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Towards Photocontrol over the Helix–Coil Transition in Foldamers: Synthesis and Photoresponsive Behavior of Azobenzene-Core Amphiphilic Oligo(*meta*-phenylene ethynylene)s

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Abstract: Introduction of photochromic azobenzene units into amphiphilic oligo(*meta*-phenylene ethynylene)s allowed photocontrol over the helix–coil transition in this important class of foldamers. Two design principles were followed in efforts to accommodate *cis*- and *trans*-azobenzene moieties within the helical structure to selectively turn the helical state on and off, respectively. Several oligomer series with varying connectivities to the central azobenzene chromophore were synthesized and these photochromic oligomers were investigated with regard to their folding behavior in both dark and irradiated states. Both the foldamers' chain lengths and the electronic structures of the azobenzene moieties had to be optimized to ensure folding differences and selective excitation of the photochrome. The design of such stimuli-responsive macromolecules, displaying large structural changes upon irradiation, should guide the design of future materials in, for example, "smart" delivery applications.

Keywords: azo compounds · chirality · foldamers · helical structures · photochromism

Introduction

Recent years have witnessed tremendous progress in the design of artificial backbones capable of adopting well-defined secondary structures—in particular of the helix type—in solution.[1] The helical folding process is governed by noncovalent interactions such as hydrogen bonding, metal coordination, and electrostatic and π,π-stacking interactions, among others. The helix–coil transition is therefore most frequently induced by increasing the temperature, changing the solvent composition, or adding folding-promoting/-disrupting agents. Typical denaturation experiments provide insight into the stability of the helical conformation and the cooperativity involved in the folding process. However, methods that use light, perhaps the most advantageous external stimulus, to control helix–coil conformational transitions in foldamers have been limited.

Photochromic molecules,[2] displaying two independently addressable switching states, have been used to affect structure and function at the molecular level.[3] In an attempt to utilize photochromic moieties to control helix–coil transitions in various polypeptide backbones, two approaches have been followed: the side-chain approach and the tether approach.[4,5]

Side-chain approach:[4] In this approach, photochromic units have been introduced in the side chains of various polypeptide backbones. Spiropyran units, for example, have been incorporated as side chains in poly(L-glutamic acid).[6] Photoisomerization of these units results in the conformational transition of the poly(L-glutamic acid) backbone from the random coil to the α-helical structure. Similarly, azobenzene units have been attached to the side chains of poly(L-glutamic acid). Irradiation induces a conformational transition from the random coil to the α-helical structure.[7] Furthermore, poly(L-lysine) appended with azobenzene chromophores has been shown to transform from a β-sheet structure to an α-helix structure upon photoisomerization.[8] The remarkable conformational transitions in all of these cases were found to be strongly dependent on the polymer's environment and employed solvent mixtures and hence were attributed to the changes in the polarity of the photochromic side chains affecting the surrounding media. The side-chain approach has also been successfully utilized to photomodulate the helix–coil transition in related poly(isocyanate)s with appended azobenzene photochromes.[9]

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Tether approach:[5] In this approach, the azobenzene unit has been used as a cross-linker between two different (cysteine) segments of a peptide backbone. In one case the photochromic molecule links the i and $i+4$ cysteine groups and photogeneration of the *cis*-azobenzene favors a helical backbone conformation. In the opposite case, the azobenzene unit connects the i and $i+11$ cysteine residues and so the *trans*→*cis* isomerization destabilizes the helical conformation. The helix content of a peptide is thereby shown to be controlled by the steric requirements of the azobenzene linker, which are conveniently modulated by photoisomerization.[10]

Thus far, however, no examples of photomodulation of the helix–coil transition within (artificial abiotic) foldamers through incorporation of the photochromic molecules into the main chain of the helical backbone have been reported. We have recently disclosed the first successful design of a photoswitchable foldamer prototype based on azobenzene-core amphiphilic oligo(*meta*-phenylene ethynylene)s (O*m*PEs).[11] Here we wish to give a full account detailing our extensive work relating to the synthesis of various azobenzene-containing O*m*PEs foldamers and investigation of their photoresponsive behavior.

Results and Discussion

Design

Choice of the stimulus and the photochromic moiety: The use of light as an external stimulus is particularly attractive, due to its noninvasive nature, ease of control and dose, the potential temporal and spatial resolution of exposure, and the absence of generated byproducts. These advantageous properties clearly make light the stimulus of choice, yet necessitate selection of an appropriate switchable chromophore.[2] Ideally, the photochromic system should consist of two independently addressable switching states, interconversion of which is associated with large changes in the molecular geometry. The system should be robust, allowing for many switching cycles, and the photoreaction should be conveniently quantifiable by means of spectroscopic methods. Taking these requirements—together with synthetic accessibility—into account, we chose the azobenzene moiety as the "classic" photochromic unit, because it displays a very clean and reversible *trans*→*cis* photoisomerization that proceeds with large structural changes in the geometry of the chromophore. It should be noted that alternative more quantitatively switching and thermostable electrocyclization-based photochromes[2] such as dithienylethenes, fulgides, or spiropyrans were not chosen because the interconversion between their switching states is associated with much smaller relative geometrical changes.

Choice of the folding backbone: Amphiphilic O*m*PEs are known to adopt helical conformations in polar solvents.[12] The driving force for such folding reactions is the solvophobicity of the rather nonpolar aromatic backbone in the polar environment, resulting in an intramolecular segregation analogous to nanophase separation in block copolymers. The *meta* connectivity allows the molecule to fold back on itself, enabling favorable π,π interactions between the stacking electron-deficient aromatic repeat units. Starting at a sufficient length ($n>8$) the enthalpic gain overcompensates the entropic loss and therefore leading to preferential formation of a helical structure,[13] in which six repeat units constitute a turn.[14] Consistent with helix–coil theory,[15] quantitative analysis of absorption and fluorescence data has established a linear relationship between chain length and helix stabilization energy for $8<n\leq 18$.[13] The helix–coil transition in O*m*PE-related foldamers is governed by the nature of the solvent,[16] temperature,[17] metal complexation,[18] and acidity/basicity.[19] Thus far, however, no photocontrol over folding transitions in O*m*PE-based or other foldamers has been achieved, so we became interested in achieving this goal through the incorporation of a photochromic azobenzene moiety into the main chain of the helical backbone, as illustrated in Figure 1.

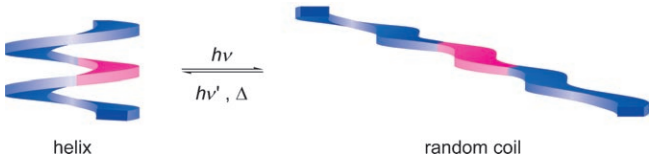


Figure 1. Incorporation of a photoisomerizable core unit (magenta) into a helical foldamer strand (blue) should allow for photoswitching of the helix–coil transition through the use of light as an external noninvasive stimulus offering potential spatial and temporal control over exposure.

Design of the foldamer system: Our working hypothesis was based on replacement of a single internal diphenylacetylene unit in an O*m*PE foldamer with differently substituted azobenzene chromophores (Figure 2). Both thermally stable helices and coils should be accessible in this way, so the helical conformation could be turned off or on by use of irradiation. The lengths of the oligomeric sequences attached to the photochromic unit would have to be adjusted in such a way that they would not be able to adopt stable helical conformations by themselves, but photoisomerization would either disrupt or create a kinked connection, resulting either in helix denaturation or in helix formation.

These two design approaches, resembling "turn-on" and "turn-off" helices, were followed by the introduction of kinked *cis*- and *trans*-azobenzene units, respectively, in the folding backbone.

1) "Turn-on" helices: In this design attempt we anticipated that incorporation of a *para*-substituted *trans*-azobenzene core in an O*m*PE foldamer should furnish a random coil, due to the linear geometry of the *para* linkage. The *trans*→*cis* photoisomerization should trigger the folding reaction as the curved geometry of the *cis* isomer should

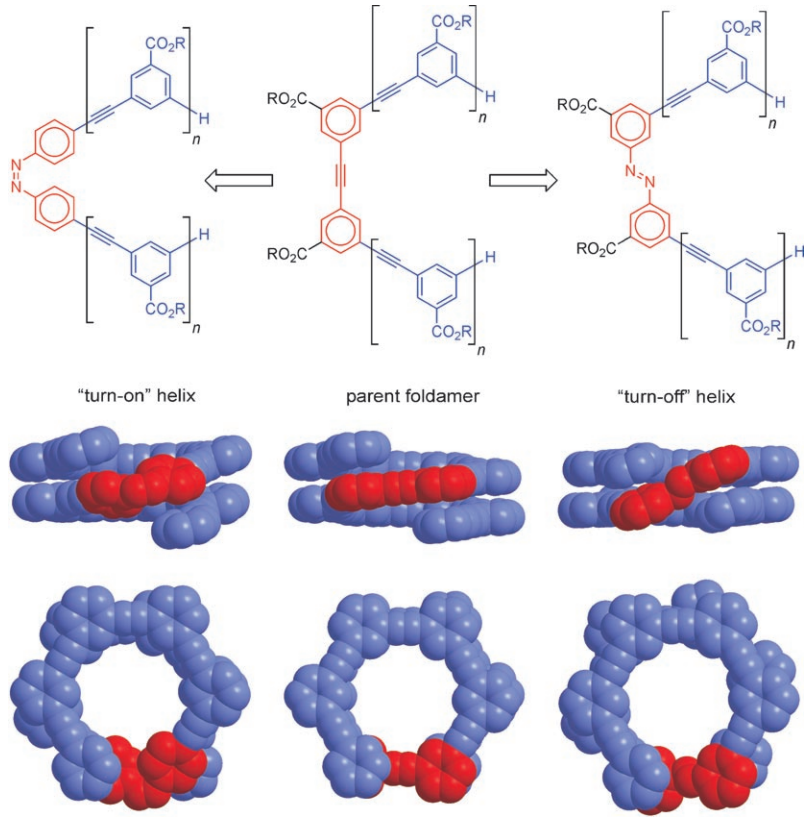
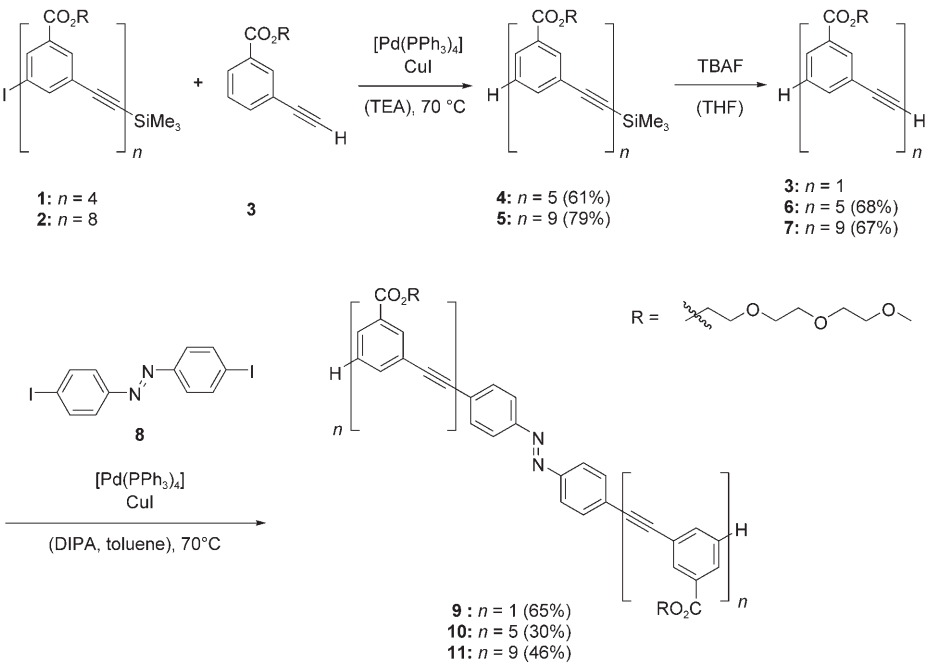


Figure 2. Structural resemblance of *para*-substituted *cis*-azobenzene (left) and *meta*-substituted *trans*-azobenzene (right) chromophores to the diphenylacetylene unit of the oligo(*m*-phenylene ethynylene) foldamer. Side (middle) and top (bottom) views of space-filling models of the expected helical conformation ($n = 5$).

in principle provide the necessary kink in the structure to allow the molecule to fold in on itself in the appropriate polar environments (Figure 2, left).

2) "Turn-off" helices: In our second design, we expected that a *meta*-substituted *trans*-azobenzene should structurally resemble a single tolane unit of the O*m*PE foldamer. In its *trans* state the chromophore should provide the necessary curvature in the structure to form a helix in polar solvents, while irradiation should result in disruption of the helical conformation by breaking the aromatic contacts due to the nonplanarity and incorrect curvature of the *cis*-azobenzene (Figure 2, right).



Scheme 1. Synthesis of the *para*-linked azobenzene-core oligomers **9**–**11**. TEA = triethylamine, DIPA = diisopropylamine.

"Turn-on" helices

Synthesis of the oligomers: Orthogonally protected tetramer **1** and octamer **2** were synthesized by a divergent/convergent growth strategy.[20,21] One terminus in each of these oligomers was capped by treatment with acetylene **3** to yield the phenyl-terminated oligomers **4** and **5**, while the other terminus was used for coupling to the appropriate bifunctional azobenzene core (Scheme 1). Removal of the trimethylsilyl groups in oligomers **4** and **5**, followed by palladium-catalyzed coupling with the azodiiodide **8**, furnished the target oligomers **10** and **11.** Model compound **9** was also synthesized by coupling acetylene **3** with the azodiiodide **8**.

The synthesized oligomers were thoroughly characterized by using several analytical tools. ^{1}H NMR spectroscopy, for example, permitted rapid identification of the molecular structure, as evidenced by symmetrical signal sets including identifiable end groups. Matrix-assisted

laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) measurements corroborated the NMR results by showing the expected $[M+Na]^+$ signals. Each oligomer exhibited a single, symmetrical peak in gel permeation chromatograms. The purities of the oligomers were determined to be greater than 99% by using gel-permeation chromatography (GPC).[20]

The central azobenzene chromophore common to oligomers **9**, **10**, and **11** is attached to oligomer segments with lengths of one, five, and nine repeat units, respectively, so the oligomeric arms on each side of the photochrome should not be able to fold in isolation. Moreover, communication between the two oligomeric arms of one chromophore is not possible because of the linear structure of the *trans*-azobenzene. However, photoisomerization should generate a curved structure associated with *cis*-azobenzene. This curvature should in principle allow communication between the two oligomeric arms through π,π-stacking interactions between the aromatic repeat units, so we expected that stable helices of 12 and 20 repeats units, respectively, should be formed from oligomers **10** and **11** upon irradiation in a helix-promoting solvent.

Photoisomerization studies: The absorption spectra of oligomers **10** and **11** each exhibit two bands, associated with the backbone and the photochrome units. The absorption maximum at $\lambda = 380$ nm (Figure 3) corresponds to the π–π* transition of the *trans*-azobenzene chromophore, while the absorption band at $\lambda = 290$ nm belongs to the phenylene ethynylene backbone. The strong bathochromic shift of the azobenzene core in oligomers **9**–**11** in relation to the native chromophore ($\lambda_{max} \approx 320$ nm) is a result of the extended π conjugation due to *para* substitution with the phenylacetylene unit.

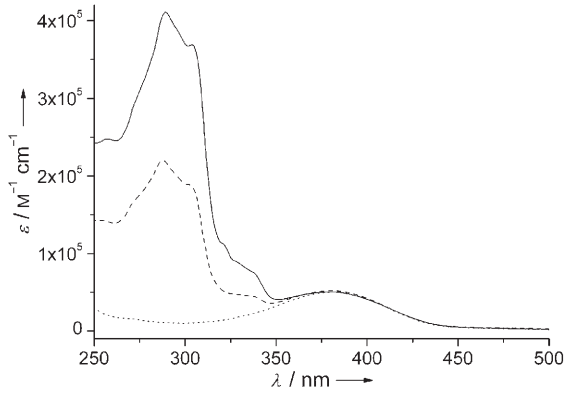


Figure 3. UV/Vis absorption spectra of oligomers **9** (•••••), **10** (-----), and **11** (——) in $CHCl_3$ (25 °C).

Irradiation of oligomer $\mathbf{10}_{trans}$ with 395 nm light for 2 min resulted in rapid conversion into the corresponding $\mathbf{10}_{cis}$ isomer. The photoisomerization event could easily be monitored with the aid of UV-visible spectroscopy: irradiation causes a decrease in the absorption of the π–π* (380 nm) band and an increase in the absorption in the backbone chromophore range at $\lambda = 290$ nm (Figure 4). This increase is related to the contribution of the *cis* isomer of the azobenzene core to this absorption band (that is, the hypsochromically shifted π–π* band). Two well-developed isosbestic points can be detected at $\lambda = 339$ and 448 nm, confirming clean interconversion between two species. The photogenerated $\mathbf{10}_{cis}$ present in the photostationary state (PSS)[22] slowly reverts back to the $\mathbf{10}_{trans}$ in the dark at room temperature confirming the reversibility of the isomerization.

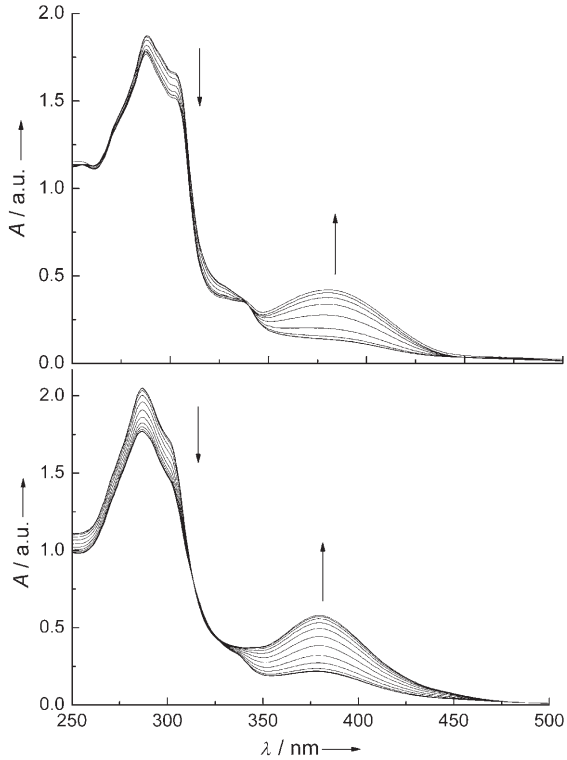


Figure 4. UV/Vis absorption spectra of oligomer **10** in $CHCl_3$ (top) and CH_3CN (bottom), showing thermal relaxation at 25 °C after irradiation at 395 nm ($[\mathbf{10}_{cis}]_{PSS}(CHCl_3) \approx 69\%$ and $[\mathbf{10}_{cis}]_{PSS}(CH_3CN) \approx 63\%$ by UV/Vis spectroscopy[22]). a.u. = arbitrary units.

Oligomer **11** was also exposed to 395 nm light for the same period of time. Similar changes to those seen in the case of oligomer **10** could be observed in the absorption spectrum, with two clear isosbestic points at $\lambda = 339$ and 448 nm. Figure 5 shows the thermal *cis*→*trans* isomerization of oligomer **11** in chloroform and acetonitrile.

Kinetics of thermal cis→trans *isomerization*: Because of the anticipated conformational changes accompanying both photochemical and thermal isomerization, we were interested in studying the kinetics to reveal potential effects on the rates of interconversion. In view of the convenient time frames of the thermal *cis*→*trans* isomerizations, with half-lives of the order of hours, thermal reversal of solutions in

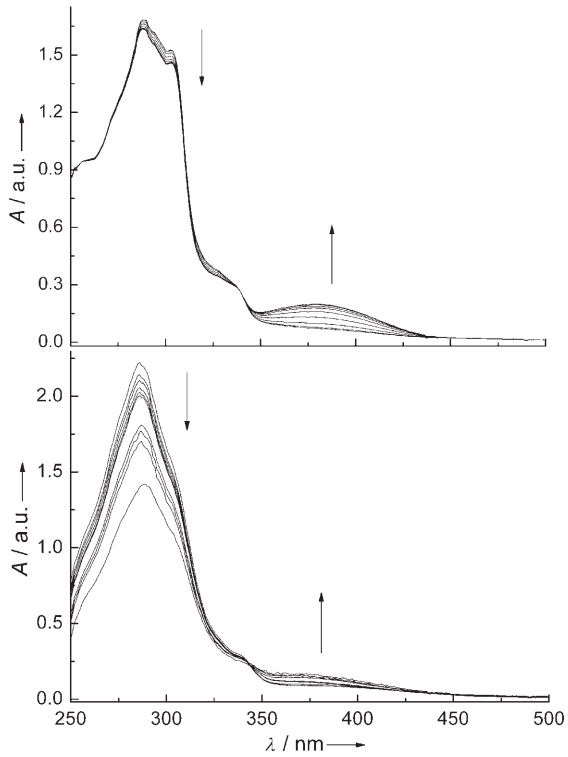


Figure 5. UV/Vis absorption spectra of oligomer **11** in $CHCl_3$ (top) and CH_3CN (bottom), showing thermal relaxation at 25 °C after irradiation at $\lambda = 395$ nm ($[\mathbf{11}_{cis}]_{PSS}(CHCl_3) \approx 63\%$ and $[\mathbf{11}_{cis}]_{PSS}(CH_3CN) \approx 44\%$ by UV/Vis spectroscopy[22]).

the photostationary state (PSS) was investigated as a function of chain length and solvent. In all these experiments the temperature was kept constant at 25 °C. We were expecting that the rates of *cis*→*trans* isomerization of oligomer **9** should be similar in two different solvents as it is too short to form a stable helix. In contrast, oligomers **10** and **11**—if they adopted stable helical conformations upon isomerization—should undergo slower back reactions in the helix-promoting solvent, as favorable π,π-stacking interactions would have to be broken in order to reach the *trans* configuration. The experimental results[20] (Table 1) revealed that the rates were strongly dependent on solvent, but no chain-length dependence, as anticipated in the case of helical folding, was found.

Table 1. Rates of thermal back reaction for oligomers **9**–**11** in chloroform and acetonitrile at 25 °C.

Oligomer	k_{rev} in chloroform [s^{-1}]	k_{rev} in acetonitrile [s^{-1}]
9 ($n = 1$)	$k = 7.89 \pm 0.04 \times 10^{-5}$	$k = 3.51 \pm 0.05 \times 10^{-5}$
10 ($n = 5$)	$k = 8.90 \pm 0.08 \times 10^{-5}$	$k = 1.26 \pm 0.09 \times 10^{-5}$
11 ($n = 9$)	$k = 9.09 \pm 0.47 \times 10^{-5}$	$k = 1.62 \pm 0.19 \times 10^{-5}$

Fluorescence spectroscopy: Fluorescence spectroscopy is a valuable tool for study of conformational changes of O*m*PE foldamers. In denaturing solvents such as chloroform, emission from individual cross-conjugated, and hence isolated, repeat units is observed, due to the absence of a folded conformation. In polar solvents such as acetonitrile, however, the helical conformation prevails, so excimer-like emission arising from the π-stacked aromatic rings is seen.[13] As fluorescence spectroscopy is a rather sensitive technique, the presence of the non-emissive but potentially emission-quenching azobenzene chromophore could complicate analysis. In the case of oligomer **10** (Figure 6, top), fluorescence

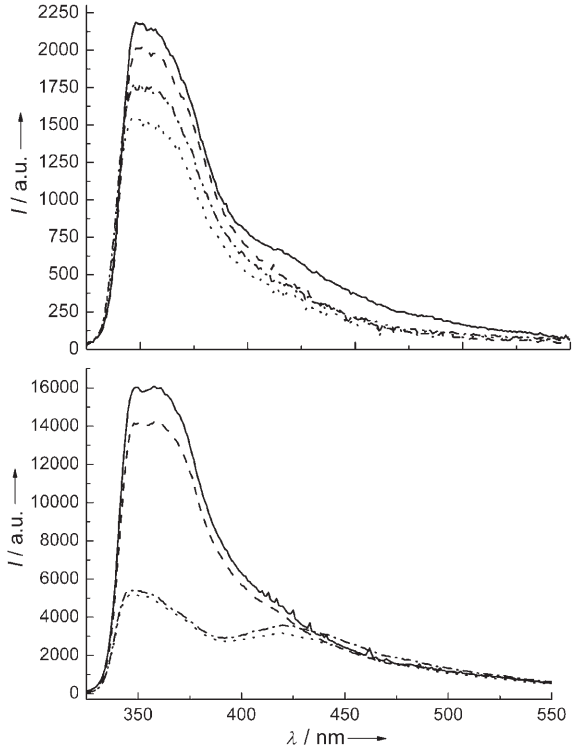


Figure 6. Fluorescence spectra of oligomer **10** (top) before irradiation (-----) and after irradiation (——) in $CHCl_3$ and before irradiation (•••••) and after irradiation (–•–•) in CH_3CN, and of oligomer **11** (bottom), before irradiation (-----) and after irradiation (——) in $CHCl_3$ and before irradiation (•••••) and after irradiation (–•–•) in CH_3CN at an excitation wavelength of 290 nm (25 °C).

spectra in chloroform show a band at $\lambda = 350$ nm before and after irradiation. In acetonitrile, the presence of a helical secondary structure before irradiation is unlikely, because the attached oligomers on both sides of the azobenzene core are not long enough to fold into stable individual helices. Hence, only the monomer emission was observed in acetonitrile before irradiation. However, irradiation of oligomer **10** in acetonitrile at $\lambda = 395$ nm causes no change in the shape of the emission spectrum, suggesting that there is no conformational change associated with the photoisomerization. Interestingly, the azobenzene moiety does not seem to influence the emission characteristics notably, perhaps as a result of its π conjugation to the neighboring phenylacetylene units.

Solutions of the longer oligomer **11** in chloroform displayed the expected monomer emission at $\lambda = 350$ nm both before and after irradiation. In acetonitrile before irradiation, however, the 350 nm band shows unexpected partial quenching of monomer emission and the appearance of a redshifted, broad featureless band centered at 425 nm. This band can be attributed to π-stacked aromatic chromophores and indicates that there is partial population of folded oligomers in solution before irradiation (Figure 6, bottom). Most probably, the electron-deficient azobenzene core engages in stronger π,π-stacking interactions, resulting in more pronounced stabilization of the helical conformation and hence folding at shorter lengths than observed with the parent amphiphilic O*m*PEs.[12] After *trans*→*cis* photoisomerization a similar spectrum is observed, indicating no significant conformational change in the folding backbone before and after irradiation. The nonplanarity of the *cis*-azobenzene core most probably destabilizes the helical conformation by disturbing the π,π-stacking interactions, as indicated by molecular modeling (Figure 2), and hence prevents formation of a stable helix. The photochromic behavior of azobenzene is caused by the nonplanar structure of the *cis* isomer, allowing for the necessary spectral differences between *trans* and *cis* isomers.[2] We therefore abandoned the turn-on helix design and focused on efforts to introduce the planar *trans* isomer into the helical backbone: that is, turn-off helices.

"Turn-off" helices

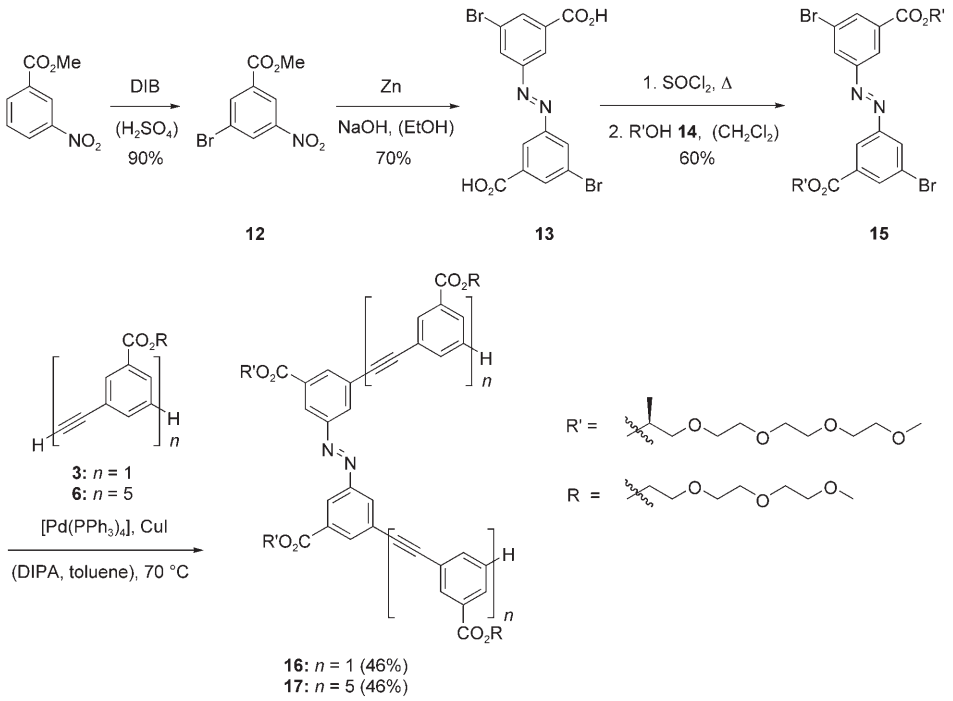
Synthesis of the oligomers: The synthesis of the azobenzene core molecule **15** was accomplished in three linear steps Scheme 2). Methyl 3-nitrobenzoate was brominated, with subsequent treatment with zinc under basic conditions to yield the desired azobenzene bis-acid **13**, which was then converted into the corresponding acid chloride in thionyl chloride at reflux. The crude bis-acid chloride was treated with the chiral alcohol **14** to furnish the desired azobenzene core **15**. The introduction of chiral alcohol **14** was deliberate, to allow study of the conformational changes of the synthesized oligomers with the help of circular dichroism (CD) spectroscopy. Finally, both bromine functionalities in the azobenzene core molecule **15** were coupled to acetylene-terminated oligomers **3** and **6**, carrying achiral side chains, to yield model compound **16** and oligomer **17**, respectively. The structural integrities and purities of these oligomers were verified by several analytical tools, including ^{1}H NMR spectroscopy, MALDI-TOF MS, and GPC.[21]

Folding studies in the dark state: The absorption spectrum of the phenylacetylene chromophore shows two absorption maxima at $\lambda = 288$ and 303 nm. These two peaks can be regarded as two vibronic bands belonging to the *cisoid* and *transoid* conformations of the phenylene ethynylene backbone. Conformational change of the O*m*PEs results in hypochromism of the 303 nm band.[12]

To investigate the folding properties of oligomer **17**, UV-visible spectra were recorded in a series of solvent mixtures ranging from pure chloroform to pure acetonitrile. Addition of acetonitrile causes a decrease in the 303 nm band and in pure acetonitrile this band vanishes completely. Plotting of the absorbance ratio ($A_{303\,nm}/A_{288\,nm}$) as a function of the solvent composition yielded a titration curve that revealed a sigmoidal shape, indicating the cooperative nature of the folding process (Figure 7).

From solvent denaturation data, the helix stabilization energy in pure acetonitrile was calculated to be ΔG (CH_3CN) $= -1.6$ kcal mol^{-1}.[21] While these results already show the folding of oligomer **17**, fluorescence spectroscopy did not aid conformational analysis, due to the presence of several unassigned emission bands (Figure 8), most probably caused by the presence of the *meta*-linked azobenzene core.

To gain additional insight into the prevailing solution conformation, CD spectroscopy was employed to study oligomer **17**, which is decorated with two interior chiral side



Scheme 2. Synthesis of the *meta*-linked azobenzene-core oligomers **16** and **17**. DIB = dibromoisocyanuric acid.

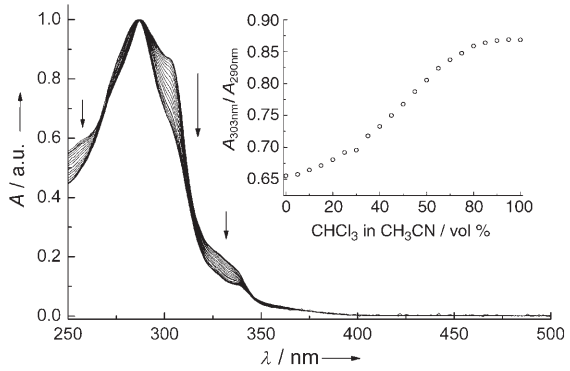


Figure 7. UV/Vis absorption spectra of oligomer **17** in $CHCl_3$ with increasing CH_3CN content (100% $CHCl_3 \rightarrow$ 100% CH_3CN). The spectra, measured at approximately the same concentration, have been normalized with respect to their maximum intensity. The inset shows a plot of the UV/Vis absorbance ratio ($A_{303\,nm}/A_{290\,nm}$) as a function of the volume percent chloroform in acetonitrile (25 °C).

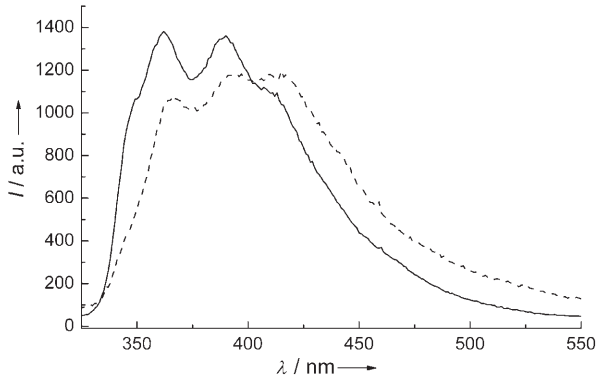


Figure 8. Fluorescence spectra of oligomer **17** in $CHCl_3$ (——) and CH_3CN (-----) at an excitation wavelength of $\lambda = 290$ nm (25 °C).

chains. Incorporation of these enantiomerically pure side chains caused efficient chirality transfer to the backbone, resulting in a twist sense bias due to the presence of a non-equivalent ratio of right- and left-handed diastereomeric helices. The generated excess helicity can conveniently be detected by using CD spectroscopy.

As expected, oligomer **17** showed no CD signal in chloroform, independently verifying the absence of any helical secondary structure in solution (Figure 9). In acetonitrile, however, a CD signal could be detected in the absorption region of the backbone ($\lambda = 250$–350 nm), confirming the ability of oligomer **17** to adopt a helical conformation in acetonitrile, as shown above by the UV-visible spectroscopy data. The observed CD signal was rather weak, however, suggesting inefficient chirality transfer, associated with the rather small energy difference separating the two diastereomeric helices, resulting in only a mediocre twist sense bias. The population of the helical conformation could further be attenuated by the addition of water to the sample solution in acetonitrile, making the environment significantly more polar and thereby increasing the solvophobic driving force

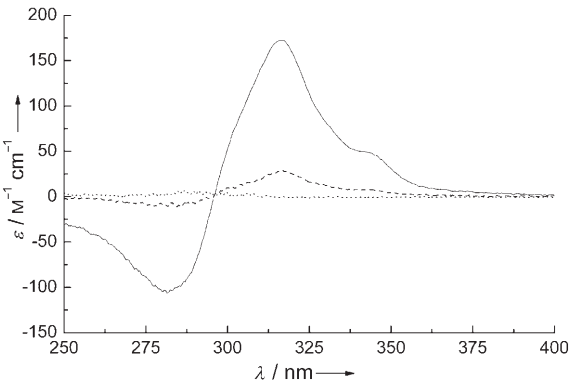


Figure 9. CD spectra of oligomer **17** in chloroform (•••••), acetonitrile (-----), and 40 vol% water in acetonitrile (——) (25 °C).

for folding. As a result of the larger overall helix content, and hence absolute excess of one helical twist sense, a more intense CD signal was observed (Figure 9). The positive Cotton effect arising from excitonic coupling of the aromatic repeat units indicates a *P*-helical twist sense.[23] Interestingly, side chains with β-methyl instead of α-methyl substitution show inverse helicity and point to "odd–even effects" in these and related oligomers.[24,25]

Irradiation studies: The photoisomerization of oligomers **16** and **17** was unsuccessful, as irradiation at $\lambda = 320$ nm resulted in irreversible changes in the absorption spectra. This behavior can be understood in the following way. In the case of the turn-on oligomers **10** and **11** the azobenzene chromophore is extended due to conjugation with both neighboring phenylacetylene units, so the π–π* absorption maximum of the photochromic moiety is centered at 380 nm. The lack of conjugation in the cases of oligomers **16** and **17**, due to the *meta* connectivity, results in a blueshifted π–π* absorption maximum at 320 nm. Because the backbone absorption dominates at this wavelength, selective excitation of the azobenzene photochrome is not possible and the light is mainly absorbed by the phenylene ethynylene units, resulting in as yet unidentified irreversible photochemistry.[26]

Selective excitation of the azobenzene chromophore: In order to allow selective excitation of the photochromic moiety, the π–π* absorption maximum has to be shifted bathochromically. One way to achieve redshifts of π–π* bands is based on the use of donor–acceptor-substituted azobenzene chromophores, but the short lifetimes of their *cis* forms present a severe limitation to our studies. Alternatively the introduction of two donor substituents into the azobenzene chromophore also gives a considerable redshift. For synthetic reasons we chose symmetrical disubstitution of the azobenzene moiety by two (4,4′) methoxy groups. The experimental results confirmed that the absorption band of the non-methoxy azobenzene core compound **15** ($\lambda_{max} \approx 320$ nm) could be shifted to longer wavelengths ($\lambda_{max} \approx 350$ nm) in this manner (Figure 10), so selective excitation

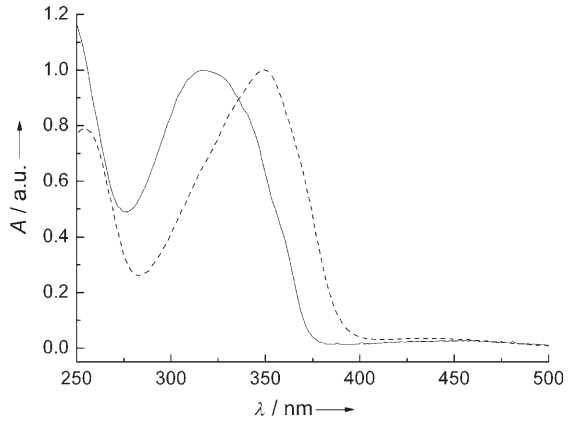
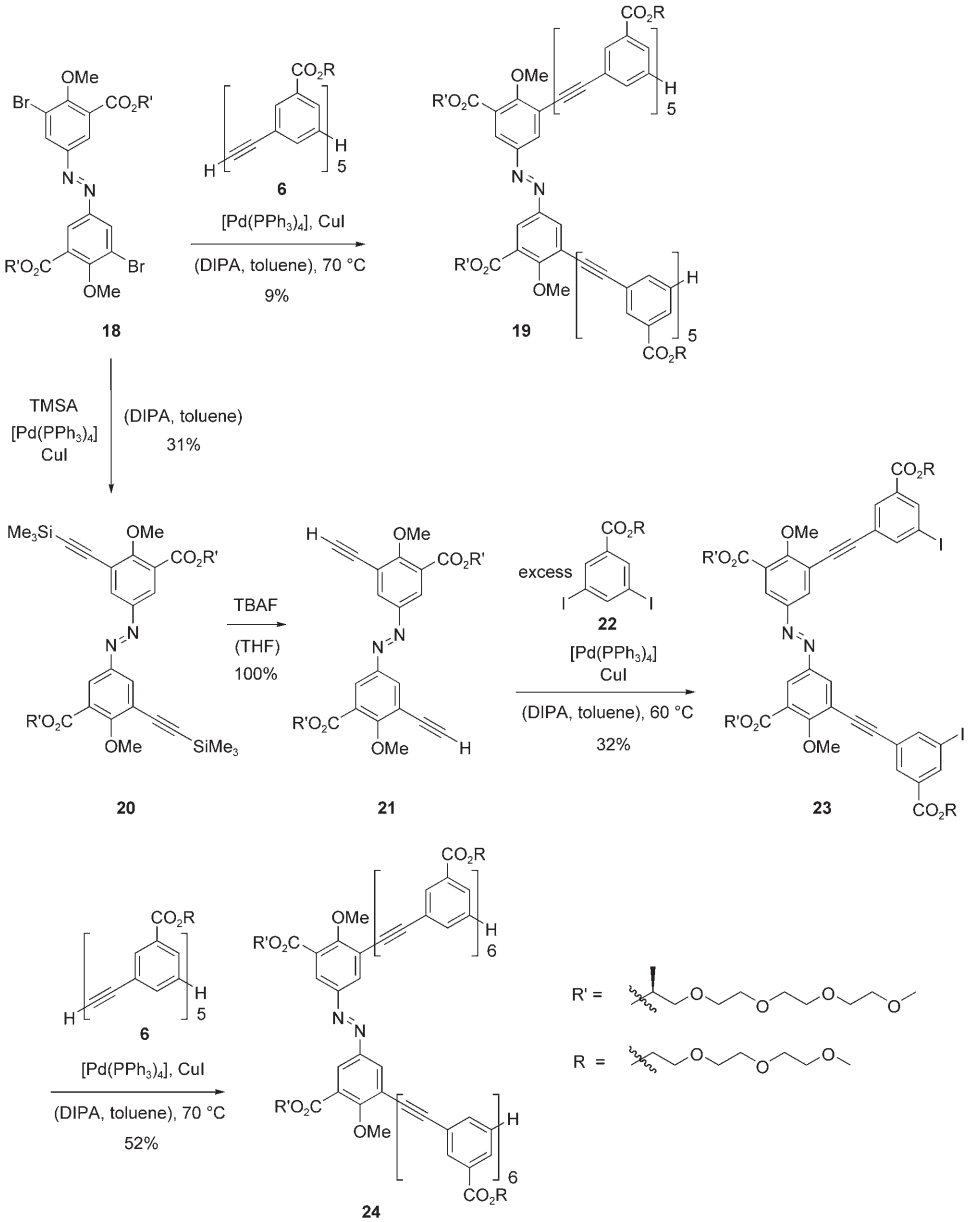


Figure 10. UV/Vis absorption spectra of compound **15** (——) and **18** (·····) in chloroform (25 °C).

of the photochromic unit can be—at least partially—achieved without interfering with the phenylene ethynylene backbone.

Synthesis of donor-substituted azobenzene core foldamers: The methoxy-substituted azobenzene-core oligomer **19** was obtained by palladium-catalyzed coupling of azobenzene dibromide **18**[11] with pentamer acetylene **6** in 9% yield (Scheme 3). The low yields of the coupling reactions are presumably the result of the more difficult oxidative addition to the *ortho*-methoxy-substituted aryl bromide. Solvent titration studies involving UV-visible and CD spectroscopy revealed that oligomer **19** did not adopt a stable helical conformation in acetonitrile. Apparently the introduction of the methoxy groups significantly changes the electronics of the azobenzene moiety—an effect desired in terms of shifting the absorption maximum—but π,π-stacking interactions between the aromatic units are consequently weakened.[27] We expected that lengthening the oligomeric segment should compensate for this effect and might perhaps result in the formation of a more stable helical conformation due to an increased number of π,π-stacking contacts, so the synthesis of oligomer **24** was carried out (Scheme 3).

Azobenzene core **18** was extended by palladium-catalyzed coupling with trimethylsilylacetylene (TMSA) to furnish compound **20**, which was deprotected by treatment with tetrabutylammonium fluoride (TBAF) to give bis-acetylene **21**. The free acetylene groups in **21** were subjected to a tenfold excess of diiodide **22** under Sonogashira–Hagihara coupling conditions at room temperature to yield compound **23**. Use of the excess of diiodide **22** allowed undesired side reactions such as oligomerization and polymerization to be avoided. Coupling of the diiodide **23** with acetylene-terminated oligomer **6** gave the desired oligomer **24**. This overall extension of the sterically hindered dibromide **18** to the more re-



Scheme 3. Synthesis of the *meta*-linked methoxy-substituted azobenzene-core oligomers **19** and **24**.

active elongated diiodide **23** resulted in significantly higher coupling efficiency for the formation of **24**. Several analytical tools such as ^{1}H NMR spectroscopy, electrospray ionization(ESI) MS, and GPC were used to characterize oligomer **24** extensively.[11]

Folding studies in the dark state: The folding behavior of azobenzene-core oligomer **24** was investigated by means of typical solvent denaturation experiments with use of UV-visible absorption to monitor the conformational transition (Figure 11). The sigmoidal shape of the obtained titration

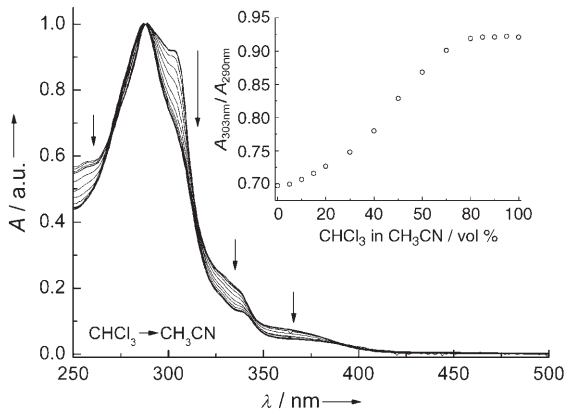


Figure 11. UV/Vis absorption spectra of oligomer **24** in $CHCl_3$ with increasing CH_3CN content (100% $CHCl_3$→100% CH_3CN). The spectra, measured at approximately the same concentration, have been normalized with respect to their maximum intensity. The inset shows a plot of the UV/Vis absorbance ratio ($A_{303\,nm}/A_{290\,nm}$) as a function of the volume percentage chloroform in acetonitrile (25 °C).

curve indicates the cooperative nature of the folding process.

Analysis of the data obtained by the UV-visible titration experiments reveals a helix stabilization energy in pure acetonitrile of $\Delta G(CH_3CN) = -1.7\,kcal\,mol^{-1}$. The replacement of the central tolane unit in the parent tetradecamer[12,13] by the azobenzene core thus gives rise to only slight helix destabilization. The destabilization effect can be attributed to the weaker π,π-stacking interactions due to the presence of the electron-donating methoxy substituents.[27]

CD spectroscopy in pure acetonitrile did not reveal a large Cotton effect, so addition of water was again utilized to increase the driving force for helical structure formation. In 60 vol% water in acetonitrile the induced CD signal is of significant intensity and the positive Cotton effect indicates the presence of an excess of the *P*-helical conformation (Figure 12), as observed in the case of oligomer **17**. These experiments complement the independently obtained UV-visible spectroscopic evidence for helix formation in the case of *trans*-azobenzene oligomer **24**.

Photoisomerization studies: Irradiation of the oligomer $\mathbf{24}_{trans}$ with use of 365 nm light to excite the central azobenzene chromophore selectively resulted in rapid conversion

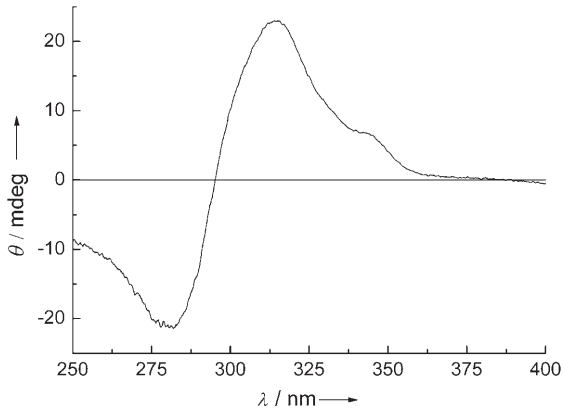


Figure 12. CD spectra of oligomer **24** in chloroform (•••••, not visible—on baseline) and in 60 vol% water in acetonitrile (——) (25 °C). θ = ellipticity.

into the corresponding *cis* isomer as monitored by using UV-visible absorption spectroscopy (Figure 13). The observed absorbance changes—decreasing π–π* (350–400 nm),

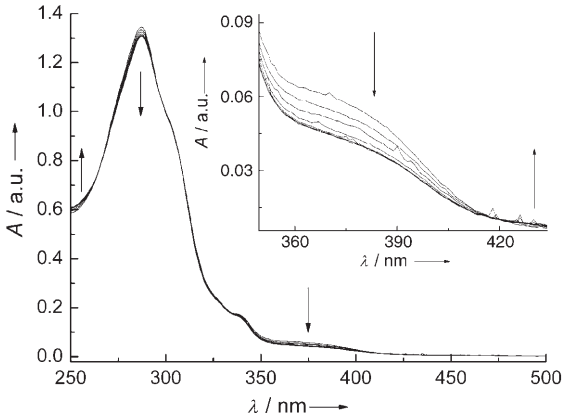


Figure 13. UV/Vis absorption spectra obtained during photochemical *trans*→*cis* isomerization of oligomer **24** caused by λ = 365 nm irradiation in acetonitrile at 25 °C (t = 0, 1, 3, 7, 15, 31, 63 s). The inset shows a magnification of the characteristic π–π* band of the azobenzene core.

weakly increasing n–π* (400–450 nm), and increasing π–π* (<265 nm) absorptions, as well as the presence of two well-defined isobestic points at λ = 265 nm and 418 nm—are indicative of the *trans*→*cis* photoisomerization process. While the photochemical *trans*→*cis* conversion is achieved within irradiation times of seconds, the thermal *cis*→*trans* reversion occurs over the time frame of several hours at room temperature.

Conformational change during photoisomerization as monitored by using CD: In order to monitor the conformational changes during both forward and backward isomerization processes, CD spectra of oligomer $\mathbf{24}_{trans}$ in folding-promoting solvent mixtures were recorded. Irradiation of the helically folded oligomer $\mathbf{24}_{trans}$ at 365 nm resulted in a rapid de-

crease in the CD signal, indicating depopulation of the helical conformation, while thermal reversion resulted in complete recovery of the initial CD signal intensity, indicating that the original complete population of the helical backbone conformation had been reinstated. The presence of a well-developed isodichroic point at 295 nm suggested a clean conversion between both conformations (Figure 14).

The composition of the mixture in the $\mathbf{24}_{cis}/\mathbf{24}_{trans}$ PSS ($\approx 40\,\%$) can be directly deduced from the ratio of the CD signals.[11] Kinetic analysis of the data at 25 °C provides the rate of the thermal *cis*→*trans* isomerization $k_{cis\rightarrow trans} \approx 3.8 \times 10^{-5}\,s^{-1}$, corresponding to a half-life of $t_{1/2} \approx 5$ h and an activation energy of $\Delta G^{\neq} \approx 23.5$ kcal mol^{-1}, typical for azobenzene-cored macromolecules in solution.[28]

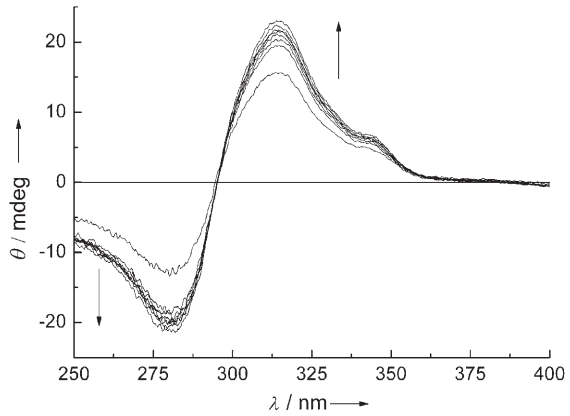


Figure 14. CD spectra obtained during thermal *cis*→*trans* isomerization of **24** in H_2O in CH_3CN (60 vol %, 9.5×10^{-6} M) at 22 °C (starting at PSS: t = 0, 1.5, 3, 4.5, 7.5, 10, 48, 53, 72 h).

Conclusion

Through a rigorous synthetic effort involving several design cycles, we have been able to demonstrate the feasibility of using light as an external stimulus to control helix–coil transitions in helically folding amphiphilic O*m*PEs. Although our initial approach targeting turn-on helices, based on incorporation of *para*-connected azobenzene within the core of the helix, was not successful, introduction of a *meta*-connected *trans*-azobenzene chromophore proved viable and resulted in the formation of stable turn-off helices. Photochromic *trans*→*cis* isomerization of the central azobenzene chromophore disrupts the helix while thermal *cis*→*trans* reversion restores the original helical conformation. Such light-triggered systems can potentially function as photoresponsive dynamic receptors and hence promise applications in the field of "smart" delivery devices.

Ongoing work in our laboratory is concerned with the design of polymeric analogues featuring better spectral separation of photoisomerizable unit and the helical backbone in order to achieve more quantitative switching between compact helical and extended coil structures.

Experimental Section

For details of the general methods, optical spectroscopy, irradiation experiments, derivation of the rate constants for thermal *cis*→*trans* isomerization, and syntheses, please see the Supporting Information.

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