Communications

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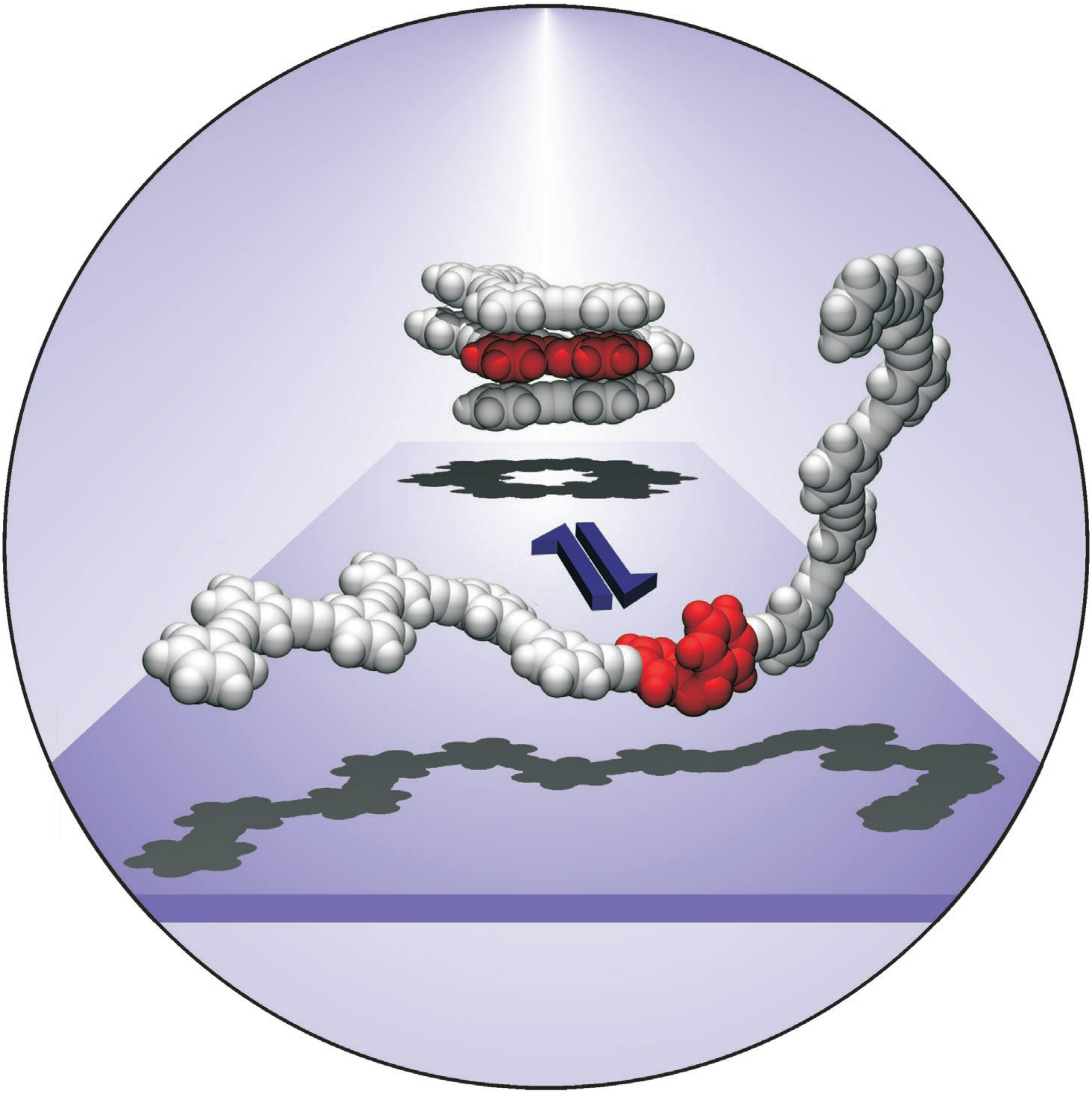

Irradiation of a foldamer bearing a central photochromic azobenzene moiety causes unfolding of the hollow helical secondary structure—a first step towards the design of smart delivery vehicles. For more details, see the communication by S. Hecht and co-workers on the following pages. (Graphic generated by Ragnar S. Stoll.)

Foldamers

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Prototype of a Photoswitchable Foldamer**

*Anzar Khan, Christian Kaiser, and Stefan Hecht**

The formation of secondary structures, for example in proteins, can be mimicked by foldamers,[1] which can adopt stable, usually helical conformations in solution. Research in this area has advanced tremendously in recent years and is of great interest in the bio- and nanosciences. Foldamers are ideally suited for the design of responsive materials because of the dynamic nature of the reversible folding reaction. However, switching between the foldamer conformations typically involves changes in temperature or solvent composition.[1] Alternative stimuli such as pH[2] and metal coordination[3] involve the addition of acid or base and metal cations, respectively, and are therefore associated with the formation of by-products. Clearly, the use of light as a noninvasive stimulus that can be applied with precise control over timing, location, and intensity of exposure would be highly desirable. Photochromic molecules[4] have frequently been utilized to switch a variety of molecular and materials properties,[5] including, for example, photomodulation of the helix–coil equilibrium in linear peptides.[6]

Herein, we report the first example of a photoswitchable foldamer. Our concept is based on the incorporation of a photoisomerizable core into a foldamer strand (Figure 1). Two backbone segments are joined by the photoresponsive core such that the entire strand is long enough to be able to fold into a helical conformation. Irradiation causes a significant geometrical change of the core caused by photoisomerization, which results in denaturation of the helix because each individual backbone segment is too short to adopt a stable helical conformation. Thermal (or photochemical) isomerization reverses the switching process and produces the initial, helically folded state.

Figure 1. Photoswitchable foldamers: Irradiation of the photoisomerizable kinked unit (red) in the middle of a helically folded backbone (blue) induces a reversible helix–coil transition.

Our system is based on amphiphilic oligo(*meta*-phenylene ethynylene) foldamers, which were pioneered by Moore and co-workers.[7] The introduction of a kinked and planar, *meta*-connected *trans*-azobenzene, which closely mimics the structure of a dimeric repeat unit, into the center of a dodecamer leads to target structure **1** (Scheme 1).[8] The lengths of the two oligomer segments were deliberately chosen to allow folding of the entire strand but not the individual parts. The azobenzene core was optimized so that it could be excited selectively, and novel enantiomerically pure (*S*)-α-methyltetra(ethyleneglycol) side chains were introduced to bias the sense of the helical twist and thereby allow monitoring of the conformational transition by means of circular dichroism (CD) spectroscopy.[9]

The folding behavior of oligomer **1** was investigated by using typical solvent-dependent denaturation experiments by monitoring the conformational equilibrium with UV/Vis absorption spectroscopy (Figure 2).[7] The sigmoidal shape of the resultant titration curve is indicative of a cooperative folding process, and detailed analysis reveals a helix stabilization energy in pure acetonitrile of $\Delta G(\mathrm{CH_3CN}) = -1.7\ \mathrm{kcal\,mol^{-1}}$.[9] Therefore, replacement of the central dimeric phenylene ethynylene unit in the native tetradecamer[7] with the azobenzene core leads to only slight destabilization of the helix; this destabilization is attributed to weaker π,π-stacking interactions caused by the presence of electron-donating methoxy substituents.[10]

Irradiation at 365 nm of the helically folded $\mathbf{1}_{trans}$ to excite selectively the central azobenzene chromophore led to rapid conversion into the corresponding $\mathbf{1}_{cis}$ as monitored by UV/Vis absorption spectroscopy (Figure 3a). A decrease in the π–π* (350–400 nm) absorption, a small increase in the n–π* (400–450 nm) absorption, and an increase in the π–π* (< 265 nm) absorption, as well as two well-defined isosbestic points at 265 and 418 nm are observed. These absorbance changes are indicative of the *trans*→*cis* photoisomerization process.[4] Whereas the photochemical $\mathbf{1}_{trans} \rightarrow \mathbf{1}_{cis}$ conversion takes place within seconds, the thermal $\mathbf{1}_{cis} \rightarrow \mathbf{1}_{trans}$ reversion occurs over the time frame of several hours at room temperature.

To monitor the conformational changes during both the forward and reverse isomerization processes, CD spectra of solutions of **1** were recorded in solvent mixtures that promote folding (Figure 3b).[11] The CD spectrum of $\mathbf{1}_{trans}$ in aqueous acetonitrile shows a strong positive Cotton effect, which is indicative of the helical conformation, while no CD signal has been observed in denaturing solvents, such as chloroform. The CD signal arises from exciton coupling within the helical backbone and is the result of chirality transfer from the chiral side chains of the core to the helix. Interestingly, the observed spectral shape, which indicates a *P*-helical twist sense, is exactly opposite to that of oligomers carrying side chains with the chiral methyl group in β position.[9] Although irradiation

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[*] A. Khan, C. Kaiser, Dr. S. Hecht
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2979
E-mail: hecht@mpi-muelheim.mpg.de

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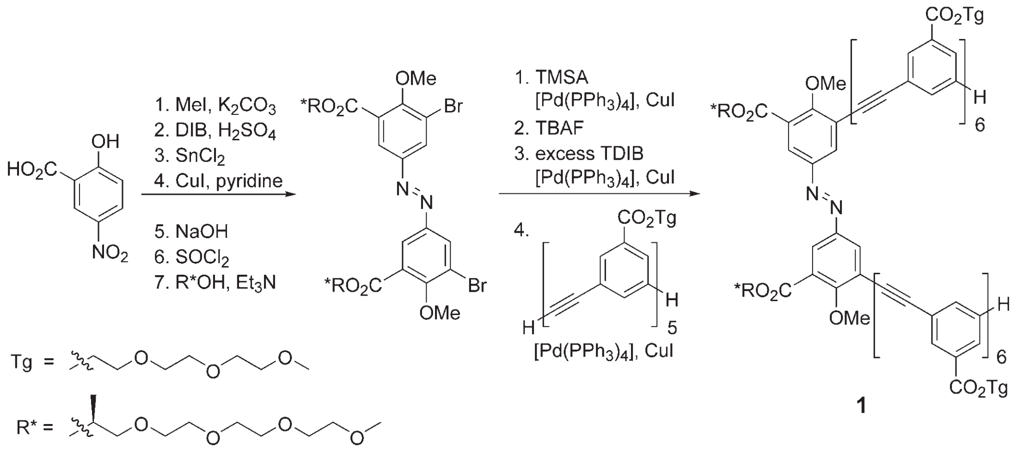
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Synthesis of photoswitchable foldamer **1**. DIB = dibromoisocyanuric acid, TMSA = trimethylsilylacetylene, TBAF = tetrabutylammonium fluoride, TDIB = triethyleneglycol 3,5-diiodobenzoate.

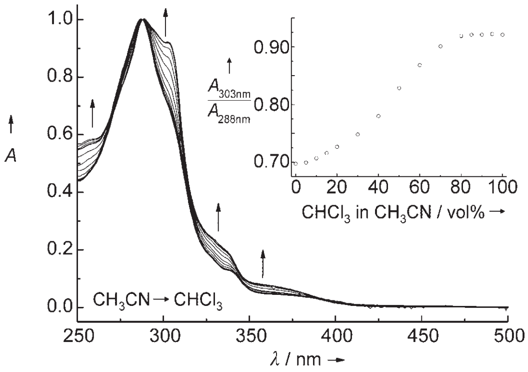


Figure 2. UV/Vis absorption spectra of **1** in acetonitrile (4.7×10^{-6} M) with increasing chloroform content (100 vol% $CH_3CN \rightarrow$ 100 vol% $CHCl_3$) at 25 °C. The inset shows the absorbance ratio $A_{303\,nm}/A_{288\,nm}$ as a function of solvent composition.

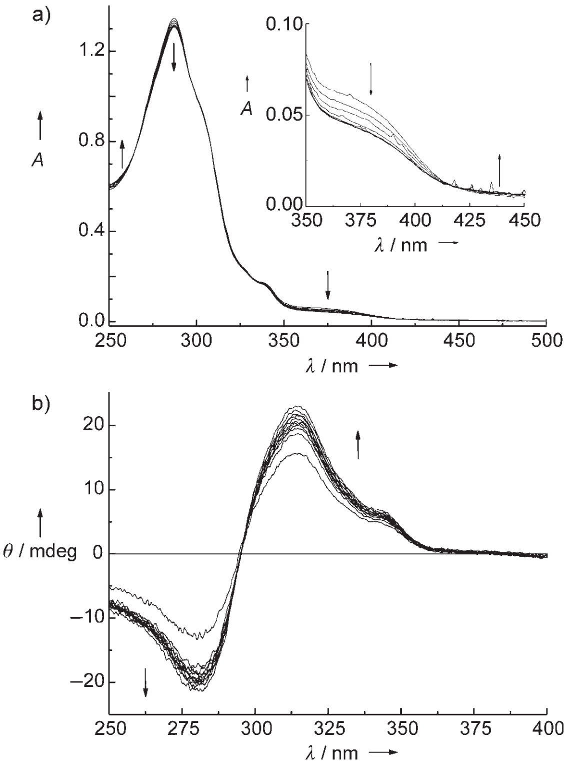


Figure 3. a) UV/Vis absorption spectra obtained during photochemical *trans*→*cis* isomerization of **1** caused by irradiation at 365 nm in acetonitrile (5.9×10^{-6} M) at 25 °C ($t = 0, 1, 3, 7, 15, 31, 63$ s). The inset shows a magnification of the decreasing π–π* absorption band of the azobenzene unit. b) CD spectra obtained during thermal *cis*→*trans* isomerization of **1** in 60 vol% H_2O in CH_3CN (5.7×10^{-6} M) at 22 °C (starting at PSS: $t = 0, 1.5, 3, 4.5, 7.5, 10, 48, 53, 72$ h).

leads to rapid decrease of the CD signal, which indicates depletion of the helical conformation through unfolding, thermal reversion leads to complete recovery of the initial CD signal intensity, thus indicating refolding of the backbone.[12] The presence of a distinct isodichroic point at 295 nm suggests a clean conversion between the two conformations. Surprisingly, the observed conformational transition is not evident from the band shape of the UV/Vis absorption spectra. The composition of the mixture in the photostationary state (PSS) can be deduced directly from the ratio of the CD signals ($\mathbf{1}_{cis}/(\mathbf{1}_{cis}+\mathbf{1}_{trans}) \approx 40\,\%$).[8] Analysis of the data also provides the rate constant for the thermal *cis*→*trans* isomerization $k_{cis\rightarrow trans}$ at 25 °C of approximately $3.8\times10^{-5}\,s^{-1}$, which corresponds to a half-life $t_{1/2}$ of around 5 h and an activation energy $\Delta G^{\neq}$ of approximately 23.5 kcal mol^{-1}; these values are typical for azobenzene-based macromolecules in solution.[13]

We have designed a photochromic foldamer and demonstrated switching of the helix–coil folding transition. Light-triggered systems such as **1** can provide fundamental insight into the folding and unfolding mechanisms by enabling time-resolved measurements[14] and promise applications in photoresponsive (bio)materials[5,15] and smart delivery devices based on photoresponsive dynamic receptors.[16] Our work in progress is focused along these directions, in particular, on the extension of the described system to photoresponsive polymeric folding backbones with increased *cis* content in the PSS.

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[1] D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893–4012.

[2] a) C. Dolain, V. Maurizot, I. Huc, *Angew. Chem.* **2003**, *115*, 2844–2846; *Angew. Chem. Int. Ed.* **2003**, *42*, 2738–2740; b) E. Kolomiets, V. Berl, I. Odriozola, A.-M. Stadler, N. Kyritsakas, J.-M. Lehn, *Chem. Commun.* **2003**, 2868–2869.

[3] a) M. Barboiu, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5201–5206; b) M. Barboiu, G. Vaughan, N. Kyritsakas, J.-M. Lehn, *Chem. Eur. J.* **2003**, *9*, 763–769; c) R. B. Prince, T. Okada, J. S. Moore, *Angew. Chem.* **1999**, *111*, 245–249; *Angew. Chem. Int. Ed.* **1999**, *38*, 233–236.

[4] a) *Photochromism—Molecules and Systems* (Ed.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **2003**; b) *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**; c) Special Issue: "Photochromism: Memories and Switches", *Chem. Rev.* **2000**, *100*, 1683–1890; d) *Organic Photochromic and Thermochromic Compounds* (Eds.: J. C. Crano, R. J. Guglielmetti), Kluwer Academic/Plenum Publishers, New York, **1999**; e) *Organic Photochromes* (Ed.: A. V. El'tsov), Consultants Bureau, New York, **1990**.

[5] S. Hecht, *Small* **2005**, *1*, 26–29, and references therein.

[6] For the side-chain approach, see: a) O. Pieroni, A. Fissi, N. Angelini, F. Lenci, *Acc. Chem. Res.* **2001**, *34*, 9–17; for the tether approach, see: b) G. A. Woolley, *Acc. Chem. Res.* **2005**, *38*, 486–493; for related polyisocyanates with azobenzene-containing side chains, see: c) S. Mayer, R. Zentel, *Prog. Polym. Sci.* **2001**, *26*, 1973–2013.

[7] a) J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, P. G. *Science* **1997**, *277*, 1793–1796; b) R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 3114–3121; for a recent review, see: c) C. R. Ray, J. S. Moore, *Adv. Polym. Sci.* **2005**, *177*, 91–149.

[8] See the Supporting Information.

[9] For the use of (*S*)-β-methyltri(ethyleneglycol) side chains, see: a) R. B. Prince, L. Brunsveld, E. W. Meijer, J. S. Moore, *Angew. Chem.* **2000**, *112*, 234–236; *Angew. Chem. Int. Ed.* **2000**, *39*, 228–230; b) R. B. Prince, J. S. Moore, L. Brunsveld, E. W. Meijer, *Chem. Eur. J.* **2001**, *7*, 4150–4154.

[10] For related examples, see: a) S. Lahiri, J. L. Thompson, J. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 11315–11319; b) H. Goto, J. M. Heemstra, D. J. Hill, J. S. Moore, *Org. Lett.* **2004**, *6*, 889–892.

[11] Solutions in aqueous acetonitrile were used for the CD experiments to maximize the CD signal as a result of the increased hydrophobic driving force and therefore ensure more accurate kinetic data.

[12] An alternative explanation to account for the CD spectral changes would be a transition to a more loosely packed helical conformation. Although this conformation is rather unlikely because of the inherent strain caused by the incorporation of the nonmatching and nonplanar azobenzene core, it cannot be ruled out at present time. Fluorescence emission spectroscopy, which is a complementary experimental technique for monitoring the helix–coil transition, was found inapplicable in this particular system, and both HPLC and gel permeation chromatography have not been able to completely resolve the $\mathbf{1}_{trans}/\mathbf{1}_{cis}$ mixture.

[13] For example, see: L.-X. Liao, F. Stellacci, D. V. McGrath, *J. Am. Chem. Soc.* **2004**, *126*, 2181–2185.

[14] For example, see: W. Y. Yang, R. B. Prince, J. Sabelko, J. S. Moore, M. Gruebele, *J. Am. Chem. Soc.* **2000**, *122*, 3248–3249.

[15] For an elegant example, see: a) A. Koçer, M. Walko, W. Meijberg, B. L. Feringa, *Science* **2005**, *309*, 755–758; for a recent review, see: b) K. Kinbara, T. Aida, *Chem. Rev.* **2005**, *105*, 1377–1400.

[16] R. B. Prince, S. A. Barnes, J. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 2758–2762.