Self-Assembly of Folded *m*-Phenylene Ethynylene Oligomers into Helical Columns

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Abstract: Circular dichroism spectroscopy has been used to study the self-assembly of two series of *m*-phenylene ethynylene oligomers in highly polar solvents. The helical conformation of shorter oligomer lengths was found to be stabilized in aqueous acetonitrile solutions, while longer oligomers began to interact intermolecularly. The intermolecular aggregation of the oligomers in aqueous solutions revealed a chain length dependent association that required the presence of a stable helical conformation. Evidence for intermolecular interactions is provided by Sergeants and Soldiers experiments in which the twist sense bias of a chiral oligomer is transferred to an achiral oligomer.

Introduction

Recent advances in the control over the self-assembly of synthetic molecules have generated numerous (multi-)molecular architectures by applying principles such as hydrogen bonding, hydrophobic interactions, molecular recognition, and solvent−molecule interactions.[1] On the other hand, control over the formation of multi-molecular architectures in the micrometer scale has been achieved and impressive helical structures have been observed by Scanning and Transmission Electron Microscopy (SEM/TEM).[2] However, the hierarchical formation of these architectures by the individual molecules is a less explored area and offers a challenging subject of investigation to elucidate the structural requirements and processes at hand. Given that biological architectures are sized in the nano to micrometer scale regime underscores the importance of the fundamental understanding of these complex assembly processes. To understand the formation of such structures, let alone to mimic them, a detailed knowledge of their hierarchical formation is important.

The folding of nonbiological oligomers into well-defined solution conformations is an area of active study and recent advances have provided ordered structures,[3] occurring both in apolar[4] and polar[4d,5,6] solvents as well as in water.[4d−e,7] As an example, the architectures formed by β peptides have been shown to possess increased stability with respect to their natural analogues.[8] However, the creation of larger, multimolecular architectures by these nonbiological oligomers has not been investigated in great detail.[4a−b] This is in contrast to discotic molecules which have been shown to self-assemble in columns in solution.[9] Via specific assembly, well-defined long columns

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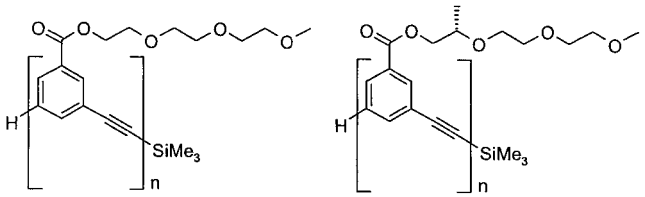
can be formed allowing for control over their chirality and their formation, either isodesmic or cooperative, has been elucidated.[10] With use of electron microscopy, the presence of intertwined helices based on such discotics and other chiral architectures has been clarified and the occurrence of aggregation has been indicated at a higher level of the well-defined supramolecular self-assemblies.[11]

For the creation of active and enantiospecific functional architectures from the nonbiological oligomers, multi-molecular assemblies are required. In this paper, we present results on the hierarchical self-assembly of *m*-phenylene ethynylene oligomers provided with chiral and achiral side chains into single helices and higher architectures. It has previously been shown that amphiphilic *m*-phenylene ethynylene oligomers (i.e., **1**) can be driven to fold into helical conformations by solvophobic forces.[6] In addition, it has been demonstrated that the helical twist sense of these oligomers can be biased, e.g., by the incorporation of a single chiral binaphthyl unit into the backbone[12] or via complexation of a chiral guest molecule in the cavity.[13] It was also possible to bias the twist sense of the oligomers via chiral side chains (oligomers **2**).[14,15] Upon formation of a well-defined helical conformation, the side chains interact and transfer their chirality to the backbone. Using solvent-denaturation experiments monitored by CD and UV−vis spectroscopy, the twist sense bias of the helix was found to lag behind the initial folding of the oligomer. These results indicate a hierarchical order in the folding of the oligomers. The stability of the helical conformation of the oligomers should be increased due to additional solvophobic interactions in a more polar environment. Furthermore, it can be expected that the single helices will show intermolecular interactions upon an increase in the concentration of oligomer or polarity of the solvent.[16] In the solid state, the limit of high concentration, it has been shown that a hexagonally packed arrangement of stacked helices exists.[17] In this paper we discuss how the hierarchy in the self-assembly process can be extended from isolated molecules in solution (i.e., unimers) to a higher level by the cooperative formation of supramolecular columns via stacking of the chiral helical oligomers upon the addition of the more polar solvent water. We provide evidence for the growth of large supramolecular architectures in the form of columns that interact to yield structures with opposite chirality to that of the individual helical unit. In particular, "Sergeant and Soldiers"[18] experiments were performed to elucidate the cooperativity of these different processes. Moreover, the oligomers in aqueous solutions revealed a chain length-dependent aggregation.



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

Figure 1. Chemical structures of achiral oligomer series **1** and chiral oligomers series **2**.[19]

Results & Discussion

Aggregation in Aqueous Acetonitrile. To promote backbone interactions for stabilization of the helix and to investigate whether multi-molecular architectures could be obtained, studies were performed on aqueous acetonitrile solutions. The optical characteristics of the oligomers were monitored with UV−vis and CD spectroscopy to visualize the stacking of the apolar backbone (UV−vis) and the order and helicity within the self-assemblies (CD). Shown in Figure 2 are the CD spectra of dodecamer **2** ($n = 12$) and octadecamer **2** ($n = 18$) in varying amounts of water/acetonitrile. The Cotton effect observed for the dodecamer increases upon increase of the water content from 0 to 40% (v/v) (Figure 2, left). The presence of an isodichroic point at 295 nm indicates that the oligomer is adopting a similar conformation in each of the solvent mixtures. A similar behavior (increase of θ_{max}) was observed for the shorter octamer **2** ($n = 8$) and decamer **2** ($n = 10$). In contrast, the longer octadecamer **2** ($n = 18$) shows dramatically different behavior as it is placed into an aqueous environment (Figure 2, right). The increase of the water content initially results in a decrease of the Cotton effect, followed by an increase at high water content. Important

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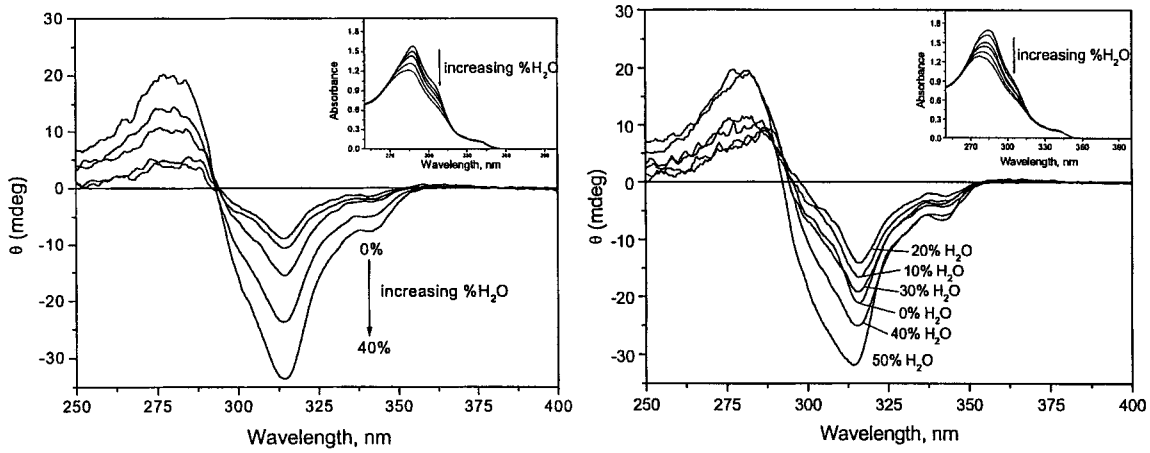

Figure 2. CD spectra of dodecamer **2** ($n = 12$) (left) and octadecamer **2** ($n = 18$) (right) in increasing amounts of water/acetonitrile (v/v). Insets show the accompanying absorbance spectra of the solutions. All measurements were recorded after equilibrating the samples at 20 °C for 10 min.

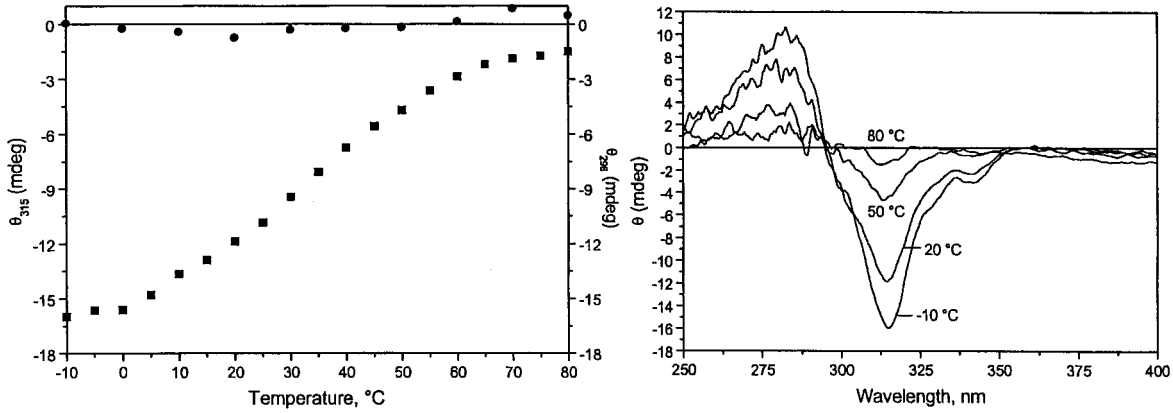

Figure 3. Plot of θ_{315} (squares) and θ_{296} (circles) vs temperature for a solution of dodecamer **2** ($n = 12$) as it was cooled from 80 to −10 °C (left). CD spectra recorded during the temperature run for the dodecamer (right). The measurements were recorded in 20 vol % water in acetonitrile with an oligomer concentration of 5.5 μM.

is the lack of an isodichroic point, which demonstrates that the oligomer is adopting different conformations or aggregation states in aqueous solutions. The tetradecamer **2** ($n = 14$) and hexadecamer **2** ($n = 16$) show a behavior between that of the dodecamer and octadecamer, but are both also characterized by a decrease of the Cotton effect, followed by an increase upon increase of the water content. Hypochromicity is observed in the absorbance spectra of all oligomers as the fraction of water is increased.[20] Even though the UV-vis data provide little information concerning the conformation of the oligomers, they do indicate an increase of the stability of the folded oligomers with increasing water content. These results thus indicate that the oligomers stack in aqueous solutions. This stacking in helical columns upon addition of water accounts for an increased stability of the helical conformation for the shorter oligomers: the octamer through the dodecamer. The longer oligomers already have a stable helical conformation in acetonitrile and the stacking induced by the addition of water results in little additional stability of the helical conformation. The stacks formed by the longer oligomers result in an alternative conformation or mode of aggregation as evidenced by the lack of an isodichroic point. This finding suggests that intermolecular aggregation stabilizes the helical conformations and with the presence of a stable columnar helical conformation of the oligomers, aggregation into different multimolecular architectures occurs.

To further elucidate the intermolecular aggregation of the helices in columns, the temperature-dependent behavior of their aqueous solutions was examined. Previous results have shown that an increase of temperature results in a decrease in the stability of the helical conformation.[6b,14] Shown in Figure 3 is a plot of the CD signals at 315 and 295 nm against temperature for a solution of the dodecamer in 20% water/acetonitrile. The decrease of the temperature of the solution results in an increase of the CD signal at 315 nm in a sigmoidal fashion. A similar plot of the CD signal at 295 nm (isodichroic point) shows no change as the temperature is decreased. For the longer octadecamer, a different behavior is observed (Figure 4). A plot of the θ_{max} at 315 nm against temperature shows an initial increase as the temperature is lowered from 80 to 55 °C. However, as the temperature is decreased further, the CD signal decreases and finally shows a positive CD signal. A plot of the intensity of the 295 nm band is nearly constant from 80 to 55 °C, but increases as the temperature is lowered further. The loss of the isodichroic point at 295 nm coincides with the decrease of the CD maximum at 315 nm. The accompanying CD spectra show the initial increase in CD signal and the subsequent change to the opposite sign (Figure 4). Although the two extreme CD spectra (80 and −10 °C) are not their mirror images exactly, the inversion of the Cotton effect indicates that there is a

(19) The syntheses of the achiral **1** (ref 6b) and chiral oligomer series **2** (ref 14) have previously been reported.

(20) A similar hypochromicity has been observed for apolar oligomers upon aggregation of the helices in apolar solvent (ref 15).

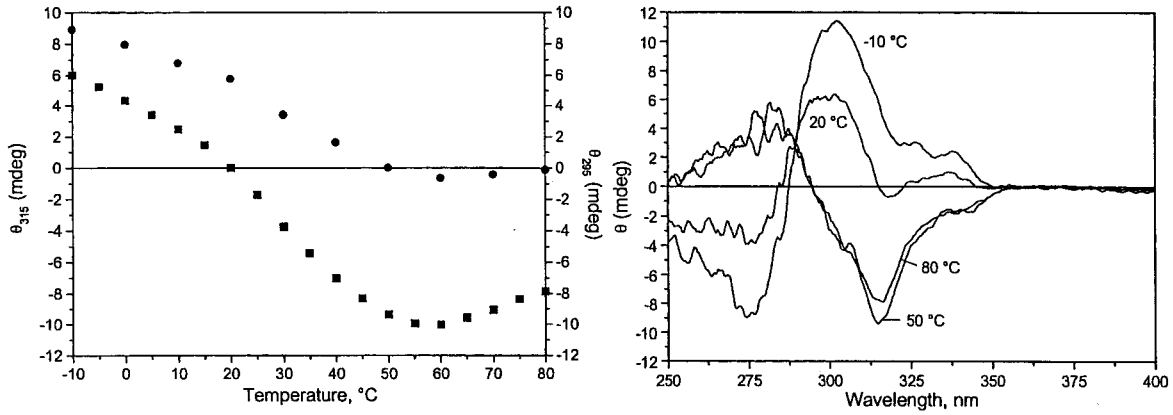

Figure 4. Plot of θ_{315} (squares) and θ_{295} (circles) vs temperature for a solution of octadecamer **2** ($n = 18$) as it was cooled from 80 to −10 °C (left). CD spectra recorded during the temperature run for the octadecamer (right). The measurements were recorded in 20 vol % water in acetonitrile with an oligomer concentration of 3.8 μM.

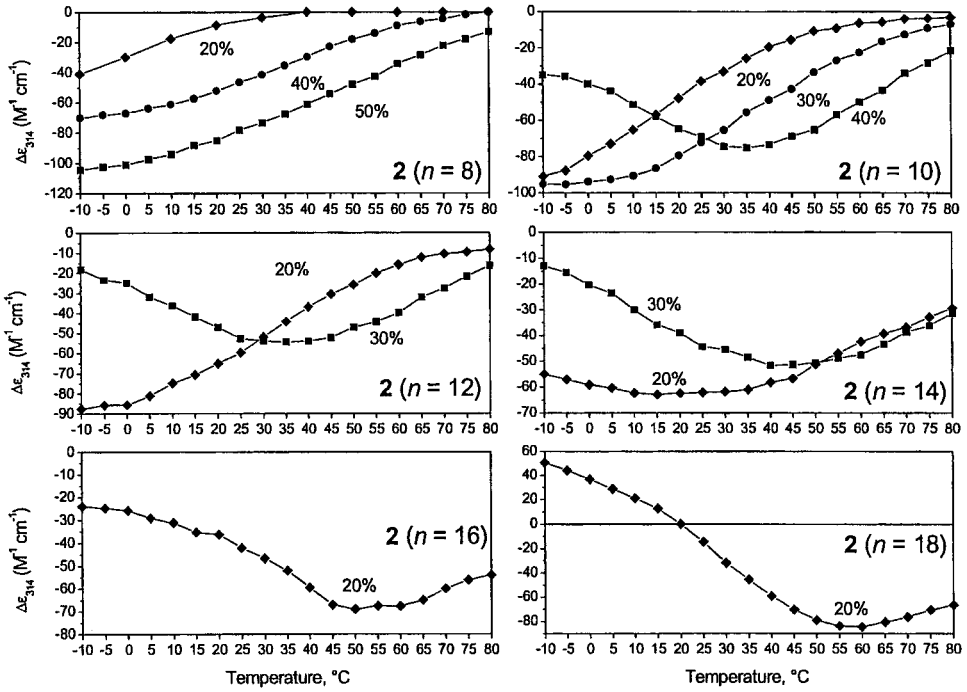

Figure 5. Plots of $\Delta\epsilon_{314}$ vs temperature for octamer **2** ($n = 8$) through octadecamer **2** ($n = 18$) in varying amounts of water/acetonitrile (v/v). All solutions were cooled from 80 to −10 °C.

temperature-dependent change in the handedness of the chiral supramolecular structure.

The temperature dependence of the Cotton effect was examined for all of the oligomers in several aqueous acetonitrile solutions (Figure 5).[21] For the shortest oligomer, the octamer, previous measurements in acetonitrile showed no evidence of optical activity. However, a Cotton effect could be observed in the aqueous solutions. For a 20% water solution, no CD signal is observed until 20 °C, but at lower temperatures, the Cotton effect increases rapidly. The addition of more water allows for a stable helix at even higher temperatures. The temperature denaturations for the octamer all show a sigmoidal curve. These results indicate that the addition of water stabilizes the helical conformation and the accompanying UV spectra show that this occurs because of stacking of the helical oligomers. From the other graphs in Figure 5 it can be seen that the increase of the oligomer length results in a deviation from the sigmoidal behavior of the temperature denaturations in solvents with high water content. It can be seen that as the oligomer length or volume percent water is increased the plot begins to show an initial increase followed by a decrease of the θ_{max}, similar to the octadecamer discussed above.

A comparison of all oligomers in 20% water/acetonitrile is shown in Figure 6. These results indicate that there is a clear chain length dependence on the aggregation properties. For the shorter oligomers (octamer−dodecamer) sigmoidal curves are seen; as the temperature decreases an increase in the CD signal at 314 nm is observed. The longer oligomers (tetradecamer−octadecamer) no longer show sigmoidal transitions; as the chain lengthens there is a steady growth in the positive direction of the CD signal at low temperatures. These results show that superstructure formation by the oligomers can be attributed to the presence of the helical conformation.

Intermolecular Cooperative Transfer of Chirality. We have shown that in aqueous acetonitrile solutions the oligomers

(21) All variable-temperature data were determined to be at equilibrium and independent of time since a spectrum recorded at 20 °C during the run and a spectrum measured at 20 °C at the end of the run (after heating the solution up from −10 °C and equilibrating for 10 min) were identical.

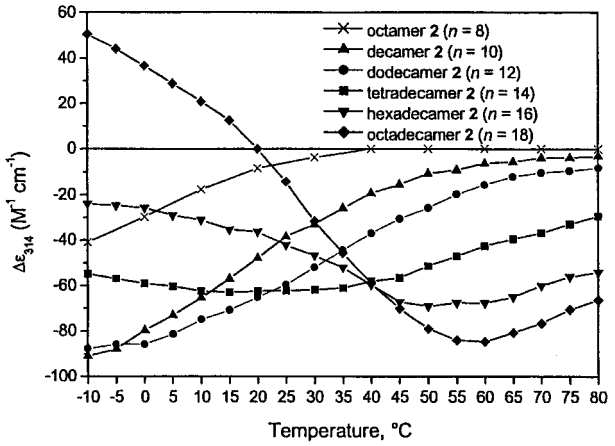

Figure 6. Plots of $\Delta\epsilon_{314}$ vs temperature for octamer **2** ($n = 8$) through octadecamer **2** ($n = 18$) in 20 vol % water in acetonitrile. All solutions were cooled from 80 to −10 °C.

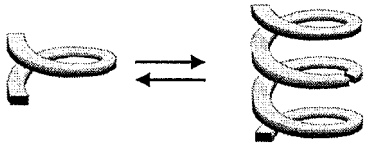

Figure 7. Proposed aggregation mode of the oligomers.

aggregate in a fashion that requires the presence of a stable helical conformation. It is hypothesized that the aggregation occurs via the formation of columns of stacked helices (Figure 7). Such a chiral supramolecular system is well-matched for the transfer of chiral information from one oligomer to the other. The stacking of a helix with no twist sense bias (i.e., one with achiral side chains) on top of a helix whose twist sense is biased (i.e., one with chiral side chains) would possibly impart a twist sense bias to the initially unbiased helix. To investigate this, several intermolecular "Sergeant and Soldiers"[18] experiments were performed on achiral oligomers series **1** (soldiers) and chiral oligomers series **2** (sergeants).

When solutions of varying amounts chiral octamer **2** ($n = 8$) and achiral octamer **1** ($n = 8$) were prepared in 50% water/acetonitrile (v/v), the absorbance spectra superimpose over one another and no conclusions can be made about intermolecular association, although the results do indicate the formation of similar helical conformations by both oligomers. However, when the same solutions are examined by CD spectroscopy, deviations from linearity are observed. A plot of CD signal intensity at 314 nm against mole percent chiral octamer results in a small positive deviation from linearity (Figure 8 (circles)). If a similar experiment is performed without the addition of achiral oligomer a linear dependence of the CD signal on mole percent chiral octamer **2** ($n = 8$) is observed (Figure 8 (squares)). The positive deviation from linearity and lack of concentration-dependent CD clearly shows that the chirality is being transferred from the chiral to the achiral octamers.[22]

To examine the intermolecular transfer of chirality in greater detail, the aggregation behavior of chiral **2** ($n = 18$) and achiral **1** ($n = 18$) octadecamers was studied in several mixtures of aqueous acetonitrile. In 100% acetonitrile, the CD signal was found to be linearly dependent on the mole percent of chiral octadecamer (Figure 9, top left). These results indicate that if intermolecular aggregation is occurring there is no transfer of

(22) All measurements were assumed to be at equilibrium since the observations were independent of time (spectra were measured 10 min after preparation, then again 24 h later).

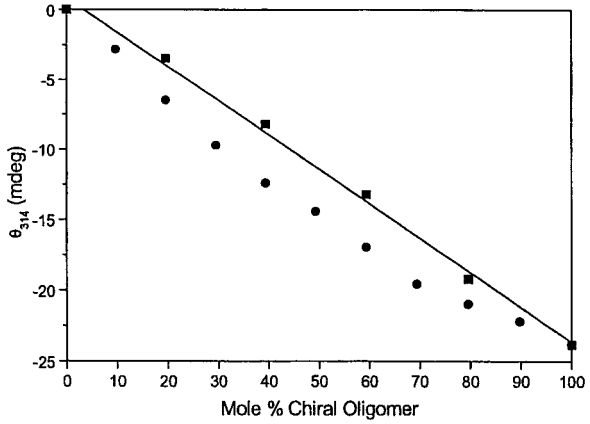

Figure 8. Plot of θ_{314} vs mol % chiral octamer **2** ($n = 8$) for solutions of varying amounts of chiral and achiral **1** ($n = 8$) octamers (circles). Squares show the effects on θ_{314} as the chiral octamer is diluted without the addition of achiral oligomer. The solid line is the least-squares linear fit of the chiral octamer dilution data (correlation coefficient = 0.998). All spectra were recorded in 50% acetonitrile/water (v/v). The experiments containing both achiral and chiral octamer were recorded with a total oligomer concentration of 7.0 μM, while for the experiments containing only chiral octamer the concentration was increased linearly from 0 to 7.0 μM.

chirality. More importantly, they show that the CD signals observed in 100% acetonitrile can be attributed to a purely intramolecular effect. Examination of solutions in increasing amounts of water showed a positive deviation from linearity meaning that the magnitude of the CD signal is larger than expected for an ideal mixture (Figure 9). Even more interesting is the observation that the maximum CD signal of certain mixtures of chiral and achiral oligomers is greater than that of the purely chiral octadecamer. A possible explanation for this behavior is that there is a more efficient packing between achiral molecules than the chiral molecules, since in the former no branching methyl group is present.[23] The transfer of chirality to achiral oligomers appears to be dependent on the presence and intermolecular aggregation of a helical conformation, which is supported by the larger transfer of chirality, observed for the longer octadecamers. These observations favor the proposed mode for the transfer of chirality, which is shown in Figure 7. The stacking is promoted due to the highly polar aqueous environment and efficient intermolecular stacking would allow for the chirality to be transferred to the achiral helices.

The transfer of chirality as observed using the "Sergeant and Soldiers" measurements is not very large. For the octadecamer it seems that on average 50% chiral oligomer **2** ($n = 18$) is needed for a full bias of the helicity of the achiral oligomers **1** ($n = 18$). This result is in contrast to the amplification of chirality as observed for helical columns of discotic molecules for which a strong cooperativity has been found.[10a−b,23] Three explanations can be thought of that result in a small amplification of chirality. First of all the size of the aggregates is detrimental. Aggregates consisting of only 2 or 3 molecules can only result in a small amplification of the chirality. The aggregate size should, however, strongly depend on the amount of water present, as increase of the water content results in stronger aggregation. In fact at high water contents (>60%) the solutions become turbid evidencing large aggregates. No evidence for an influence of this can be observed in Figure 9.

(23) Similar results were obtained for the association of a discotic molecule into helical columns in water: Brunsveld, L.; Lohmeijer, B. G. G.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem. Commun.* **2000**, 2305−2306.

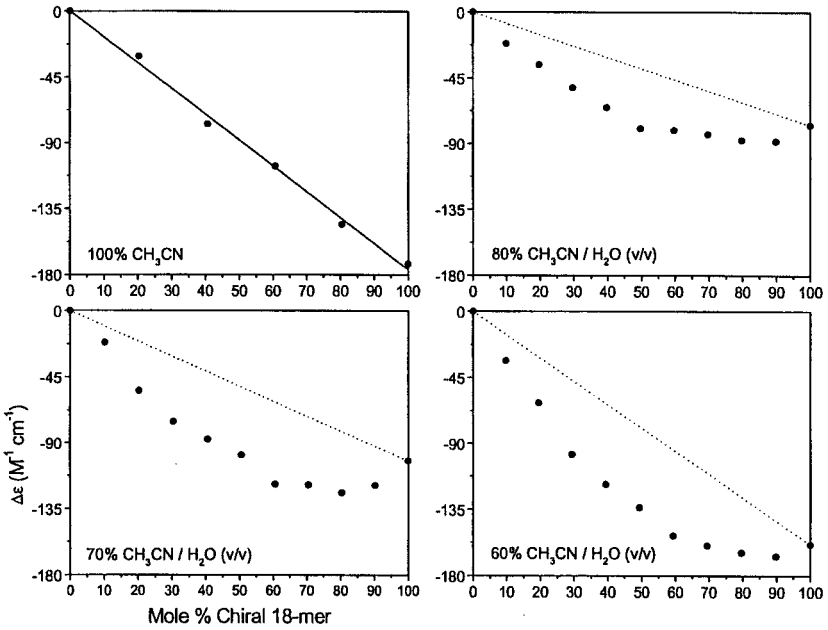

Figure 9. Plot of $\Delta\epsilon_{314}$ vs mol % chiral octadecamer **2** ($n = 18$) for solutions of varying amounts of chiral and achiral **1** ($n = 18$) octadecamers in different concentrations of water/acetonitrile (v/v). All spectra were recorded in solutions with a total oligomer concentration of 3.3 μM. The dotted lines are the expected signals that should arise upon dilution of a sample containing only chiral octadecamer. The solid line is the least-squares linear fit of the chiral octadecamer dilution data (top left, correlation coefficient = 0.998).

It should be noted, however, that the chirality of the aggregates, annex shape, at higher amounts of water changes, which might counteract the influence of increasing aggregate size (Figure 4). As a second option it should be considered that the stacking interactions between the oligomers, though being strong, are not very specific. In such a situation, the chirality of the helix would not be strongly recognized as such by the folded achiral oligomers. In other words, the cooperativity length of chirality amplification is very small. Such results have been found for the aggregation of polythiophenes,[24] for which the intermolecular interactions are also only of the generic solvophobic type, in contrast to specific interactions such as hydrogen bonding.[10a−b,23] Finally, from our previous results[14] and those presented here it is not possible to quantify the diastereomeric excess of the chiral helix. If for oligomers **2** the side chains do not account for a homochiral situation, but rather for a small diastereomeric excess, the amplification of chirality will be small as well. In such a situation also the "majority rules" principle[25] would not apply to these supramolecular assemblies and only small effects will be found. Recent results concerning intramolecular amplification of chirality, obtained for a series of oligomers containing both chiral as achiral side chains, have indicated the intramolecular induction of chirality to be cooperative, but not as impressive as observed in conventional polymers.[18,25,26] The most plausible explanations of the small amplification of chirality thus lie in the small directing power of the generic solvophobic effect and absence of full diastereomeric purity of the chiral helices. The use of more specific interactions would possibly account for a stronger amplification.

Conclusions

In conclusion, circular dichroism spectroscopy has proven to be an extremely valuable tool for examining the collapsed conformation and stacking of *m*-phenylene ethynylene oligomers. Examination of oligomers in aqueous solutions revealed a chain length dependent aggregation. Apparently, oligomers that adopt stable helical conformations aggregate into columns when the polarity of the solvent is increased by the addition of water. The formation of these columns results in the reversal of the CD signal, most probably because of a reversal in twist sense bias due to intercolumnar interactions, similar to what has previously been observed for helical columns of discotics.[2c,4b,11g] Mixtures of chiral and achiral oligomers in an aqueous environment showed a nonlinear dependence of θ_{max} on mole percent chiral oligomer indicating the intermolecular transfer of chirality. This transfer of chirality is hypothesized to occur through the intermolecular stacking of helical conformations and has been shown to be slightly cooperative.

This work represents a study at the mesoscopic level to understand the formation of large chiral aggregates as observed previously by electron microscopy.[2,4b,11g,27] Similar to structures observed with electron miscroscopy techniques, we have shown that the self-assembly into larger architectures results in the reversal of chirality. Electron microscopy studies on the aggregates studied here should help in the elucidation of the exact nature of this phenomenon.[28] Furthermore, the stepwise and reversible hierarchical growth of the chiral assemblies reveal valuable information to better understanding the folding and assembly of proteins and polynucleotides and should, eventually, lead to the formation of functional nonbiological multimolecular species.

Experimental Methods

Absorbance, Fluorescence, and Circular Dichroism Measurements. The UV absorption spectra were recorded on a Perkin-Elmer Lambda 900 spectrophotometer using 1-cm rectangular quartz cells. Circular dichroism spectra were recorded on a Jasco J-600 spectropolarimeter using 1-cm cylindrical quartz cells. UV−vis and CD,

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(25) Green, M. M.; Garetz, B. A.; Munoz, B.; Chang, H.; Hoke, S.; Cooks, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 4181−4182.
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(28) Kuebel, C.; Mio, M. J.; Moore, J. S.; Martin, D. C. To be published.

variable-temperature spectra were obtained by equilibrating the sample at the desired temperature for 15 min with a temperature-controllable cuvette holder.

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