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Foldamers

Reversible and Quantitative Denaturation of Amphiphilic Oligo(azobenzene) Foldamers**

*Zhilin Yu and Stefan Hecht**

Photoresponsive materials have been a highly attractive field of research because they allow to harness the true potential of the spatiotemporal resolution of light stimuli for applications that include data storage and actuation, among others.[1] To maximize the response of these materials it is clearly advantageous to design molecular building blocks with increased sensitivity. In this context, we have recently engaged in the construction of photoswitchable foldamers,[2–4] which allow the translation of incoming photons into large yet reversible structural changes by exploiting the cooperative and hence highly efficient helix–coil conformational transition.[5] Our first reported prototype, which has one photochromic azobenzene core embedded in an amphiphilic oligo(*meta*-phenylene ethynylene) (O*m*PE) backbone, proved the concept, yet irradiation only led to approximately 40% denaturation; thus improved foldamers are needed before the true potential of our approach can be exploited. Herein we report on a new foldamer family composed entirely of azobenzene monomer units and discuss its folding and photoisomerization behavior. By optimizing the chain length of these foldamers, a quantitative and reversible light-induced folding transition can be achieved.

To assemble the target compounds, azobenzene repeat units were connected by ethynylene bridges, hence allowing facile synthesis by Pd-catalyzed Sonogashira–Hagihara reactions. The resulting foldamers are structurally related to the amphiphilic O*m*PEs reported by Moore and co-workers[6], yet every other ethynylene fragment has been replaced by an azo group, thus providing the desired photoswitchability (Scheme 1, top). According to the available structural insights into O*m*PEs[7] and initial modeling studies, it is reasonable to assume that three azobenzene units constitute one turn in the folded helical structure (Scheme 1, bottom). Polar achiral as well as chiral oligo(ethylene glycol) side chains were attached to provide the necessary solvophobic driving force for folding in a polar medium and to induce excess helicity for analysis of the helical folding by circular dichroism (CD) spectroscopy. The chain lengths were chosen such that the oligomers are minimally stabilized in their helical structure and the driving force is just sufficient to ensure the folding in acetonitrile solution.

Synthesis of several members of the new oligomer series was achieved by repetitive coupling of an azobenzene dimer building block that carries orthogonal reactive groups at both of its termini (see compound **5** in Scheme S1[8] in the Supporting Information). The resulting oligomers $\mathbf{10_5}$, $\mathbf{12_6}$, and $\mathbf{14_7}$ (Scheme 1; the first number denotes the number of phenylene units, the subscript number gives the number of azobenzene moieties) were fully characterized by NMR spectroscopy, MALDI-TOF MS, and gel permeation chromatography (GPC).

To verify the envisioned helical structure of the new foldamer series in polar solvents in its OFF state, that is, *all-E* configuration, solvent titration experiments of oligomers $\mathbf{10_5}$, $\mathbf{12_6}$, and $\mathbf{14_7}$ were conducted and monitored by UV/Vis absorption as well as CD spectroscopy. Upon decreasing polarity caused by increasing ratios of chloroform to acetonitrile, evolution of a second absorption band located at around 310 nm was observed (Figure 1, left), thus indicating the population of *transoid* conformations and hence unfolding.[6] This result is supported by the corresponding CD spectra that show a decreasing Cotton effect upon an increase in the amount of chloroform (Figure 1, right). This observation indicates that excess *P*-helicity[9] is only induced by the chiral side chains in solutions with a high content of acetonitrile, thus suggesting that the backbone adopts a helical conformation only in a polar environment.[10] Assuming quantitative two state folding–unfolding transitions, the corresponding helix stabilization energies of foldamers $\mathbf{12_6}$ and $\mathbf{14_7}$ in neat acetonitrile, $\Delta G(CH_3CN)$, were deduced from the resulting sigmoidal titration curves (Table 1). It is worth noting that for the shortest oligomer $\mathbf{10_5}$, no complete folding in neat acetonitrile was observed (see Figure S6[8]) because of the lack of a sufficient number of stabilizing π–π contacts; hence no helix stabilization energy could be determined. Comparison of the derived $\Delta G(CH_3CN)$ values, that is, $-2.30\,\text{kcal}\,\text{mol}^{-1}$ and $-3.45\,\text{kcal}\,\text{mol}^{-1}$ respectively, with values for our previously reported tetradecamer that has only one central azobenzene core ($\Delta G(CH_3CN) = -1.7$ kcal mol^{-1}) shows that incorporation of additional electron-withdrawing azobenzene moieties leads to enhanced helix stabilization because of energetically more favorable π–π stacking interactions.[11] From these spectroscopic investigations it is apparent that our foldamers, starting from the dodecamer $\mathbf{12_6}$, are completely folded in a helical structure in acetonitrile at room temperature in their *all-E* configuration, that is, in the dark state.

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[*] M. Sc. Z. Yu, Prof. Dr. S. Hecht
Department of Chemistry, Humboldt-Universität zu Berlin
Brook-Taylor-Strasse 2, 12489 Berlin (Germany)
Fax: (+49) 30-2093-6940
E-mail: sh@chemie.hu-berlin.de
Homepage: http://www.hechtlab.de

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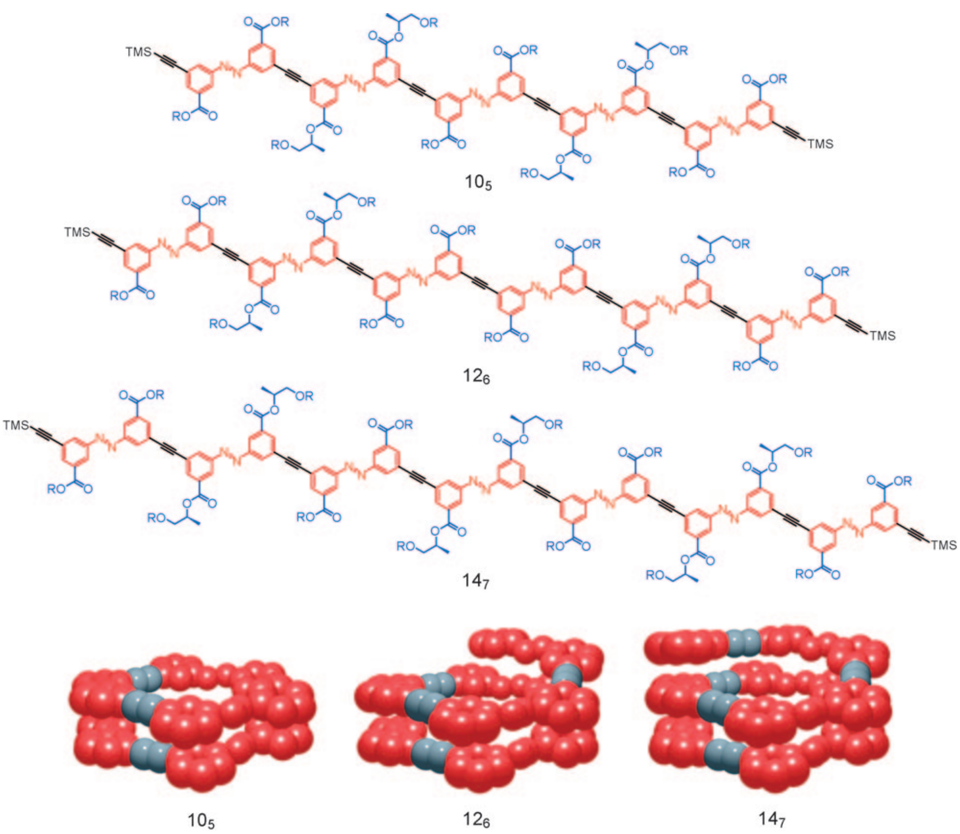

Scheme 1. Chemical structures of investigated oligomers ($R = -(CH_2CH_2O)_3CH_3$) with increasing chain length and corresponding molecular models that illustrate the approximate relative orientation of the photochromic azobenzene moieties in the helical conformation (MM2 level of theory, side chains were omitted for clarity).

Upon UV-irradiation of the folded oligomers, $E \rightarrow Z$ isomerization of the azobenzene photochromes is induced as is evident from the UV/Vis absorption spectra (Figure 2, left), which show the typical features of both a $\pi \rightarrow \pi^*$ transition that decreases in intensity at 310 nm and an $n \rightarrow \pi^*$ transition that increases in intensity at 450 nm. Owing to the cross-conjugated backbone that leads to an electronic decoupling and hence additive behavior of the chromophores, isosbestic points are observed at 405 nm in all cases, despite complex equilibria between the various isomers (number and position of Z configurations). Comparison with model compound **6**$_3$, which contains the same azobenzene units but is too short to fold into a helical structure, showed that changes in the UV/Vis spectra upon irradiation are in fact mainly due to $E \rightarrow Z$ isomerization (see Figure S8 and S9[8]).[12] In acetonitrile solution, the $E \rightarrow Z$ isomerization is associated with large structural changes and the resulting Z-configured azobenzene units cannot fit into the original helical structure, therefore leading to light-induced unfolding as apparent from the CD spectra (Figure 2, right). In the case of all three oligomers, the CD bands show a

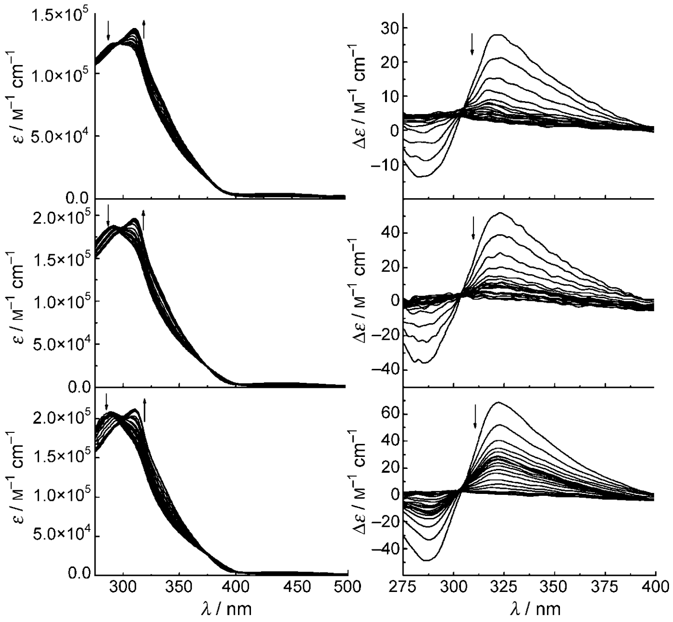

Figure 1. UV/Vis absorption (left) and CD spectra (right) of oligomers **10**$_5$ (top), **12**$_6$ (middle), and **14**$_7$ (bottom) in their *all-E* form in acetonitrile with increasing chloroform content ($CH_3CN \rightarrow CHCl_3$ with 5 vol% increments) at 25 °C.

Table 1: Folding and photoswitching behavior of oligomers **10**$_5$, **12**$_6$, and **14**$_7$ in CH_3CN at 25 °C.

		10$_5$	**12**$_6$	**14**$_7$
ΔG (CH_3CN) [$kcal\,mol^{-1}$]		n.d.[a]	-2.30 ± 0.07	-3.45 ± 0.21
k ($E \rightarrow Z$) [s^{-1}][b]		$2.62 \pm 0.05 \times 10^{-2}$	$1.53 \pm 0.08 \times 10^{-2}$	$8.35 \pm 0.20 \times 10^{-3}$
k (*unfold*) [s^{-1}][c]		$5.17 \pm 0.11 \times 10^{-2}$	$2.88 \pm 0.03 \times 10^{-2}$	$1.13 \pm 0.03 \times 10^{-2}$
Z-content in PSS [%][d]	Z_{term}	n.d.[a]	43.3 ± 0.3 %	39.8 ± 0.2 %
	$Z_{int\text{-}1}$	n.d.[a]	–[e]	24.9 ± 0.1 %[f]
	$Z_{int\text{-}2}$	n.d.[a]	27.5 ± 0.5 %	17.4 ± 0.4 %
	Z_{core}	n.d.[a]	29.5 ± 0.5 %	24.9 ± 0.1 %[f]
	Z_{av}	n.d.[a]	33.4 ± 0.4 %	27.1 ± 0.1 %

[a] $\Delta G(CH_3CN)$ could not be determined because of incomplete folding in neat CH_3CN; [b] derived from UV/Vis spectra; [c] derived from CD spectra; [d] determined by ^1H NMR spectroscopy (for terminal, internal, and core azobenzenes as shown in Figure S12–13,[8] Z_{av} = mathematical average); [e] there is only one internal azobenzene in foldamer **12**$_6$; [f] one kind of internal azobenzene (int-1) could not be distinguished from the core azobenzene and hence their average value is given.

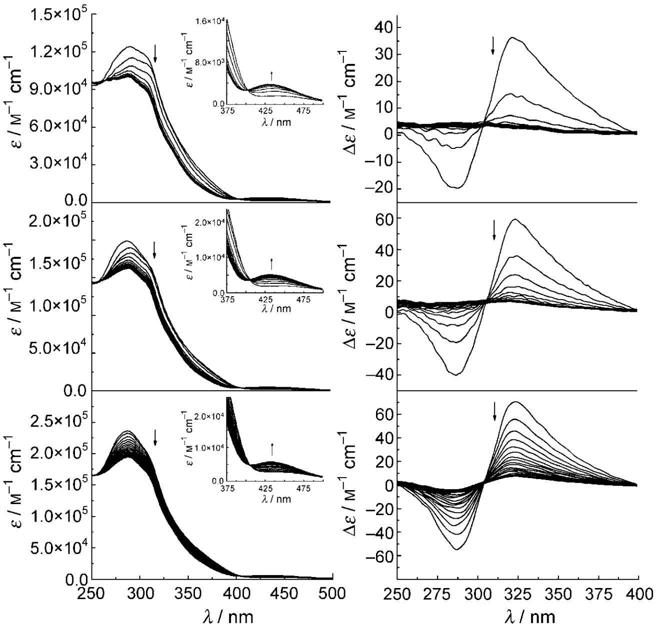

Figure 2. UV/Vis absorption (left) and CD spectra (right) of photochemical $E{\rightarrow}Z$ isomerization of oligomers **10_5** (top), **12_6** (middle), and **14_7** (bottom) during the course of irradiation at $\lambda_{irr} = 358$ nm in CH_3CN at 25 °C. The insets in the UV/Vis spectra show an enlargement of the increasing $n{\rightarrow}\pi^*$ absorption band of the azobenzene units.

dramatic decrease in signal intensity upon irradiation associated with the loss of excess helicity and therefore indicating a depopulation of the overall helical conformation, that is, helix denaturation.[13] While in the case of the longest oligomer **14_7** a small Cotton effect remains upon reaching the photostationary state (PSS), the CD signals for the shorter oligomers **12_6** and **10_5** vanish almost completely; however, in the case of **10_5** the denaturation occurs on a shorter time scale.

To better understand the complex unfolding process in our oligomers, the $E{\rightarrow}Z$ isomerization event, which is evident from UV/Vis absorption spectra, and the denaturation event, which is reflected in the CD spectra, were analyzed separately (Table 1), although both processes occur in concert. Kinetic analysis shows that both the rates of the $E{\rightarrow}Z$ isomerization as well as the denaturation increase with decreasing oligomer length, that is, in the order **14_7**→**12_6**→**10_5**.[14] As the number and location of the isomerized azobenzene moieties should be critical for the denaturation process, the exact local composition of the PSS was investigated by ^{1}H NMR spectroscopy (Table 1). In oligomers **12_6** and **14_7**, the content of Z-azobenzene in the PSS is between 17 % and 43 % depending on the location, that is, on average two azobenzene moieties are converted into their Z isomers. In both cases, the extent of $E{\rightarrow}Z$ isomerization was significantly higher for the terminal azobenzene units (Z_{term}) as compared to the internal and core azobenzene moieties (Z_{int} and Z_{core}), which show rather similar Z contents. Note that in contrast in the PSS in acetonitrile solution, model compound **6_3** has almost the same Z-azobenzene content in different locations, that is, 67 % for the core and 69 % for the terminal photochromic units, (see Figure S8 and S15[8]).

On the basis of these data, we can speculate about the overall light-induced unfolding process. The $E{\rightarrow}Z$ isomerization of an interior azobenzene unit would cause immediate unfolding, that is, only one switching event would denature the helix completely. However, this isomerization seems to constitute a less likely pathway in view of the slower kinetics of unfolding, despite the increased number of internal azobenzenes for longer oligomers, as well as the obtained average number of roughly two Z-azobenzenes in the PSS. Instead, it appears that unfolding is predominantly induced by unwinding the ends of the helix. If $E{\rightarrow}Z$ isomerization occurs at one terminus in a given oligomer with n repeat units, it leads to an oligomer with an effectively decreased chain length ($n-1$), thereby resembling its shorter "cousin" (see Figure S16[8]). Hence, only one isomerization event is necessary to completely unfold the shortest oligomer **10_5**, while on average two isomerization events are necessary to unfold the longer oligomers **12_6** and **14_7**. Note that in the case of **14_7**, even two isomerization events at the termini would result in formation of a quasi-**10_5**, which should still be partially folded, thus explaining the residual CD signal in the PSS.[15] The increased efficiency of $E{\rightarrow}Z$ isomerization at the helix termini can be explained by the lower enthalpic cost, that is, breaking of only one π–π stacking contact, while in the case of isomerizing internal as well as central azobenzene units, at least two such interactions, either to adjacent intraturn or interturn neighbors, have to be broken. In view of these arguments, it seems reasonable to assume that the isomerization events depend on one another, which means that isomerization is facilitated in proximity to a Z isomer. Considering that there should be no preference for exciting a particular azobenzene unit, the most likely overall process involves initial excitation of any azobenzene moiety in the helix, followed by rapid energy transfer between the helically stacked chromophores to a trap site, that is, the termini, undergoing the most efficient subsequent $E{\rightarrow}Z$ isomerization. Consequently, this event shifts the trap site towards the inside and leads to the progression of isomerization events towards the helix interior.

Importantly, upon irradiation with visible light ($\lambda_{irr} >$ 405 nm), the foldamers can be readily converted back into their all-E isomers, which consequently re-adopt the initial helical conformation as shown by CD spectroscopy. Repetitive switching cycles by employing alternating irradiation with UV and visible light demonstrate the full reversibility of our photoswitchable foldamers (see Figure S17 and S18[8]). Furthermore, the temporal evolution of both the UV/Vis and CD spectra during the switching cycles coincides and hence no significant time lag for both the folding and unfolding events was observed.

In summary, we have designed a new family of photoswitchable foldamers composed entirely of azobenzene repeat units and have investigated their light-induced unfolding as a function of chain length. Oligomer **12_6** shows the best performance as it is completely folded in the dark, yet rapidly, quantitatively, and reversibly unfolds upon UV irradiation. Further investigations concerned with the variation of the relative orientation of the azobenzene photochromes and the implementation of energy gradients,[16] that is, incorporation of different donor and acceptor chromophores to guide the excitation energy and hence confine $E \rightarrow Z$ isomerization to a defined location within the helix are underway. Furthermore, detailed time-resolved spectroscopic investigations will provide insight into the dynamics of the entire light-induced unfolding process, that is, the energy migration and the coupling of $E \rightarrow Z$ photoisomerization with conformational reorganization. For the future we envision to organize the optimized photoswitchable foldamer building blocks into larger assemblies to directly and hence efficiently convert light into mechanical work,[17] thus exploiting a collective and cooperative light-driven unloading of our compressed molecular "springs".

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[12] Close inspection of the UV/Vis spectroscopic changes of the foldamers reveal an additional minor component related to unfolding, which is associated with a slight increase in the *transoid* absorption band, and hence the observed less intense decrease in the region of the azobenzene $\pi \rightarrow \pi^*$ absorption, when compared to the unfolded model compound $\mathbf{6_3}$. This result evidently shows a contribution of the *transoid*-conformation to a slightly incipient increase of the ratio of $\varepsilon_{310\mathrm{nm}}/\varepsilon_{289\mathrm{nm}}$ for the foldamers (see Figure S10; ref. [8]).

[13] An alternative interpretation that involves the loss of helical twist sense bias without unfolding of the foldamers is highly unlikely as our foldamers are only weakly stabilized in the folded conformation because of their short chain lengths. In addition, the enantiopure side chains, which transfer their chiral information to the helix backbone, are attached throughout the entire helical structure (see Ref. [9]). This assumption is further supported by careful UV/Vis-spectroscopic analysis (see Ref. [11]), which shows an unfolding component (in addition to $E \rightarrow Z$ isomerization). Hence our system is in contrast to the one described in Ref. [3b].

[14] Experiments run with identical optical densities of the oligomers at the irradiation wavelength yielded the same rates within experimental error (see Figure S12 and Table S1; Ref. [8]).

[15] An alternative explanation for the residual CD signal in $\mathbf{14_7}$ that involves a small amount of *all*-(*E*) remaining in the PSS seems less likely, because it is not observed in the case of the shorter oligomers, although fewer azobenzene units increase the likelihood of the *all*-(*E*) form.

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