Twist Sense Bias Induced by Chiral Side Chains in Helically Folded Oligomers**

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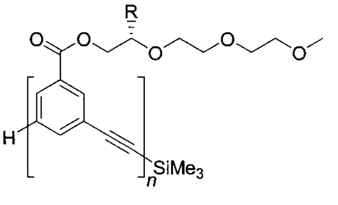
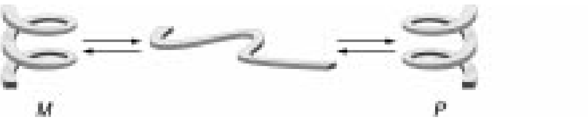
There is growing interest in the design of synthetic chain molecules that acquire well-defined conformations in solution,[1–4] analogous to the folded state of proteins or nucleic acids. Toward this end, there remains much to be learned about the structure and dynamics of conformationally ordered polymer molecules, and in particular about how to achieve conformational uniqueness in solution.[5–7] Studies on solvent–polymer interactions reveal the important role that solvophobicity[8] can play in driving polymers into compact conformations.[9] However, it is evident from theoretical studies that the collapsed state of most chain molecules, especially homopolymers, is highly degenerate.[10, 11] In advancing foldable chain molecules from disordered, collapsed states to conformational uniqueness, it is important to understand how to use weak interactions cooperatively, and how to derive order from both side-chain as well as main-chain interactions.

We have previously shown[4, 12] that phenylene-ethynylene oligomers (i.e., **1**) can be driven to fold into helical[13] conformations by solvophobic forces. Recently we also demonstrated that incorporation of a single chiral binaphthol unit into the backbone induces a bias in the helical twist sense.[14] However, the kinked binaphthol monomer significantly decreased the stability of the folded conformation. Here we demonstrate that a small, chiral perturbation to the side chain[15–17] causes a bias to the helical twist sense without disrupting the conformational stability [Eq. (1)]. These results indicate that side chains can play a role in helping to promote conformational order. Moreover, solvent and thermal denaturation studies monitored by absorption and circular dichroism spectroscopies reveal insight into the cooperative nature of the folding process and the manner in which this conformational order develops. Specifically, these studies show that there is a significant progression in conformational order following the initially formed helical state.



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

1: R = H
2: $R = CH_3$



(1)

To perform these studies we prepared a series of *m*-phenylene ethynylene oligomers with chiral side chains (**2**). These oligomers are analogous to the previously reported achiral series **1**, except for the introduction of a methyl group at the second carbon atom of each of the side chains. This places the stereochemical information in reasonably close proximity to the aromatic backbone. The chiral unit was derived from L-ethyl lactate, which is readily available in high enantiomeric purity, using standard synthetic transformations.[18] All oligomers were characterized by ^1H NMR spectroscopy, HPLC, size-exclusion chromatography (SEC), and mass spectrometry and shown to be greater than 99% pure. The synthesis and analytical data of all compounds can be found in the Supporting Information.

UV absorption measurements established the conditions that caused oligomers **2** to adopt a helical conformation. This is revealed from the ratio of absorbances at 287 and 303 nm as we have previously reported (the helical conformation has a significantly lower A_{303}/A_{287} ratio than the random conformation).[4, 12] It was found that, within experimental error, the conformational transitions of the chiral oligomers **2** displayed the same chain-length and solvent dependence as their achiral counterparts **1**. Thus, the introduction of a methyl group in the side chain did not destabilize the helical state.

Circular dichroism (CD) measurements were performed in order to study the twist sense bias.[19] In chloroform, chiral oligomers **2** showed no ellipticity in the backbone chromophore (250–400 nm), regardless of chain length and temperature studied. This is not surprising because in chloroform the oligomers are expected to be in a random-coil conformation; hence, there is little possibility for transferring chiral information from the side chains to the backbone.

In sharp contrast to the behavior in chloroform, a remarkable Cotton effect was observed for dilute solutions of oligomers **2** in acetonitrile at room temperature. The ellipticity was dependent on chain length and was zero only for oligomers not long enough to adopt a helical conformation ($n < 10$). As shown in Figure 1, the UV spectrum of **2** ($n = 8$) in acetonitrile exhibits a bandshape characteristic of the random coil conformation and a CD spectrum that displays no ellipticity. However, the UV spectrum of **2** ($n = 18$) in acetonitrile exhibits the bandshape indicative of the helical conformation and a CD spectrum that displays a bisignate Cotton effect. These results suggest that the transfer of chiral information from the side chains to the main chain can only

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occur once order is present in the backbone. The putative helical conformation likely places the side chains in close proximity, thereby heightening their ability to interact in a cooperative manner to give rise to the diastereomeric preference of one twist sense over the other.

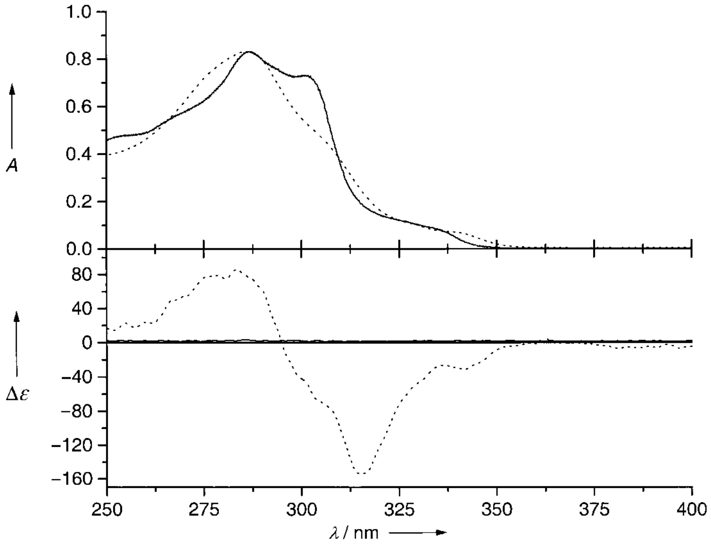

Figure 1. Normalized absorption (top) and CD spectra (bottom) of **2** ($n=8$, solid line; $n=18$, dashed line) in acetonitrile. A = absorbance.

A measure of chiral induction is given by the anisotropy factor $g_{\mathrm{abs}} = \Delta\varepsilon/\varepsilon$ at 316 nm. Figure 2 shows how g_{abs} varies with chain length for dilute solutions of **2** in acetonitrile at several temperatures. It is evident from this plot that there is a critical chain length below which no chiral induction is observed (i.e., $n < 10$). This coincides with the length needed to form a stable helical conformation for **1**.[12] It is also apparent that beyond the critical size, the chiral induction grows steadily as the chain lengthens (Figure 2). Also, the chiral induction decreases when the samples are heated. Mixtures of **1** and **2** ($n=18$) showed a linear relationship between ellipticity and mole percent of **2**. This, together with vapor pressure osmometry experiments,[4] confirms that these are primarily unimolecular phenomena.

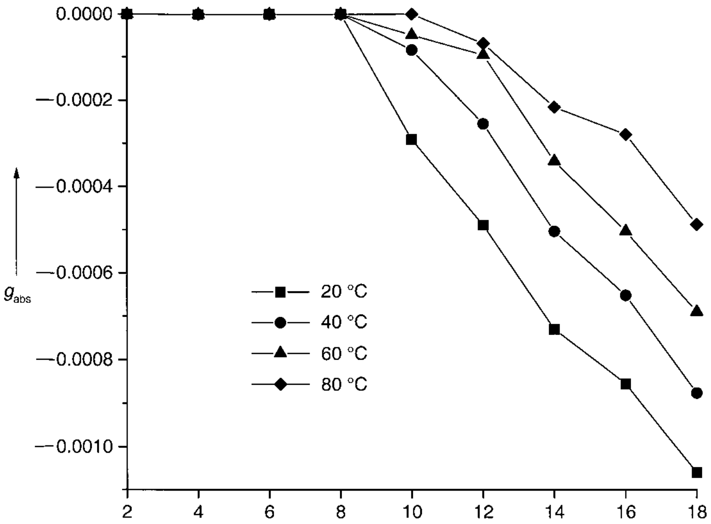

Figure 2. Plot of the chiral induction, expressed in terms of the anisotropy factor $g_{\mathrm{abs}} = \Delta\varepsilon/\varepsilon$, as a function of chain length l at different temperatures for solutions of **2** in acetonitrile. The data were recorded at 316 nm.

Previous studies have shown that the helix–coil transition can be driven by changes in solvent or temperature.[4, 12] The effect of solvent on oligomers that display a preferential twist sense was monitored by absorption and CD spectroscopies. Typical solvent denaturation curves are shown in Figure 3. The addition of chloroform to dilute solutions of **2** in acetonitrile resulted in an increase in the ratio of absorbances at 303 and 287 nm (Figure 3a).[20] This increase is associated with the loss of helical order as we have previously shown.[4, 12] When the same solvent denaturation is monitored by CD spectroscopy, it is only at high acetonitrile compositions that a Cotton effect is observed (Figure 3b).[20] The sudden onset and rapid growth in molar ellipticity at high acetonitrile concentrations is indicative of cooperative interactions.

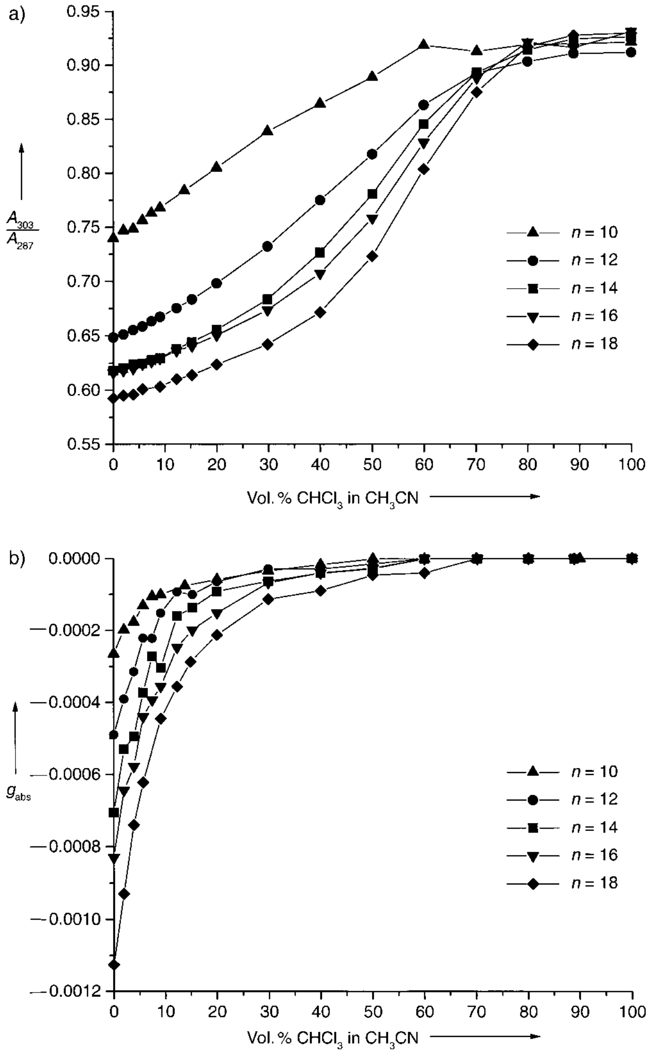

Figure 3. Solvent denaturation curves of **2** measured by a) the UV absorbance ratio A_{303}/A_{287} and b) the circular dichroism (g_{abs} at 316 nm).

It should be emphasized that the onset of the twist sense bias occurs at a solvent composition that is well beyond the helix–coil transition as monitored by UV spectroscopy. These different transition behaviors are interesting and may reveal important aspects about the nature of this solvophobically induced organization. It is important to remember that UV spectroscopy detects the presence of a stable helical conformation, while CD spectroscopy detects the presence of diastereomeric excess. The solvophobicity of the hydrocarbon backbone, which is presumably much larger than that of the polar side chains, could explain why the backbone adopts helical order well before bias is imparted to the helix twist sense. From the CD data, the diastereomeric excess originates at approximately the same chloroform composition regardless of chain length (Figure 3b). Based on this observation it is plausible that ordering of the solvated side chains, a process that lags behind helix formation, is the mechanism by which chirality is transferred to the backbone. The analogy might be made to the "molten globular state" of proteins, a state in which the peptide backbone possesses a native-like conformation while having disordered side chains.[21, 22]

An alternative way to explain the observed transition behavior is to consider the dynamics and conformational uniqueness of the backbone. At high chloroform compositions (but when the oligomers are still helical, as judged by UV spectroscopy) there are possibly a large number of energetically similar, helical-like backbone conformations that interconvert rapidly. Here the analogy might be made to the "compact denatured state" of proteins, a collapsed form in which there is a broad ensemble of backbone and side-chain conformations even though there is extensive hydrophobic clustering.[23] The UV spectrum simply fails to provide the needed resolution to distinguish between a well-ordered, conformationally unique backbone and a mixture of helical-like conformers. The dynamics and structural diversity available to the backbone in this conformational state may preclude cooperative interactions among the side chains that give rise to the twist sense bias. Upon increasing the amount of acetonitrile, a smaller set of backbone helical conformations becomes populated, allowing the side chains to order and transfer their chirality to the main chain. Regardless of which of these explanations is correct, the transfer of chirality appears to be a highly cooperative process that requires a progression of conformational order beyond the initially formed helical state. The sharpness of the CD transition points toward a high twist sense bias that obviously cannot be deduced from the magnitude of the Cotton effect.

In conclusion, we have demonstrated that it is possible to bias the twist sense of a solvophobically driven helical conformation by the attachment of chiral side chains. These results show that the side chains can play more than just an ancillary role in these conformationally ordered oligomers. The diastereomeric bias only appears after the backbone acquires a conformationally ordered state. Solvent denaturation studies showed that a helical conformation is a necessary, but not a sufficient condition for inducing a diastereomeric bias. In particular, the onset of the twist sense bias was shown to lag significantly behind the appearance of helical conformations, possibly because a large ensemble of "collapsed" conformations is initially formed. To further elucidate the nature of the folding and chirality transfer, additional experiments in more polar media will be undertaken.

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Mixed-Valent Heptairon Complex with a Ground-State Spin Value of $S = 12/2$ Constructed from a Triiron Cluster Ligand[**]

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Complexes assembled from metal-containing subunits[1–12] have attracted much attention in view of their very interesting structures, for example, ferric wheels,[1] and properties, for example, molecular-based magnetism,[2] and multistep, multielectron redox reactions.[3] Designing the spatial arrangement

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