2**), and 305 K (**3**).

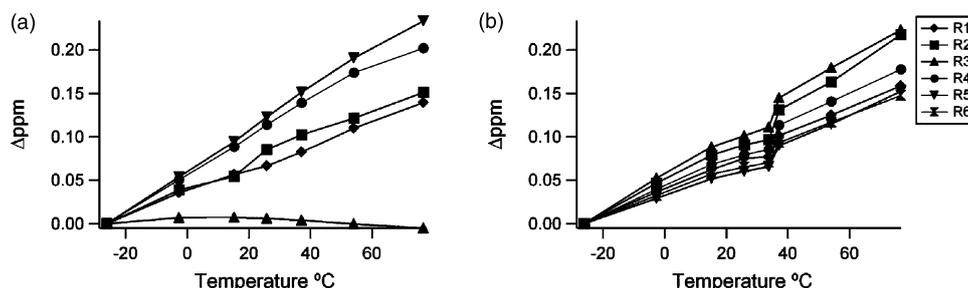


Fig. 3 Temperature titrations for oligomers **2** (a) and **3** (b) in CD_3CN from -26 to 77 °C (600 MHz, -26 to 77 °C, CD_3CN , 1.25 mM).

conformers. Taken together, the solvent- and temperature-dependent chemical shifts for the ring protons of **2** and **3** provide strong evidence for ‘correctly’ folded helical conformations.

Although the 1D NMR evidence for helical folding of these oligomers is strong, additional support from 2D NMR would be reassuring. As a result, ROESY experiments were performed on **1–3** and the results for **2** and **3** are shown in

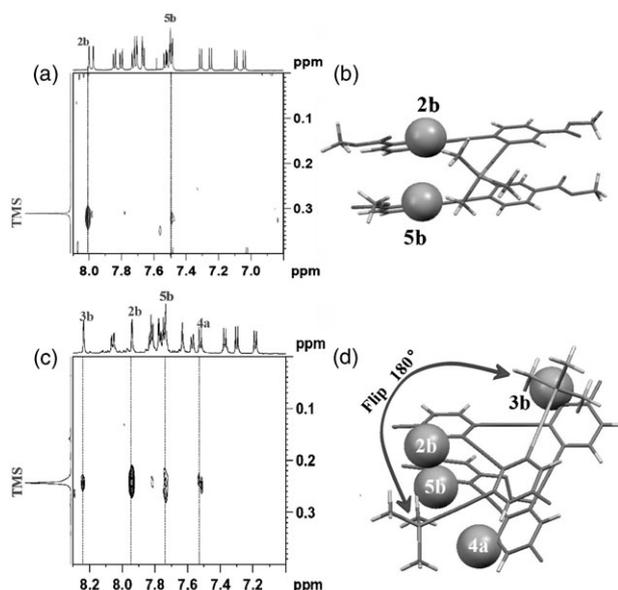


Fig. 4 (a,c) ROESY spectra of **3** (a) and **2** (c) in CD_3CN (600 MHz, 1.25 mM, 270 K, mixing time 0.3 s) (b,d) Energy minimized (MMFF)⁷ helical conformation highlighting the TMS cross peak protons for **3** (b) and **2** (d), (d) shows both interactions of the TMS by ‘flipping’ 180° .

Fig. 4. For **3**, two cross peaks are found between the terminal TMS and aryl protons **2b** and **5b** (see Fig. 4a and b) corresponding to calculated values of 3.4 and 3.5 Å, respectively, in good agreement with the model calculations of 3.5 Å (**2b**) and 3.0 Å (**5b**). These ROE correlations place the three groups (TMS, R_2 and R_5) together locally in space, which is completely consistent with the compact helical structure expected for the ‘correctly’ folded conformation. Due to the presence of R_5 in this larger oligomer, which is absent in **1**, it appears that a hydrophobic binding pocket is created for the TMS by the stacking of $\text{R}_{1,4}$ and $\text{R}_{2,5}$. Pentamer **2** has similar ROE correlations between the TMS and **2b**, **5b**, **4a** (see Fig. 4c and d) consistent with a helical conformation and the formation of a hydrophobic pocket. It also has a new cross peak between the TMS and **3b**, suggesting that the TMS can ‘flip’ to the other side by a 180° rotation around the $\text{R}_{1,2}$ linkage. This is shown in Fig. 4d with two TMS groups extending from R_1 illustrating that the TMS interacts with both locations during the ROE experiments. Similar cross peaks between the TMS and **2b** as well as **3b** are observed for **1** (see ESI†) in addition to those originally reported between the TMS and triazene. These additional correlations observed for **1** and **2** are consistent with the expected dynamic nature of short helices. It is interesting to consider that hydrophobic packing of the TMS end group may stabilize the helix analogously to end-capping in short helix peptides where an acetyl is placed on the N-terminus yielding an additional hydrogen bond to the last turn.⁸

Conclusions

In conclusion, helical folding in longer *o*-PE systems was confirmed by their solvent- and temperature-dependent behavior. ROE correlations confirm folding and the dynamic

nature of the conformers (**1** and **2**) as the TMS 'flips' from one side to the other and reveals a binding pocket for the TMS as the oligomer length increases (**2** and **3**). While the lack of baselines observed on NMR titration curves seems to indicate a conformational equilibrium between unfolded and folded states, examination of each ring within the oligomer provides evidence for a 'correctly' folded helix and rules out partially stacked conformers.

Acknowledgements

T.V.J. thanks the Ford Foundation and G.N.T. thanks the NSF-CAREER Award (CHE-0449663) for funding.

References

- (a) R. P. Cheng, *Curr. Opin. Struct. Biol.*, 2004, **14**, 512–520; (b) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893–4011; (c) M. S. Cubberley and B. L. Iverson, *Curr. Opin. Chem. Bio.*, 2001, **5**, 650–653; (d) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173–180.
- (a) R. H. Grubbs and D. Kratz, *Chem. Ber./Recl.*, 1993, **126**, 149–157; (b) S. Shotwell, P. M. Windschief, M. D. Smith and U. H. F. Bunz, *Org. Lett.*, 2004, **6**, 4151–4154; (c) T. V. Jones, R. A. Blatchly and G. N. Tew, *Org. Lett.*, 2003, **5**, 3297; (d) T. V. Jones, M. M. Slutsky, R. Laos, T. F. A. de Greef and G. N. Tew, *J. Am. Chem. Soc.*, 2005, **127**, 17235–17240; (e) A. Khan and S. Hecht, *J. Poly. Sci. A*, 2006, **44**, 1619–1627.
- (a) J. C. Nelson, J. G. Saven, J. S. Moore and P. G. Wolynes, *Science*, 1997, **277**, 1793–1796; (b) R. B. Prince, J. G. Saven, P. G. Wolynes and J. S. Moore, *J. Am. Chem. Soc.*, 1999, **121**, 3114–3121; (c) L. H. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. S. Atreya, D. K. Sukumaran, T. Szyperski and B. Gong, *J. Am. Chem. Soc.*, 2004, **126**, 16528–16537; (d) H. Jiang, J. M. Leger and I. Huc, *J. Am. Chem. Soc.*, 2003, **125**, 3448–3449; (e) J. Q. Nguyen and B. L. Iverson, *J. Am. Chem. Soc.*, 1999, **121**, 2639–2640; (f) T. Kim, L. Arnt, E. Atkins and G. N. Tew, *Chem.–Eur. J.*, 2006, **12**, 2423–2427.
- (a) K. Kirshenbaum, A. E. Barron, R. A. Goldsmith, P. Armand, E. K. Bradley, K. T. V. Truong, K. A. Dill, F. E. Cohen and R. N. Zuckermann, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 4303–4308; (b) A. Hayen, M. A. Schnitt, F. N. Ngassa, K. A. Thomasson and S. H. Gellman, *Angew. Chem., Int. Ed.*, 2004, **43**, 505–510; (c) D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, **21**, 2015–2022; (d) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219–3232.
- ROESY was found to be a better technique for these molecules given the ambiguity of NOESY within the weight range of oligomers 1–3.
- (a) S. H. Seo, T. V. Jones, H. Seyler, J. O. Peters, T. H. Kim, J. Y. Chang and G. N. Tew, *J. Am. Chem. Soc.*, 2006, **128**, 9264–9265; (b) R. Blatchly and G. N. Tew, *J. Org. Chem.*, 2003, **68**, 8780–8785; (c) M. M. Slutsky, T. V. Jones and G. N. Tew, *J. Org. Chem.*, 2007, **72**, 342–347.
- Wavefunction, Inc.–Spartan 2004 software (Molecular mechanics force field, MMFF minimization).
- A. Chakrabarty, A. J. Doig and R. L. Baldwin, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 11332–11336.