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# Conformational Ordering of Apolar, Chiral *m*-Phenylene Ethynylene Oligomers

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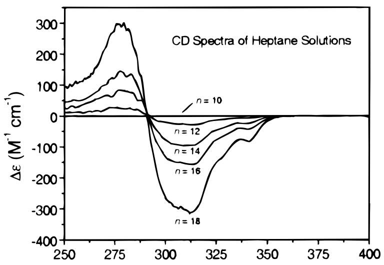
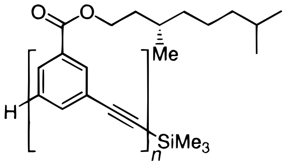
## ABSTRACT





**A series of *m*-phenylene ethynylene oligomers containing nonpolar, (*S*)-3,7-dimethyl-1-octanoxy side chains have been synthesized and studied. In apolar alkane solvents, oligomers of sufficient length ($n > 10$) were found to adopt a helical conformation with a large twist sense bias. In contrast, in chloroform the oligomers adopt a random coil conformation. Surprisingly, the strong twist sense bias was determined to be highly time dependent and is partially attributed to intermolecular aggregation.**

van der Waals and hydrophobic interactions are used effectively to bring about order in biological systems, but their rational use in supramolecular chemistry has been rather limited. Studies on solvent−polymer interactions reveal the important role that solvophobicity[1] can play in driving polymers into compact conformations,[2] and simple lattice models[3] as well as experiments on proteins[4] reveal the importance of molecular level heterogeneity in producing conformationally ordered sequences. We have previously shown that solvophobic forces can be used to drive *m*-phenylene ethynylene oligomers (**1**) into helical conformations in solution.[5,6] In these oligomers, an amphiphilic-type of heterogeneity is present in that polar side chains are attached to the all-carbon backbone. We wondered if it would be possible to broaden the scope of this effect to include a system in which the heterogeneity results from the attachment of a lipophilic side chain. The addition of apolar side chains renders the aromatic backbone polar with respect to the side chains. The ability to induce conformational order in such an oligomer is intriguing for at least two reasons. First, since both the side chain and backbone are hydrocarbon segments,

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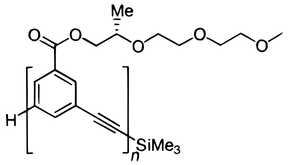
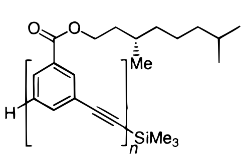
the heterogeneity in this system is intuitively less pronounced. Second, the promotion of helical order in a lipophilic solvent would bode well for the possibility of forming helical channels in bilayer membranes. Herein is reported the synthesis and study of a series of oligomers (**2**) with chiral, apolar side chains.



**1**



**2**

$n = 2, 4, 6, 8, 10, 12, 14, 16, 18$

The synthesis of oligomer series **2** was performed in solution using a divergent/convergent growth strategy.[7] (*S*)-3,7-Dimethyl-1-octanol was selected as the starting material of the side chain since it is easily obtained in high enantiomeric purity.[8] All oligomers were characterized by $^1$H NMR spectroscopy, HPLC, and size-exclusion chromatography (SEC) and shown to be >99% pure. For the MALDI-MS measurements, only the desired $[M + Na]^+$ adduct was observed. Each of the oligomers **2** exhibited a single, symmetrical peak by SEC, indicating the absence of starting materials or the presence of undesired oligomers.

UV absorption measurements were performed on oligomers **2** in order to establish the conditions that result in a helical conformation. We monitored the ratio of absorbance bands at 287 and 303 nm as previously reported for **1** (the helical conformation has a significantly lower $A_{303}/A_{287}$ ratio than the random conformation).[5] In chloroform the 303 and 287 nm bands are present in the same relative intensity regardless of chain length, indicating that these oligomers are in a random coil conformation (Figure 1, top).[9] These observations are in contrast to what is observed in heptane (Figure 1, bottom). The octamer (**1**, $n = 8$) and decamer (**1**, $n = 10$) display absorbance spectra similar to that observed in chloroform, whereas the longer oligomers (**1**, $n = 12$, 14, 16, and 18) in heptane exhibit a decrease in the intensity of the 303 nm band and a broadening of the absorbance maximum (most pronounced for the longest oligomers).[10] For the previously studied oligomers **1**, the decrease in the 303 nm band has been attributed to the collapse of the oligomer to a helical conformation, which can only occur once the oligomer is long enough to fold back on itself.[5] These results suggest that the use of selective solvation to drive conformational order can be extended to nonpolar solvents through the judicious choice of side chains.

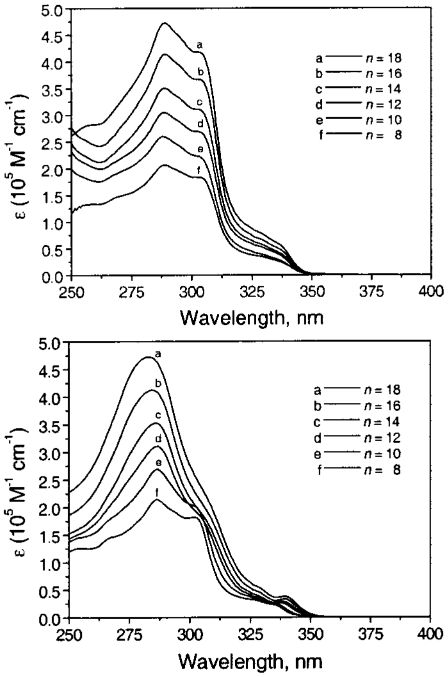


**Figure 1.** Plots of $\epsilon$ vs $\lambda$ for chiral octamer **2** ($n = 8$) through octadecamer **2** ($n = 18$) in chloroform (top) and heptane (bottom). Note the decrease in the intensity of the 303 nm band in heptane as the oligomer length is increased beyond **2** ($n = 10$, bottom).

Circular dichroism measurements were performed in order to study the twist sense bias of the helical conformation. In chloroform, none of the oligomers showed a Cotton effect from the backbone chromophore. This is not surprising given that in chloroform the oligomers were found to be in a random coil conformation; hence, there is little possibility of transferring the chiral information from the side chains to the backbone. In sharp contrast to the behavior in chloroform, a remarkable Cotton effect was observed for the chiral oligomers in dilute solutions of heptane (Figure 2). As shown in Figure 2, the ellipticity was found to be chain-length dependent and was observed for oligomers long

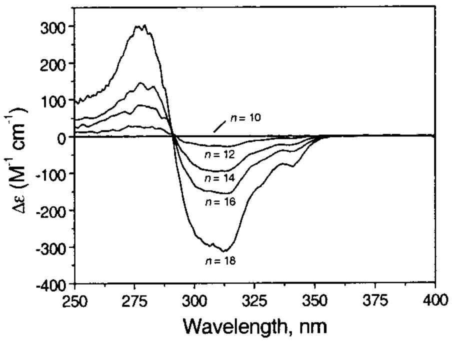


**Figure 2.** Plots of $\Delta\epsilon$ vs $\lambda$ for chiral decamer **2** ($n = 10$) through octadecamer **2** ($n = 18$) in heptane at 20 °C. Note the presence of an isodichroic point at 292 nm.

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[9] The shorter oligomers (**1**, $n = 2$, 4, and 6) have been studied and show no solvent dependent conformational transitions. They are present in a random coil conformation under all conditions.

[10] It was determined that for **1** ($n = 18$) in heptane at concentrations above 1 $\mu$M, Beer's law was not followed anymore and a decrease of the molar ellipticity and broadening with concomitant blue shift of the absorbance maximum could be observed.

enough to adopt a helical conformation as determined by UV spectroscopy (**2**, $n > 10$). The presence of an isodichroic point at 292 nm suggests that all of the oligomers adopt a similar collapsed conformation whose twist sense bias increases as a function of chain length.[11] In combination with the UV data, these results indicate that the transfer of chirality from the side chain to the backbone can only occur once order is present in the backbone. It is likely that the helical conformation places the side chains in close proximity, thereby heightening their ability to interact in a cooperative manner and giving rise to the diastereomeric preference of one twist sense over the other.

The conformational transition of the apolar oligomers **2** was studied by changes in solvent composition to distinguish between cooperative and noncooperative processes. For these experiments, chloroform was used as the "good" solvent and heptane was employed as the "poor" solvent.[12] Shown in Figure 3 is a plot of the absorbance ratios ($A_{303}/A_{289}$, top) and $\Delta\epsilon$ at 316 nm (bottom) as a function of the volume percent chloroform in heptane. The addition of chloroform to dilute solutions of oligomers in heptane resulted in an increase in the ratio of absorbances at 303 and 289 nm. This increase is associated with the loss of helical order as previously shown. For the 18-mer (and less pronounced for the shorter oligomers), the change is clearly sigmoidal. When monitoring the same solutions by CD spectroscopy, it is only at a very high volume percent of heptane (>90%) that a Cotton effect is observed. In a fashion similar to that of the polar oligomers **1**,[6] the onset of the twist sense bias occurs abruptly at a solvent composition that is well beyond the conformational transition as monitored by UV spectroscopy. Although the underlying phenomena responsible for this behavior is not well understood, it is apparent that the transfer of chirality is a highly cooperative process that requires a progression of conformational order beyond the initially formed helical state. It is noteworthy that for the apolar oligomers **2** the Cotton effect disappears at much a smaller volume % chloroform than for the polar oligomers.[13] This is most likely due to the greater rate at which solvent polarity changes upon addition of chloroform to heptane, in contrast to the smaller change upon addition of chloroform to acetonitrile.

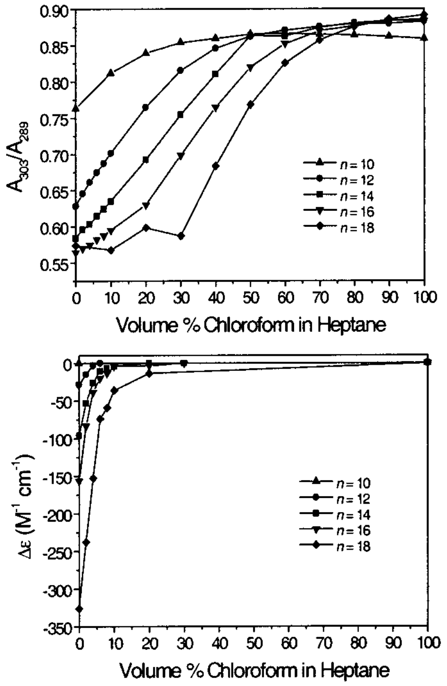

**Figure 3.** Plot of UV absorbance ratio ($A_{303}/A_{289}$, top) and CD signal ($\Delta\epsilon$ at 316 nm, bottom) for decamer **2** ($n = 10$) through octadecamer **2** ($n = 18$) vs the volume % chloroform in heptane.

The conformational transition of apolar oligomers **2** was further studied by changes in temperature. Temperature-dependent UV and CD measurements in heptane demonstrated that decreasing the temperature of a solution of **2** ($n = 18$) from 80 to 30 °C gives rise to stabilization of the helical conformation as evidenced by a decreasing $A_{303}/A_{289}$ ratio. The twist sense of the helices is not biased at temperatures above 30 °C, however, since no Cotton effect was observed. Below 30 °C there is a Cotton effect and the absorbance maximum decreases with a concomitant blue shift, similar to the spectral changes that occur at increased concentrations.[14] Therefore, the temperature-dependent results of folding into a helical conformation below 30 °C are explained by aggregation that coincides with the expression of chirality. It is easy to imagine that the *m*-phenylene ethynylene oligomers **2** form a large aromatic scaffold that promotes aggregation into columnar architectures at higher concentrations and low temperatures.[15] These columns stabilize the helical states of the oligomers by imposing a restriction of motion onto the oligomers, resulting in a twist sense bias as expressed by an increase of the CD effect. The variable temperature CD data are consistent with a behavior where intermolecular aggregation contributes to twist sense bias.

Variable temperature measurements performed on oligomer series **2** were determined to be highly time dependent. These results are in contrast to previously studied oligomers **1**, which were found to reach equilibrium within a few minutes. To investigate the origin of this strong time dependence, several variable temperature and time-dependent

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[11] The $\Delta\epsilon$ of **1** ($n = 18$) is constant up to concentrations of ca. 1 $\mu$M but significantly increases at higher concentrations.

[12] The terms "poor solvent" and "good solvent" are used in the usual polymer chemistry sense. See: Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, 1953; p 424.

[13] The onset of the twist sense bias for the polar oligomers **1** lies at a solvent composition of at least 50% chloroform in acetonitrile (dodecamer), whereas this is approximately 10% chloroform in heptane for the apolar oligomers. The folding of the polar oligomers also occurs at solvent compositions that consist of a higher chloroform percentage (70%) than for the apolar oligomers (~50%).

[14] The broadening and blue shift of absorbance maximum that occur at increasing concentration or lower temperatures are typical for an intermolecular aggregation process. See: Cornelissen, J. J. L. M.; Peeters, E.; Janssen, R. A. J.; Meijer, E. W. *Acta Polym.* **1998**, *49*, 471.

[15] Aggregation via $\pi-\pi$ stacking is highly favorable in alkanes, for an example, see: Palmans, A. R. A.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2648.

studies were performed on solutions of **2** ($n$ = 18) in dodecane using absorbance and CD spectroscopy. To reach an optically inactive state, the solution was heated to 60 °C for 20 min. The sample was then placed into a thermostated 20 °C cuvette, and absorbance and CD spectra were recorded as a function of time. As shown in Figure 4 (bottom), no optical activity was observed in the backbone chromophore at 60 °C.

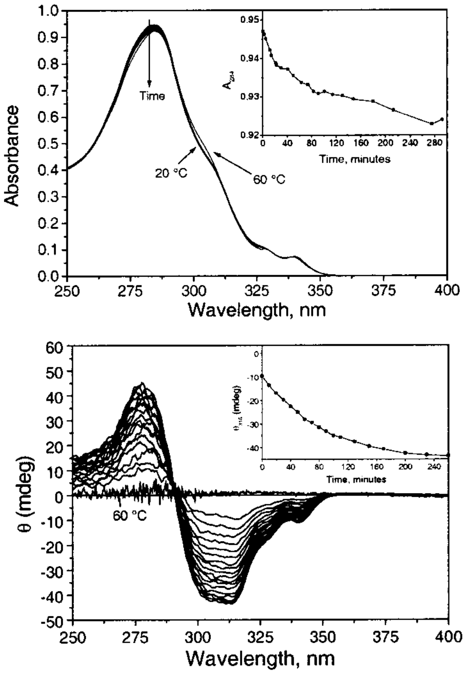

**Figure 4.** Overlay of the absorbance (top) and circular dichroism (bottom) spectra collected over time for a solution of octadecamer **2** ($n$ = 18) that was heated to 60 °C for 20 min and then placed in a thermostated 20 °C cuvette. The insets show the plots of the absorbance intensity at 284 nm (top inset) and CD intensity at 315 nm (bottom inset) as a function of time. All spectra were recorded on the same 3.9 $\mu$M solution in dodecane.

The oligomer, however, was present mainly in its helical form as could be detected by UV spectroscopy (top). At 20 °C, a plot of the CD signal against time shows that in dodecane it takes approximately 4 h for the CD signal to reach equilibrium (bottom inset). The presence of an isodichroic point at 292 nm indicates that the oligomer maintains the same conformation and state of aggregation with time. The UV spectra recorded over this same period indicate a small decrease of the molar absorptivity and a small blue shift of the band at 284 nm. The results show that in time the oligomers are gaining order, presumably due to regular packing into columns; similarly, optically active polythiophenes show a strong time dependence due to intermolecular aggregation, evidenced as well by small spectral changes in the UV spectra and an increasing CD intensity.[16] Upon addition of heptane to the chloroform solution, the oligomers first collapse into a helical state and then begin to aggregate intermolecularly. Since the twist sense of the oligomers is not biased yet, achiral columns are formed initially. In pure heptane the chiral side chains are capable of biasing the chirality of the helices, but due to the stable aggregates, the bias is only fully imparted after long equilibrium times.[17] It remains a question still, however, whether aggregation is necessary for the bias of the twist sense or if it is just coinciding with the twist sense bias under these highly apolar conditions.

In conclusion, the attachment of chiral, apolar side chains to *m*-phenylene ethynylene oligomers **2** allows for a twist sense bias in the helically folded conformation driven through the selective solvation with a nonpolar solvent. It was determined that the twist sense bias was only present for oligomers of sufficient length to adopt a stable helical conformation ($n > 10$). Intermolecular aggregation was found to play an important role in the twist sense bias that coincided with the occurrence of optical activity. These results indicate that nonpolar interactions can be used for controlling the ordering of nonbiological oligomers. The combinations of monomer units from oligomer series **1** and **2** in a single chain could allow for the development of systems with even higher degrees of conformational order through sequence heterogeneity.

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

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[16] (a) Langeveld-Voss, B. M. W. Ph.D. Thesis, Eindhoven University of Technology, 1999. (b) Pieterse, K.; Meijer, E. W. Eindhoven University of Technology, unpublished results.

[17] The polar oligomers **1** do not show this time dependence, consistent with its behavior being a purely intramolecular phenomenon.