ORGANIC LETTERS

2000
Vol. 2, No. 2
135−138

Helical Twist Sense Bias in Oligo(phenylene ethynylene)s Induced by an Optically Active Flexible Tether

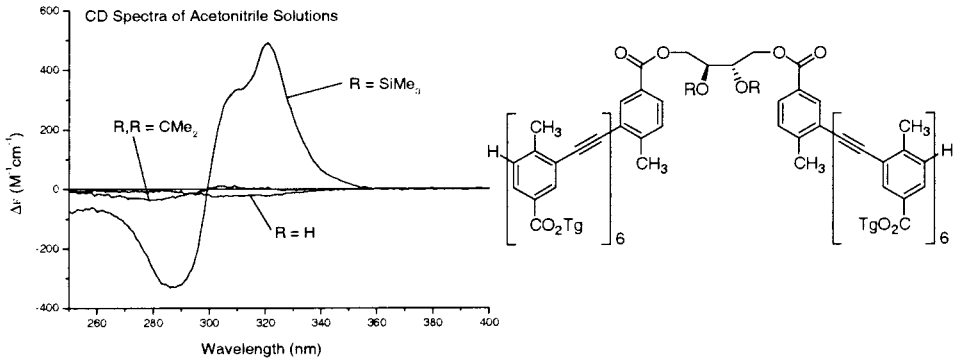
Mary S. Gin and Jeffrey S. Moore*

Departments of Chemistry and Materials Science & Engineering, 600 South Mathews Avenue, The University of Illinois at Urbana−Champaign, Urbana, Illinois 61801

moore@scs.uiuc.edu

Received November 1, 1999

ABSTRACT



A series of tethered phenylene ethynylene oligomers, which undergo a solvent-dependent conformational transition from a random coil to a helix, has been synthesized. The use of trimethylsilyl ether protecting groups on the (+)-tartaric acid-derived tether results in the formation of helices with a large twist sense bias. In contrast, an isopropylidene ketal protecting group or no protecting group is not only ineffective at helical discrimination but may even inhibit helix formation.

The design of oligomers and polymers with well-defined secondary structures is an active area of research, aimed at creating synthetic systems that can mimic biological polymers in their ability to derive function from structure.[1] Perhaps the most common secondary structural motif identified in these synthetic systems is the helix, a structure that can exist in either a right- or left-handed twist sense.[2] Several strategies have been used to bias the twist sense of helical conformations of chain molecules, including the use of chiral monomers,[3] additives,[4] and initiators.[5]

Previous work in our group has demonstrated the ability of phenylene ethynylene oligomers (**3**, eq 1) to undergo a solvent-dependent conformational transition from a random

(1) (a) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Holmes, D. L.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 7665. (d) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (e) Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303. (f) Smith, A. B.; Guzman, M. C.; Sprengler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirshmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947.

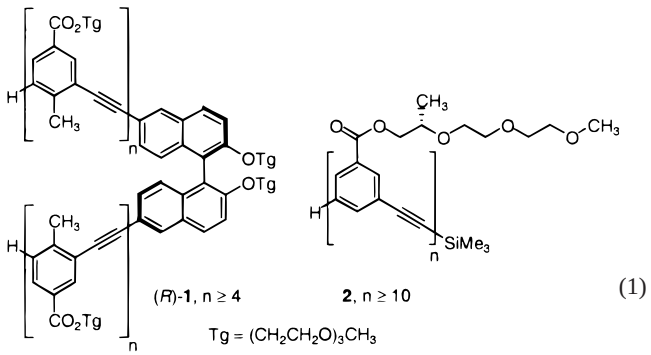
(2) (a) Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1845. (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587. (c) Blake, A. J.; Cooke, P. A.; Doyle, K. J.; Gair, S.; Simpkins, N. S. *Tetrahedron Lett.* **1998**, *39*, 9093. (d) Williams, D. J.; Colquhoun, H. M.; O′Mahoney, C. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1643.

(3) (a) Yashima, E.; Maeda, Y.; Okamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 8895. (b) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303. (c) Schlitzer, D. S.; Novak, B. M. *J. Am. Chem. Soc.* **1998**, *120*, 2196. (d) Takata, T.; Furusho, Y.; Murakawa, K.; Endo, T.; Matsuoka, H.; Hirasa, T.; Matsuo, J.; Sisido, M. *J. Am. Chem. Soc.* **1998**, *120*, 4530. (e) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, *268*, 1860.

(4) (a) See ref 3a and Yashima, E.; Maeda, K.; Okamoto, Y *Nature* **1999**, *399*, 449. (b) Akagi, K.; Piao, G.; Kaneko, S.; Sakamaki, K.; Shirakawa, H.; Kyotani, M. *Science* **1998**, *282*, 1683.

(5) (a) Ito, Y.; Miyaki, T.; Hatano, S.; Shima, R.; Ohara, T.; Suginome, M. *J. Am. Chem. Soc.* **1998**, *120*, 11880. (b) Wittung, P.; Eriksson, M.; Lyng, R.; Nielsen, P. E.; Norden, B. *J. Am. Chem. Soc.* **1995**, *117*, 10167.

10.1021/ol9912074 CCC: $19.00
Published on Web 12/23/1999



(1)

3

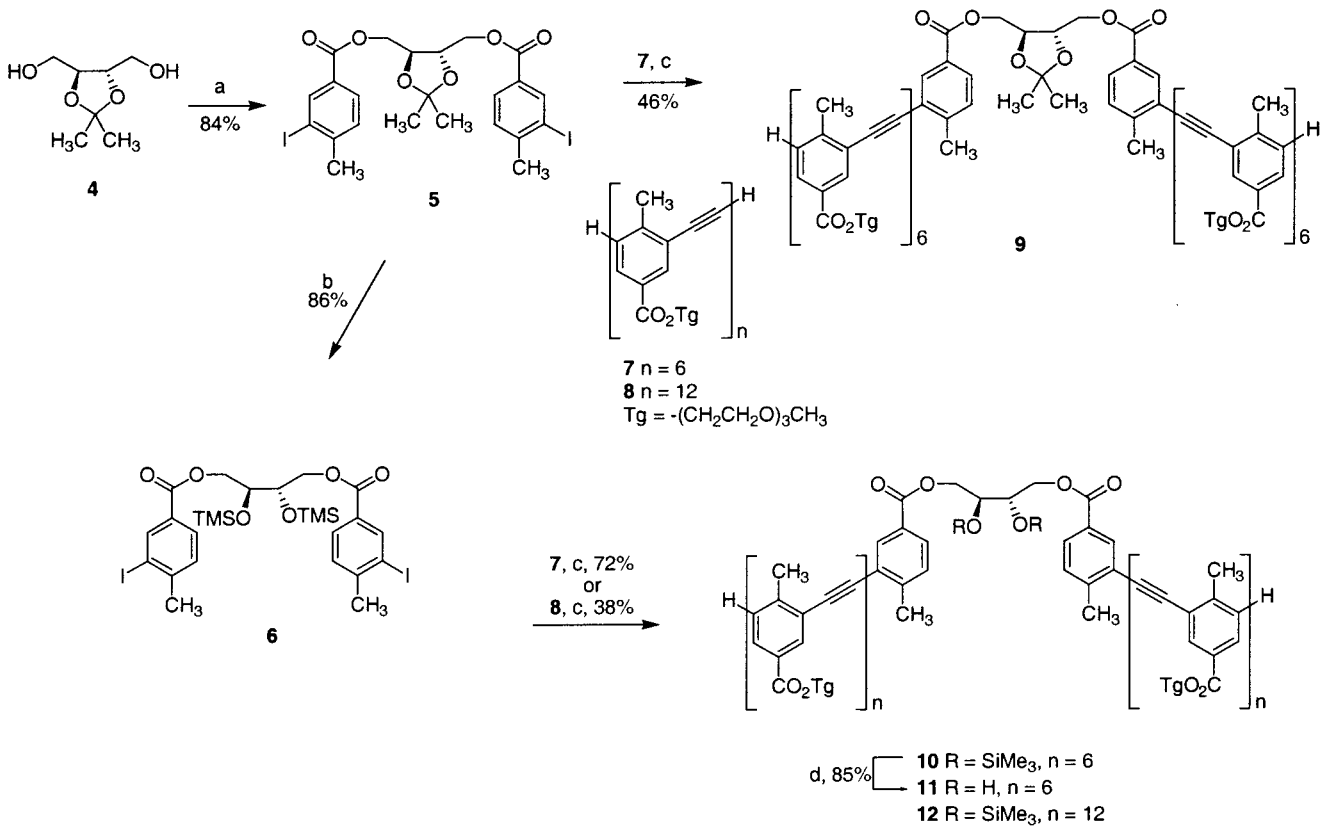
structure in chloroform to a helical structure in acetonitrile.[6] In addition, we have demonstrated that a strong bias can be imparted on the helical twist sense of these oligomers by incorporating an optically active binaphthyl moiety in the backbone (**1**, eq 1).[7] Weaker twist sense discrimination has been effected through the use of chiral side chains (**2**)[8] and by binding chiral guests in the helical cavity (**3**·pinene).[9]

Herein is reported the preparation of a tartrate-derived flexible tether that favors the formation of one helical twist sense over the other, an effect that is highly dependent on the nature of the tether functionality.

Three tethers, all derived from (+)-diethyl L-tartrate were prepared for this study: one with a hydrophobic isopropylidene ketal protecting group, one with trimethylsilyl ether protecting groups, and one with no protecting groups on the hydroxyl functionality (Scheme 1). The preparation of the tethers commenced with the conversion of diethyl tartrate to **4**[10] via protection of the interior hydroxyl groups (acetone, BF_3·OEt_2) and subsequent reduction of the diester functionality ($LiAlH_4$). Esterification of the resultant primary hydroxyl groups with 3-iodo-4-methylbenzoic acid and DCC afforded the tethered aryl iodide **5** in 84% yield. Subsequent Pd-catalyzed coupling with 2 equiv of hexamer **7**[7] then afforded **9** in modest yield. The trimethylsilyl ether-functionalized tethered aryl iodide **6** was prepared from **5** (CF_3CO_2H, H_2O; TMSCl, Et_3N, 4-DMAP, 86%) and then coupled to **7** in an analogous fashion to give **10** in 72% yield. Following coupling, the trimethylsilyl ethers could be removed to give diol **11** (Bu_4NF, AcOH, 85%). Dodecamer **8**[7] was also coupled with **6** to give **12** in modest yield.[11]

UV spectra of oligomers **9**−**11** in both chloroform and acetonitrile are shown in Figure 1a. As expected, all three

Scheme 1



Reagents and conditions: a) 3-iodo-4-methylbenzoic acid, DCC, Et_3N, 4-DMAP. b) i. CF_3CO_2H, H_2O; ii. TMSCl, Et_3N, 4-DMAP. c) $Pd(dba)_2$, CuI, Ph_3P, Et_3N, 75 °C. d) Bu_4NF, AcOH

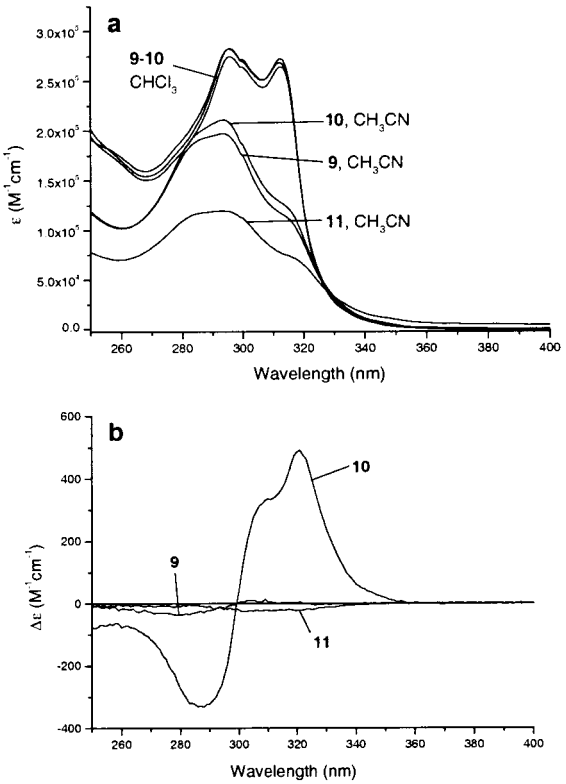


Figure 1. (a) UV spectra of **9**−**11** in chloroform and acetonitrile. (b) CD spectra of **9**−**11** in acetonitrile.

compounds exist in a random conformation in chloroform, as evidenced by the comparable intensities of the absorption bands at 313 and 295 nm. In acetonitrile the intensities of the 313 nm bands relative to the 295 nm bands are diminished, indicating that the oligomers reside in a helical conformation.[6] This evidence of helix formation is noteworthy, as the untethered hexamers are too short to form helices. Thus, the tether is clearly enabling interaction of the two oligomers.

With evidence of helix formation in hand, we obtained the CD spectra to determine whether any bias in the helical twist sense could be observed (Figure 1b). Indeed, the CD signal of bis-trimethylsilyl ether **10** in acetonitrile was very large, having a bisignate shape typical of what we have previously observed for these helical oligomers.[7−9] Isopropylidene **9**, however, had a very weak bisignate signal, a surprising result considering the similar, hydrophobic nature of both the isopropylidene ketal in **9** and the trimethylsilyl ethers in **10**. Furthermore, diol **11** had a weak, nonbisignate signal, calling into question whether **11** even adopts a helical conformation. When dissolved in chloroform, all three compounds displayed very weak CD signals as anticipated for oligomers in random conformations.[12] A slight negative signal, similar to that of diol **11** in acetonitrile, was obtained, presumably due to the asymmetry of the tether proximal to the interior chromophores. It should be noted that for all the oligomers the intensities of the CD signals were linearly dependent on concentration over a 10-fold range, thus ruling out contributions due to aggregation.

The CD signal of tethered dodecamer **12** in acetonitrile was more intense than that of tethered hexamer **10**. Comparison of the CD spectra of **10** and **12** in acetonitrile to the signals of the binaphthyl tethered oligomers (*S*)-**1** (n = 6, 12, eq 1) reveals that the intensities are nearly identical for oligomers of the same length (Figure 2). It is possible that

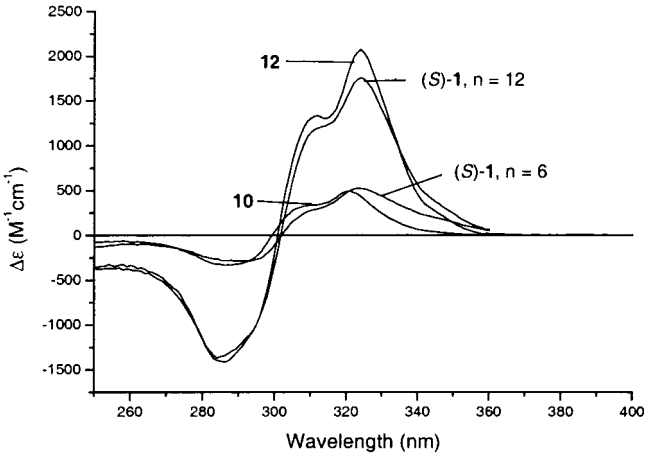
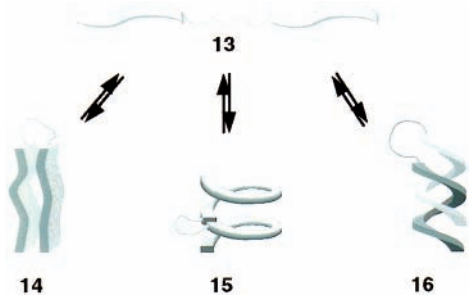


Figure 2. CD spectra of (*S*)-**1** (n = 6, 12), **10**, and **12** in acetonitrile.[13]

the similar intensities indicate a coincidentally identical, but incomplete, excess of one helical twist sense over the other. A more likely explanation is that complete twist sense selectivity has been achieved with these two dissimilar tethers.

The use of a flexible chain to tether two oligomers necessitates the consideration of alternative conformations to the simple single helix (**15**, Scheme 2). Some possible

Scheme 2



(6) (a) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114. (b) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793.

(7) Gin, M. S.; Yokozawa, T.; Prince, R. B.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 2643.

(8) Prince, R. B.; Brunsveld, L.; Meijer, E. W.; Moore, J. S. *Angew. Chem., Int. Ed.* In press.

(9) Prince R. B.; Barnes, S. A.; Moore, J. S. Submitted for publication.

(10) Batsanov, A. S.; Begley, M. J.; Fletcher, R. J.; Murphy, J. A.; Sherburn, M. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1281.

(11) Oligomers **9**−**12** were characterized by ^{1}H NMR, HPLC, and MALDI MS and were determined to be pure within our limits of detection.

interactions of the tethered oligomers include no interaction (**13**), aromatic stacking into a parallel strand (**14**), and threading of two helices into a double helix (**16**). The similarity of the CD signals of **10** and **12** to those of **1**, which is constrained to a single helix conformation, implies that **10** and **12** also reside in a single helix conformation. By the same token, the absence of a bisignate shape in the CD spectrum of **11** raises the possibility that it resides in one of the alternative conformations.

We turned to molecular modeling in an attempt to gain insight into the structures of **10** and **11**, as well as the manner in which the silyl ethers influence the helical conformation (Figure 3).[14] The minimum energy structure identified for **17**, an analogue of **10** in which the ester side chains were omitted, was one in which the trimethylsilyl groups were placed in the hydrophobic interior of the helix. Such an intramolecular templating event could conceivably give rise to the large signals observed. In contrast, the lowest energy structure found for the diol analogue **18** was not helical. Rather, the oligomers appear to have stacked into a parallel strand structure analogous to that of **14** (Scheme 2). It is plausible that this stacking interaction leads to the significant hypchromicity of the UV spectrum of acetonitrile solutions of **11** (Figure 1a). More work is needed to verify these conclusions; however, the modeling results do point to significant differences in the conformations preferred by oligomers **10** and **11**, consistent with experimental observations.

On the basis of the preceding discussion, at least two possibilities exist for the conformation of **9** in acetonitrile. The weak bisignate CD signal of **9** in acetonitrile could be a result of a nearly unbiased single helix conformation. Alternatively, a small portion could reside in a biased, single helix conformation, while the majority exists in unbiased parallel strand conformations.

In conclusion, we report the ability of an optically active tartrate-derived tether to impart a large bias on the helical twist sense of tethered oligomers in acetonitrile. The sensitivity of this system to substitution on the tether is remarkable, as the bis-trimethylsilyl protected diol is extremely effective, but the isopropylidene-protected or unprotected diol is unable to bias the conformation. Studies are currently underway to determine which structures are actually present in these systems.

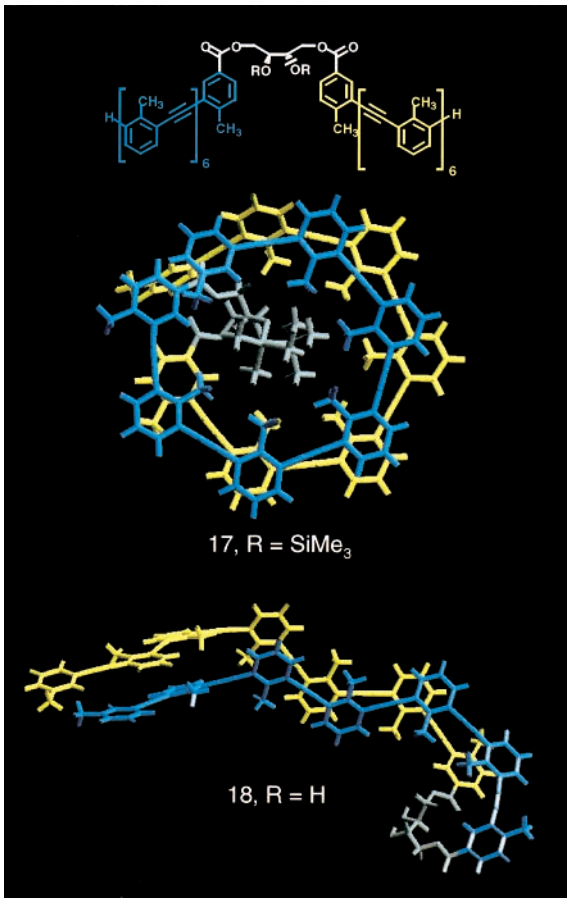


Figure 3. Minimized structure of an analogue of **10** in which the ester side chains were omitted.[14]

Acknowledgment. This research was funded by the National Science Foundation (Grant DMR 98-08433).

Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9912074

(12) CD spectra in chloroform are not shown.

(13) The spectra of (*R*)-**1** have been multiplied by (−1) for a more direct comparison with the spectra of **10** and **12**. It has been demonstrated that the use of (*S*)-binaphthol in the synthesis of (*S*)-**1** ($n = 6$) affords CD spectra identical and opposite to those of (*R*)-**1** ($n = 6$, see ref 7).

(14) Monte Carlo searches were performed using Macromodel 5.5 and the OPLS* GB/SA force field.