CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201201624

Cooperative Switching Events in Azobenzene Foldamer Denaturation

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Photoresponsive molecular systems exhibiting a high degree of sensitivity are an important prerequisite for the creation of advanced optical and photonic materials with abilities to function as controlled release systems, remote-controlled catalysts, and also memory and storage devices.[1] In particular, molecular systems based on the geometrical metamorphosis originating from the photoisomerization of azobenzene moieties have attracted significant attention because of their potential in future micro-/nano-optomechanical applications.[2] To enhance the photoresponse of the molecular system, two approaches can be followed: the intrinsic performance of the individual azobenzene photochrome can be optimized,[3] or multiple azobenzene moieties can be integrated into a larger macromolecule. In the latter case, the photochromes should at least retain their independent isomerization ability[4] and ideally they would work in concert, giving rise to cooperative behavior to be exploited. In this context, we[5] and others[6] have designed photoswitchable foldamers in which the photoisomerization event triggers a cooperative (un)folding transition. However, cooperativity thus far only arises from the transduction mechanism, that is, the conformational helix–coil transition subsequent to photoactivation.[7] Herein, we investigate the interconnection between individual photoswitching events initiating the light-induced (un)folding process, and for the first time we were able to unravel a foldamer that displays positive cooperativity with regard to the primary photoactivation step.

To reveal the relationship between individual photoisomerization events and their influence on the cooperative folding transition, we designed and synthesized a series of regioisomeric oligo(*meta*-phenylene ethynylene) foldamers with only two photochromic azobenzene units, placed symmetrically at different locations in the backbone. Limiting complexity by restricting the number of possible isomers to three only, that is, *E,E* and *E,Z* as well as *Z,Z*, allows the contributions of these individual isomers in the (un)folding process to be quantified, both in terms of photochemical reactivity (quantum yield) and conformational preferences (helicity).[8] Three oligo(*meta*-phenylene ethynylene) foldamers were chosen as target structures: **12_2-*term***, **12_2-*int***, and **12_2-*core***, where the two azobenzene moieties were placed symmetrically either in the termini or the interior or the core (Scheme 1). The length of the backbone was chosen to amount to 12 phenylene repeat units, which has been shown to be the minimal length to assure for complete folding of the parent oligo(*meta*-phenylene ethynylene) foldamers in acetonitrile at room temperature.[9] To force folding of these oligomers in acetonitrile solution, polar oligo(ethylene glycol) side chain have to be attached to each repeat unit by electron-deficient ester linkages.[10] Furthermore, chiral lactate-derived oligo(ethylene glycol) side chains[5a] were introduced to bias the twist sense in the helical conformation, thereby allowing the conformational behavior to be monitored by circular dichroism (CD) spectroscopy. The target compounds were subsequently characterized with regard to their structure, composition, and purity by various techniques, including ^{1}H NMR spectroscopy and MALDI-TOF mass spectrometry as well as UPLC coupled to UV/Vis and mass detection.[11]

The conformational transition of the prepared foldamers was characterized by typical denaturation experiments involving solvent titration in combination with UV/Vis and CD spectroscopy. Upon addition of chloroform to the acetonitrile solutions, all three oligomers undergo an unfolding transition from a helical conformation to a random coil, as shown by the increasing *transoid* absorption band in the UV/Vis spectra that is located at approximately 310 nm (Supporting Information, Figure S6, left) as well as vanishing Cotton effects in the CD spectra.[11,13] Analysis of the solvent denaturation experiments shows that all three oligomers adopt stable helical conformations in acetonitrile and provides the corresponding helix stabilization energies $\Delta G(\mathrm{CH_3CN})$ (Supporting Information, Table S1). The stability of the helices is dramatically increased when the two azobenzenes are relocated from the termini towards the center of the backbone. We attribute this finding to the fact that the stronger π,π stacking interactions involving electron-deficient azobenzenes are further enhanced in the core owing to the lower local degree of freedom as compared to the termini, where the last azobenzene units are bound more loosely, giving rise to a weaker stacking. In comparison, the foldamer composed entirely of azobenzene units, **12_6**, adopts an even more stable helical structure with $\Delta G(\mathrm{CH_3CN}) = -2.30\ \mathrm{kcal\,mol^{-1}}$, thus illustrating the general stabilizing effect of azobenzene–azobenzene stacking interactions.[5c] In

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201201624.

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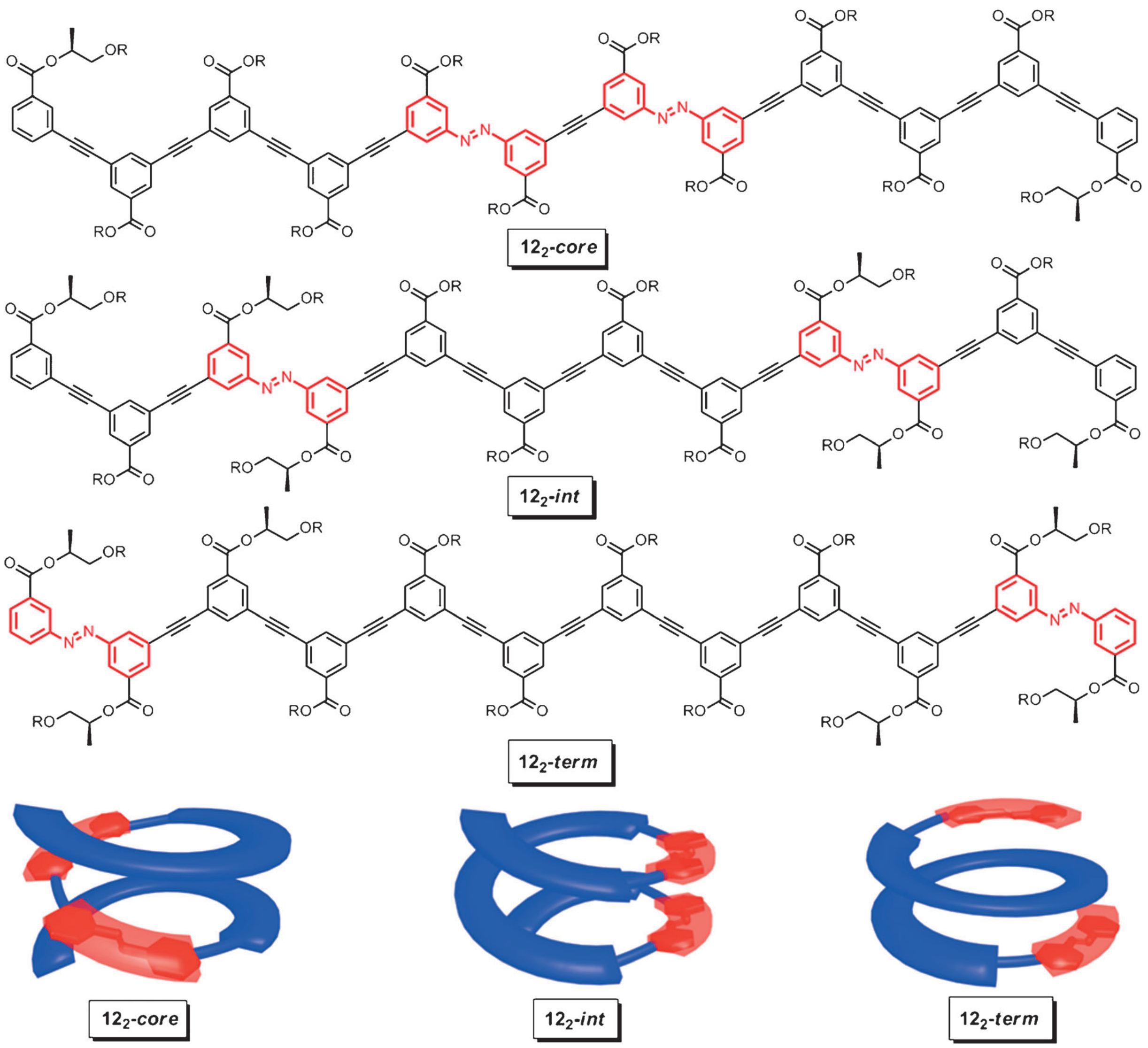

Scheme 1. Chemical structures of investigated oligomers **12_2-*term***, **12_2-*int***, and **12_2-*core*** ($R=(CH_2CH_2O)_3CH_3$) and (below) corresponding representations of the helical structures and the respective positions of the azobenzene photochromes (shown in red).[12]

addition to UV/Vis monitoring, the Cotton effects present in the CD spectra of all foldamers in polar solvents completely vanished in pure chloroform owing to the absent solvophobic driving force for helix formation.[14]

Exposure of photochrome-containing foldamers to UV light induces *E*→*Z* isomerization of the azobenzene moieties that subsequently leads to unfolding,[5,6] which was confirmed by CD and UV/Vis spectroscopy. During the course of irradiating samples of the foldamers with UV light ($\lambda_{irr}=365$ nm), the recorded absorption spectra show decreasing π,π^* absorption maxima at 284 nm on the one hand and increasing n,π^* absorption maxima at about 450 nm on the other (Supporting Information, Figure S6, right). Both features are reminiscent of azobenzene *E*→*Z* photoisomerization reactions. Simultaneously, the Cotton effect of all foldamers in the CD spectra (Figure 1 a) decreases during irradiation, indicating denaturation of the foldamers during the course of *E*→*Z* photoisomerization.

It should be emphasized that CD spectroscopy measures the excess of one helical screw sense over the other. The observed decreasing CD signal intensities are therefore related to a loss of excess helicity, which can originate from the helix–coil transition (unfolding) as well as a change in twist sense bias (chirality transfer from the side chains). While the former scenario is generally assumed to be the case when using CD spectra as evidence for photoinduced helical collapse, the latter could thus far not be excluded. However, by comparing the CD spectral changes with the evolution of the individual isomers as determined by an independent analytical method, that is, UPLC, we are now able to reveal the intrinsic helicity of each isomer and hence analyze all of the individual contributions to overall helicity as measured by CD.

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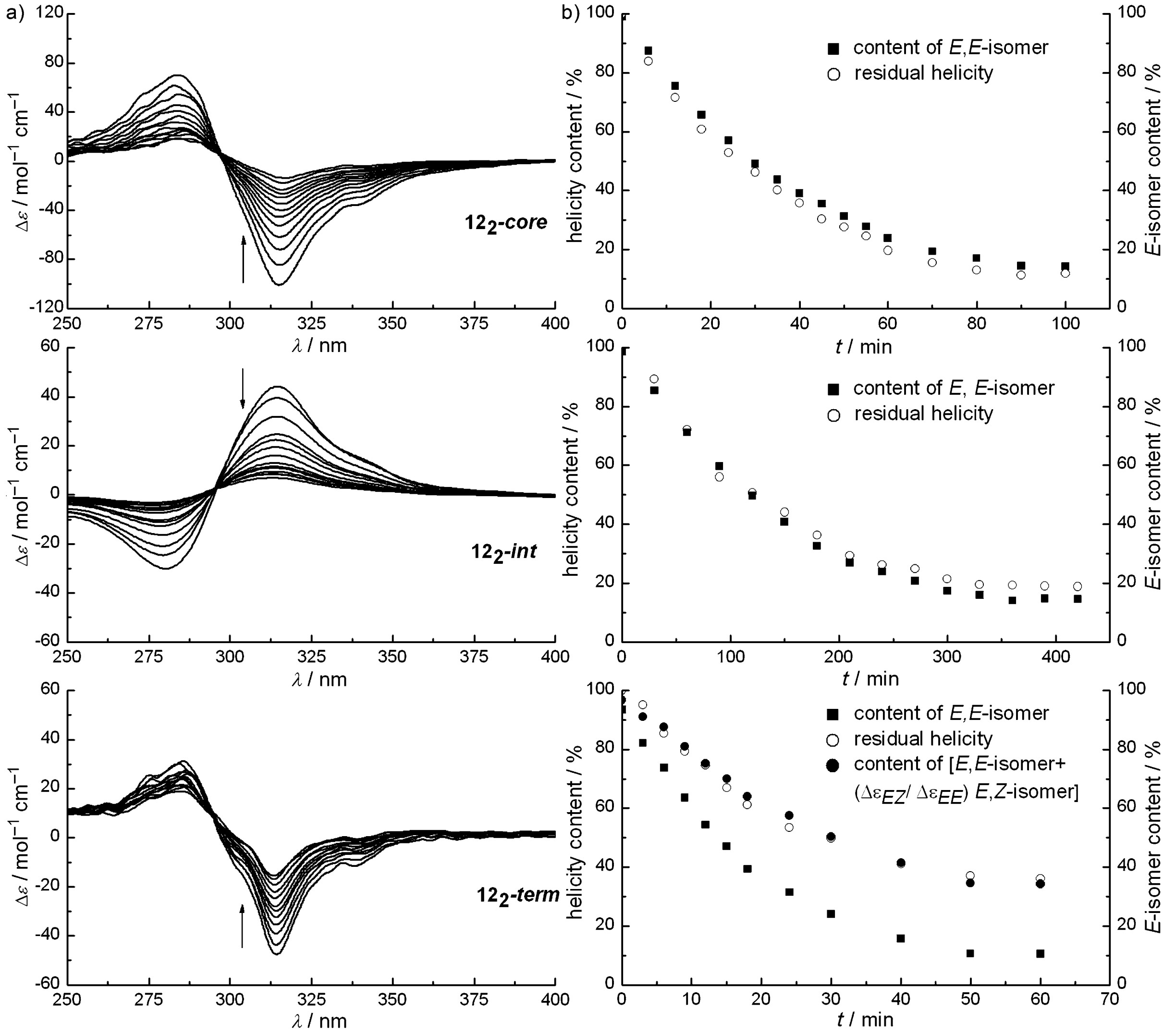


Figure 1. a) CD spectra of photochemical $E \rightarrow Z$ isomerization for all three foldamers during the course of irradiation at $\lambda_{irr}=365$ nm in CH_3CN at 25 °C. b) Corresponding relative intensities of Cotton effect and isomer ratios during the course of irradiation.[15]

In this symmetrical bisazobenzene system, the three relevant species, that is, *E,E*, *E,Z*, and *Z,Z* isomers (Figure 2) present at the photostationary state (PSS) in both acetonitrile and chloroform solutions vary between 1.9 % and 68.7 % as determined by UPLC (Table 1, top). In acetonitrile solution, the content of the *E,E* isomers were depleted to a comparable level, that is, 14.2 %, 14.6 %, and 10.7 %, while simultaneously the contents of the *Z,Z* isomers were enhanced to 48.9 %, 55.4 %, and 42.9 % for **12$_2$-*core***, **12$_2$-*int***, and **12$_2$-*term***, respectively. In contrast, a lower content of *E,E* isomers and a higher amount of *Z,Z* isomers was observed for all oligomers in chloroform as compared to acetonitrile. As the solvent effect on the intrinsic azobenzene $E \rightarrow Z$ photoisomerization is negligible in this case,[5c] this suggests that folding generally lowers the efficiency of the photoisomerization reaction.

Assuming that the formed *Z* isomer acts as a stopper for helix formation that requires a critical chain length of ap-

Table 1. Isomer content [%] in the photostationary state of foldamers **12$_2$-*core***, **12$_2$-*int***, and **12$_2$-*term*** and corresponding quantum yields Φ [%] for all of the individual azobenzene photoisomerization events.

	12$_2$-*core*		**12$_2$-*int***		**12$_2$-*term***	
	CH_3CN	$CHCl_3$	CH_3CN	$CHCl_3$	CH_3CN	$CHCl_3$
E,E isomer[a]	14.2	6.1	14.6	3.1	10.7	1.9
E,Z isomer[a]	36.9	42.7	30.3	37.7	46.4	29.4
Z,Z isomer[a]	48.9	51.2	55.4	59.2	42.9	68.7
$\Phi_{EE \rightarrow EZ}$[b]	1.6	6.0	2.0	6.5	7.8	5.8
$\Phi_{EZ \rightarrow EE}$[b]	0.8	1.3	1.3	0.9	2.5	0.7
$\Phi_{EZ \rightarrow ZZ}$[b]	3.7	5.8	2.5	4.3	8.1	2.8
$\Phi_{ZZ \rightarrow EZ}$[b]	4.9	4.2	6.5	4.7	15.9	3.7

[a] PSS analysis was determined by integration of isomer peaks in UPLC traces monitored by absorbance at the wavelength of the isosbestic point. [b] $\Phi_{EE \rightarrow EZ}$, $\Phi_{EZ \rightarrow EE}$, $\Phi_{EZ \rightarrow ZZ}$, and $\Phi_{ZZ \rightarrow EZ}$ denote the quantum yields for the transitions (*E,E*→*E,Z*), (*E,Z*→*E,E*), (*E,Z*→*Z,Z*), and (*Z,Z*→*E,Z*), respectively. $\Phi_{EE \rightarrow EZ}$ was obtained under initial-state low conversion; that is, <5 %.

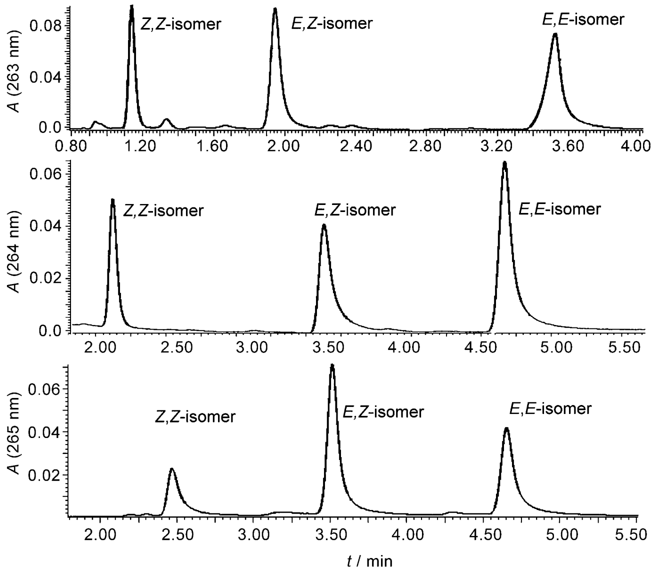


Figure 2. Representative UPLC traces during the course of irradiation showing baseline separation of all three isomers for all foldamers, that is, **12_2-*core*** (top), **12_2-*int*** (center), and **12_2-*term*** (bottom).

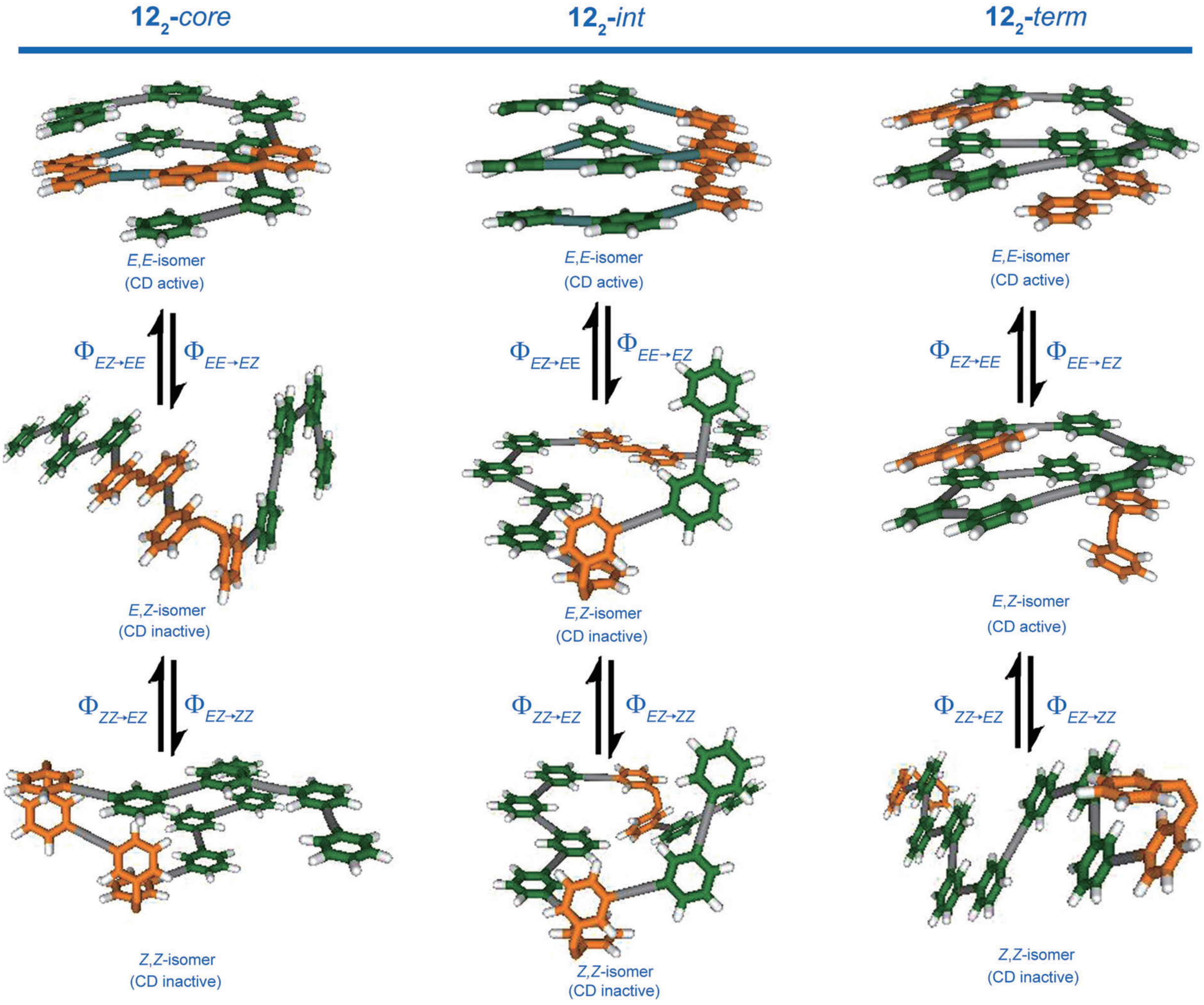
proximately 10–12 repeat units,[16] it is apparent that in **12_2-*int*** and **12_2-*core*** the helix will be completely denatured even if only one azobenzene photoisomerization event is occurring, which means the formed *E*,*Z* isomer should display no CD signal. Therefore, in the cases of **12_2-*int*** and **12_2-*core***, the *E*,*E* isomer is the sole contributor to helicity in the CD spectra, and indeed a good correlation with the *E,E* isomer contents determined from the UPLC traces was found (Figure 1b, top and center). In contrast, in the case of **12_2-*term*** the first isomerization event is not sufficient to fully denature the helix, that is, the *E,Z* isomer has a residual CD signal, and both terminal azobenzene moieties have to be isomerized for complete unfolding to occur. Therefore, for **12_2-*term***, both the *E*,*E* isomer as well as the *E*,*Z* isomer give rise to a Cotton effect, as revealed by overlaying the CD and UPLC data (Figure 1b, bottom). The molar circular dichroism $\Delta\varepsilon_{E,Z}$ associated with the *E,Z* isomer was calculated by subtracting the molar circular dichroism of the dominating *E*,*E* isomer ($\Delta\varepsilon_{E,E}$) from the overall molar circular dichroism ($\Delta\varepsilon$) of the mixture by taking into account the contents of the isomers determined by UPLC.[11] Consequently, it is worth noting that in all series of the photoswitchable foldamers, the decrease of the CD signal is directly and quantitatively correlating to the extent of denaturation; that is, the CD signal decay is a precise index of the unfolding process (Scheme 2). This finding implies that there are no significant changes on the twist sense bias in these foldamers during the photoisomerization process and furthermore no particular preference for untwisting either one of the *P* or *M* helices.

As mentioned before, the efficiency of photoisomerization is dependent on the solvent, forcing the backbone to adopt either compact helical or loose random coil conformations. Within the helix, the azobenzenes are placed at different sites with distinct local environments, that is, π,π stacking interactions and exposure to solvent. To gain further insight into the effect of the exact location of the azobenzene units in the helix structure on the photoisomerization process, the quantum yields of each individual photoisomerization event were determined. As shown in Table 1, all of the individual quantum yields upon irradiation with UV light (365 nm) are ranging from 0.7% to 15.9%. It is evident that in acetonitrile solution, foldamers show a noticeable trend of decrease of $\Phi_{EE\rightarrow EZ}$ from terminal toward core azobenzene position, that is, from 7.8% for **12_2-*term*** to 1.6% for **12_2-*core***.

The efficiencies of the subsequent photoisomerization step ($\Phi_{EZ\rightarrow ZZ}$) are similar to the initial step ($\Phi_{EE\rightarrow EZ}$) in the cases of **12_2-*core*** and **12_2-*int***, but substantially improve for **12_2-*core***. From these values (Table 1, bottom) it is apparent that photoisomerization occurs more efficiently when the respective azobenzene moiety is located at the helix terminus or in an already (partially) unfolded structure. In the case of **12_2-*term***, the two photoisomerization events are seemingly independent of one another, as the initial step does not affect the efficiency of the subsequent step. On the other hand, when the azobenzene unit is placed in the interior of the helix, its ability to isomerize is largely reduced, which is clearly due to the local environment that presumably causes additional steric and/or electronic barriers. Importantly, once the initial photoisomerization in such structure, that is, **12_2-*core***, has occurred, the subsequent photoisomerization event is greatly facilitated and thus the system exhibits (positive) cooperativity[18] with regard to its switching ability. The transduction mechanism to confer such cooperative behavior is based on the conformational transition, that is, unfolding, which creates a more flexible structure with enhanced photoreactivity. This effect, yet to a smaller extent, is also observed for the other isomer with interior azobenzene moieties, namely **12_2-*int***.

In chloroform solution, where oligomers adopt a random coil conformation, the efficiencies of the individual photoisomerization events are depending neither on azobenzene location nor on the isomerization order (with an exception of $\Phi_{EZ\rightarrow ZZ}$ in the case of **12_2-*term***). This clearly supports our findings related to the influence of the folded structure on the photoisomerization of the azobenzene moieties. Note that in general the quantum yields of *E*→*Z* photoisomerization in our foldamers are intrinsically limited, which is presumably due to the unfavorable electronic properties of such rather extended π-conjugated systems.[19] Therefore, the absolute observed effect is rather small; quantum yields increase from 1.6% to 3.7% for **12_2-*core***, yet the relative magnitude of the effect is significant, that is, the quantum yield more than doubles during the process.

The use of a photoswitchable unit confers reversibility to the system and thus the photochemically triggered refolding process of the denatured structure has also been investigated. All of the foldamers can readily be converted from the *Z* isomers into the corresponding *E* isomers upon irradiation with visible light ($\lambda_{\mathrm{irr}} > 405$ nm) and consequently readopt



Scheme 2. Sketch of photoisomerization events and the relative denaturation pathways in the three investigated foldamers.[17]

their initial helical conformation as indicated by UV/Vis and CD spectra. Employing alternative irradiation by UV and visible light, repetitive switching cycles are realized and show a temporal evolution of both UV absorption maxima and the associated Cotton effect, which demonstrate the quantitative and fully reversible light-induced unfolding–refolding ability of our photoswitchable foldamers.[11]

Considering the reverse photochemical $Z\rightarrow E$ isomerization process, the obtained quantitative data (Table 1) show the opposite trend to the light-induced $E\rightarrow Z$ isomerization (see above). In all of the foldamers, the initial photoisomerization event associated with $\Phi_{ZZ\rightarrow EZ}$ is clearly more efficient as compared to the second step, namely $\Phi_{EZ\rightarrow EE}$. The extremely low values of $\Phi_{EZ\rightarrow EE}$ in acetonitrile solution indicate the presence of partially folded intermediates, which presumably pose additional barriers for the second photoisomerization event (negative cooperativity), leading to the refolded compact helical structure. Surprisingly, and in contrast to the forward sequence, the difference in the individual quantum yields is also observed in chloroform solution, a result for which the origin remains unknown.

In summary, we have designed and synthesized a series of dodecameric foldamers with two azobenzenes symmetrically placed throughout the backbone and thus in distinct locations within the folded helix structure. The conformation of all three *E,E*, *E,Z*, and *Z,Z* isomers could be assigned and as a result the intensity of the CD signal could be established as a direct index of the unfolding and refolding process. Detailed quantum yield analyses of the investigated bisazobenzene foldamers reveal that the helix–coil transition facilitates the photoisomerization efficiencies, thus giving rise to an unprecedented positive cooperative phenomenon. Our results also clearly demonstrate the importance of the local environment for the photoisomerization reaction, similarly to such reactions in biological systems, for example, retinal or rhodopsin.[20] From the perspective of constructing light-responsive macromolecules and assemblies with extreme sensitivity, the design of cooperative switching systems and their interfacing with other cooperative mechanisms, such as folding, is highly promising. Such a design principle allows the light stimulus to be efficiently translated into large conformational changes and thus paves the way to

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new optomechanical materials,[21] among others. Along these lines, ongoing research in our laboratories is devoted to designing more extended foldamer systems to increase the light-induced change in aspect ratio and to integrating them in larger objects and materials. It is clear that for achieving this goal the proper balance between efficient photochemistry and its optimal transduction into maximum conformational changes has to be found.

Acknowledgements

Generous support by the German Research Foundation (DFG with SFB 765) is gratefully acknowledged. BASF AG, Bayer Industry Services, and Sasol Germany are thanked for generous donations of chemicals.

Keywords: azobenzenes · cooperativity · foldamers · photochromism

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[12] In our nomenclature, the number 12 denotes the number of phenylene repeat units, the subscript 2 denotes the number of azobenzene units, and the suffixes *term*, *int*, and *core* denote the azobenzene location at the termini, interior, and the core, respectively.

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Received: May 9, 2012
Published online: ■■ ■■, 2012

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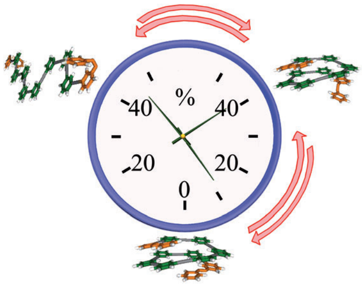
Insight into the mechanism of photoswitchable foldamer denaturation was gained by incorporating two azobenzene switching units (see figure; orange) into the helix backbone. Optimizing the location of the units leads to cooperative photoisomerization events, causing complete unfolding. The switching cooperativity coupled with the cooperative unfolding transition enables the design of highly photosensitive systems.



Cooperative Switching

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