Foldamers

Light-Controlled Conformational Switch of an Aromatic Oligoamide Foldamer

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Abstract: An aromatic oligoamide sequence composed of a light-responsive diazaanthracene-based aromatic β-sheet flanked by two variable diameter helical segments was prepared. Structural investigations revealed that such foldamers adopt two distinct conformational states: a canonical symmetrical conformation with the two helices stacked above and below the sheet, and an unanticipated unsymmetrical conformation in which one helix has flipped to directly stack with the first helix. Photoirradiation of the foldamer led to the quantitative, and thermally reversible, formation of a single photoisomer resulting from the [4+4] cycloaddition of two diazaanthracenes within the aromatic β-sheet. NMR and crystallographic studies revealed a parallel arrangement of the diazaanthracene photoisomer and a complete conversion into a symmetrical conformation requiring a rearrangement of all unsymmetrical conformers. These results highlight the potential of foldamers, with structures more complex than isolated helices, for the design of photoswitches showing nontrivial nanometric scale shape changes.

Likewise, synthetic foldamers[5] show promise in the design and fabrication of artificial systems endowed with comparable properties and constitute an underexplored approach to artificial molecular switches and motors.[6,7] Until now, most investigations have concerned isolated helically folded oligomers or polymers. Helices may undergo handedness reversal upon interacting with chiral guests, thus leading to chiral amplification and, eventually, kinetic trapping of chiral helical states,[8] or to the transfer of chiral information from one end of the helix to the other.[9] They may also undergo equilibria between folded and unfolded states triggered by light,[10] springlike extensions and contractions mediated by metal-ion binding,[11] or a change of redox state.[12] In addition, guest binding to, or release from, a helical host may be associated with single helix–double helix equilibrium,[13] with a light stimulus,[14] or with the ring contraction of a main-chain aromatic unit.[15]

Beyond isolated helices, one major challenge in foldamer science is the design of abiotic tertiary structures. Early attempts consisted of simply connecting several secondary folded modules with limited interactions between them.[16] Recent progress includes the consistent spatial arrangement of several abiotic helices,[17] as well as aromatic helix and sheet combinations.[18] The increasing size and sophistication of these structures provide opportunities for enhancing the amplitude and complexity of conformational responses to various stimuli. For instance, rotation about a single bond in a large folded object may give rise to a considerable and nontrivial change of molecular shape. Along this line, we now report the reversible, light-induced, switching between different conformations within a helix-sheet-helix aromatic amide foldamer. Specifically, we discovered a foldamer sequence that undergoes unexpected conformation dynamics leading to a noncanonical fold, and these dynamics can be reversibly controlled by means of an intramolecular photocontrol between two anthracene subunits.

The dimerization of anthracenes under irradiation by light is one of the most studied photochemical reactions. The reversible [4+4] cycloaddition of two anthracene molecules results in a photodimer connected by covalent bonds.[19] For substituted anthracenes, syn/anti and parallel/antiparallel (i.e., head-to-head and head-to-tail) isomeric products may form. Products with opposite dipole orientations are generally favored unless molecular or supramolecular constraints guide the reaction.[20–23] Thus, related 1,8-diazaanthracenes (i.e., pyrido-[3,2-g]quinolines) undergo quantitative antiparallel photodimerization in solution (Figure 1a; see Figure S1 in the Supporting Information).[24] Recently, we have shown that, when incorporated in aromatic oligoamide β-sheet foldamers, 1,8-diazaanthracene units formed parallel stacks...
observed that a related sequence having a longer, three-stranded ATATA sheet folds in a canonical manner with its two helical segments stacked on each side of the central aromatic β-sheet.\(^{[10]}\) With only two strands, as in 3, a β-sheet is expected to mediate a helix handedness reversal leading to a plane symmetrical conformation noted \((M,P)\)-s\(^3\) (see energy minimized models in Figure 2e; see Figure S17). In line with earlier observations,\(^{[10]}\) the \(^1\)H NMR spectrum of 3 in \([D\text{$_2$}]\text{acetone}\) shows one set of sharp lines whose multiplicity is favored by a better π-π overlap (Figure 1b).\(^{[18]}\) This observation led us to consider the production of parallel photoproducts guided by folding (Figure 1c). The model compound 1 was prepared to test this hypothesis (see Scheme S1). It comprises two 1,8-diazaaanthracene,\(^{[23]}\) A\(^4\), separated by a dinitro-diamino-benzene turn.\(^{[24]}\) T. Upon irradiation under anaerobic conditions at 320 < λ < 390 nm using a 50 W lamp and appropriate cutoff filters, \(^1\)H NMR monitoring showed the quantitative conversion of 1 into a single new product having the same mass in 20 minutes (see Figure S1). New signals of the former diazaanthracene H10 and H9 protons were found as singlets at δ = 5.35 and 5.70 ppm (see Figure S1). These chemical shift values are consistent with a \([4+4]\) photoreaction and the lack of H9*-scalar coupling indicates that the parallel photoproduct 2 has formed (Figure 1c; see Figures S1 and S2).\(^{[25]}\) Such a quantitative parallel photoreaction guided by folding is remarkable. It reflects not only that the antiparallel aromatic β-sheet is disfavored, but also that its conformation is not conducive of a photoreaction (see Figure S16). As expected, the reaction was shown to be thermally reversible: in C\(_2\)D\(_2\)Cl\(_2\), 2 was stable at 328 K but quantitatively converted back into 1 upon heating at 393 K for 15 hours (see Figures S3 and S4). In contrast, attempts to photochemically revert the reaction yielded by-products.

We then planned to test this photoreaction within a larger foldamer structure. The sequence 3 (Figure 1c), comprising two conical Q\(_2\)PN\(_2\) helical hexameric segments attached on both sides of a central A\(^{10}\)TA\(^4\) sheet was designed and synthesized (see Schemes S2 and S3). We have previously

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**Figure 1.** Cartoon representations of: a) an antiparallel diazaanthracene photodimer; b) a parallel arrangement of strands in a diazaanthracene β-sheet, and c) a parallel diazaanthracene photoproduct in an aromatic β-sheet. In (a,b,c) white arrows indicate local dipole orientation and blue spheres indicate nitrogen atoms. d) Color-coded formula and associated letters corresponding to amino acid, diamine, and diacid monomers. e) Oligoamide sequences 1-4. Note that 2 and 4 are the photoproducts of 1 and 3, respectively. The terminal A\(^4\) and Q units of these sequences have a methyl ester group and an 8-nitro group (instead of an 8-amino function), respectively.

**Figure 2.** Part of the 700 MHz \(^1\)H NMR spectra of 3 (1 mm) at a) 298 K in \([D\text{$_2$}]\text{acetone}\); b) 298 K in CDCl\(_3\); c) 233 K in CDCl\(_3\), and d) 213 K in CDCl\(_3\). Signals assigned to symmetrical \((M,P)\)-s\(^3\) and unsymmetrical \((M,P)\)-s\(^3\) are marked with black (●) and empty (○) circles, respectively. The black and empty squares denote the amino protons of the turn unit for \((M,P)\)-s\(^3\) and \((M,P)\)-u\(^3\); respectively. e) Side-view of the energy-minimized molecular model using Merck Molecular Force Field static (MMFFs) of plane symmetrical \((M,P)\)-s\(^3\). f) Front view of the structure in the solid state of unsymmetrical \((M,P)\)-u\(^3\). The zoom highlights the rotation of a helical segment about an amide-naphthyridine bond. A red double-headed arrow denotes a local electrostatic repulsion. g,h) Zoom on the diazaanthracene β-sheet turn unit in \((M,P)\)-s\(^3\) (from e) and \((M,P)\)-u\(^3\) (from f), respectively. The model and X-ray structures are shown in tube representation with color coded monomers as in Figure 1. Blue balls indicate endocyclic nitrogen atoms. Transparent yellow isosurfaces represent the volume of the foldamer. Hydrogen atoms, side chains and solvent molecules are not shown for clarity.
consistent with an overall symmetrical \((M,P)\)-s3 structure (Figures 2a; see Figure S5). However, the \(^1\)H NMR spectrum of \(3\) in CDCl\(_3\) revealed a more complex situation. The symmetrical species that prevails in [D\(_6\)]acetone is also present but a second set of broad signals indicates coexistence with an other species in slow exchange on the NMR time scale (Figure 2b). Upon cooling in CDCl\(_3\) down to 233 K, the proportion of this species increased to exceed 50% and signals remained somewhat broad (Figure 2c; see Figures S7 and S8). In CD\(_2\)Cl\(_2\), the signals sharpened at 243 K and below (see Figure S10), and revealed a number of amide resonances compatible with a dissymmetrical structure (Figure 2d; see Figure S10).

Solid-state investigations shed light on the conformational behavior of 3. X-ray quality single crystals were grown by slow diffusion of n-hexane into a chloroform solution.\(^{[26]}\) The solid-state structure revealed an unanticipated unsymmetrical conformation in which a helical domain has undergone a large flip to stack underneath the other helix (Figure 2f), and to which the dissymmetrical species observed in solution may tentatively be assigned.\(^{[27]}\) This conformer, which we named \(u3\), is accessible from \((M,P)\)-s3 through a 180° rotation about a single aryl–amide bond between two N units. Apart from that, both helical segments and the parallel aromatic \(\beta\)-sheet fold as expected. The single-bond rotation results in a repulsive electrostatic interaction between an amide oxygen atom and an adjacent naphthyridine endocyclic nitrogen atom (Figure 2f). This repulsion is apparently compensated by favorable contacts including through the antiparallel stacking of the second quinoline of one helix and a naphthyridine of the other helix and through the filling of the cavity of one helix by an isobutoxy side chain of the other helix (see Figure S14). These contacts would not occur for \(\beta\)-sheets with three or more aromatic strands, hence the absence of unsymmetrical conformer for longer parent sequences.\(^{[19]}\)

Moreover, the unsymmetrical conformer \(u3\) possesses a large flat aromatic surface, enabling stacking of two molecules in the solid state (see Figure S14). Conformer \(u3\) in principle exists as a mixture of two degenerate \((M,P)\) and \((P,M)\) states. The mechanism of their interconversion is unclear, in particular, whether or not it must transit through a single \(M\)-symmetrical conformation prior to photoirradiation, the overall symmetrical conformer prior to photoirradiation, the overall.

In both the crystal structure of \(u3\) and the energy minimized model of \(s3\), the two A\(^{\text{H}}\) units have a parallel orientation but are significantly offset (ca. 2.4 Å, Figures 2g,h) and not ideally preorganized for a [4+4] cycloaddition. Photoradiation of 3 in CDCl\(_3\), was nonetheless performed. Thus, a 1 mm solution was irradiated in an argon atmosphere and a photoreaction took place, albeit at a slower rate than with 1. As followed by \(^1\)H NMR spectroscopy, 80% of the starting oligomer \(3\) was converted into its photoproduct 4 after 1 hour of irradiation (Figure 4b).

The photoreacted turn is fully embedded in-between the two helices, with H9\(\#\) protons pointing towards the concave side of the sheet whereas H10\(\#\) protons point towards to convex side of the sheet (Figures 4f–h). If compared to the symmetrical conformer prior to photoradiation, the overall foldamer length increased from 2.05 to 2.15 nm as a result of photoadduct formation and also possess an enlarged cavity.

Starting from the equilibrating mixture of \(u3\) and \(s3\) conformers, light thus allows one to lock the molecule in a plane-symmetrical conformation that has been expanded by the photoreaction, and thus to remove unsymmetrical conformers (Figure 3), as when longer sheets are present. The reaction between the two A\(^{\text{H}}\) units is selective: cross-reaction with other heterocycles in the structure is avoided.\(^{[28]}\) Furthermore, the photoproduct can be thermally reverted to the mixture of \(u3\) and \(s3\). Heating 4 in CDCl\(_3\) at 328 K led to addition, the \(^1\)H NMR spectrum of 4 shows a single set of signals and indicates a symmetrical structure.
about 50% of conversion after 16 hours. Quantitative recovery of 3 required almost two days. One should note that, despite being slow, this reverse reaction is perfectly clean.

In summary, we have discovered an unanticipated unsymmetrical conformer in helix-sheet-helix foldamers, and found that the quantitative parallel photoreaction of diazaanthracenes within aromatic β-sheets exclusively and reversibly produces symmetrical conformers. The cleanliness of the photoreaction suggests that it could be implemented multiple times within a given aromatic foldamer sequence, thus leading to a global stiffening and length extension of the molecule, or that it could be reliably used to control guest binding and release. Efforts toward these objectives are currently in progress and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

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[25] Note: in the antiparallel photoproduce, these protons would appear as two doublets as the result of $J_3$ scalar coupling (see Figure S1). A detailed investigation of the photoreaction will be published elsewhere.

[26] CCDC 1897516 (3) and 1897517 (4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[27] The NMR spectrum of freshly dissolved crystal shows that equilibrium is reached too fast to be monitored by this technique.


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