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Light Driven Control of an Aromatic Oligoamide Foldamer Conformational Switch

Bappaditya Gole,^[a] Brice Kauffmann,^[b] Victor Maurizot,^[a] Ivan Huc,^{*[c]} and Yann Ferrand^{*[a]}

Abstract: We have investigated the conformation control of a foldamer switch by light. 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 oligomers adopt two distinct conformations: 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. Photo-irradiation of the foldamer led to the quantitative, and thermally reversible, formation of a single photo-product resulting from the [4+4] cycloaddition of two diazaanthracenes within the aromatic β -sheet. NMR and crystallographic studies revealed a parallel (i.e. head-to-head) arrangement of the diazaanthracene photoproduct and a complete conversion to 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 photo-switches showing nontrivial nanometer scale shape changes.

Molecular folding constitutes a formidable tool to implement switching, controlled motion and response to external stimuli at the nanometer scale. As best exemplified by the folded conformations of proteins, complex arrays of intramolecular interactions and a hierarchical structure composed of several sheet, turn, loop and helix sub-units, may give rise to sophisticated allosteric behavior;^[1] signal transduction across e.g. bilayer membranes through subtle conformational changes mediated by guest binding or by a simple phosphorylation, as in G-protein coupled receptors;^[2] or large scale controlled molecular motions coupled to the consumption of chemical energy as performed by kinesin^[3] or myosin.^[4]

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] and spring-like 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 to single helix-double helix equilibrium,^[13] to a light stimulus,^[14] or to 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 in 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 non-canonical fold, and that these dynamics can be reversibly controlled by means of an intramolecular photoreaction 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.^[20,21] Thus, related 1,8-diazaanthracenes (i.e. pyrido-[3,2-g]quinolines) undergo quantitative antiparallel photodimerization in solution (Figure 1a and S1).^[22] Recently, we have shown that, when incorporated in aromatic oligoamide β -sheet foldamers, 1,8-diazaanthracene units formed parallel stacks favored by a better π - π overlap (Figure 1b).^[18] This observation led us to consider the production of parallel photo-products guided by folding (Figure 1c). Model compound **1** was prepared to test this hypothesis (see the supporting information for details, Scheme S1). It comprises two 1,8-diazaanthracenes^[23] A^H separated by a dinitro-diaminobenzene turn²⁴ T. Upon irradiation under anaerobic conditions at 320 < λ < 390 nm using a 50W lamp and appropriate cutoff filters, ¹H NMR monitoring showed the quantitative conversion of **1** into a single new product having the same mass in 20 min (Figure S1). New signals of the former anthracene H10 and H9 protons were found as singlets at 5.35 and 5.70 ppm (Figure S1). These

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chemical values are consistent with a [4+4] photoreaction and the lack of H9*-H10* scalar coupling indicates that the parallel photoproduct **2** has formed (Figure 1c and S1-S2).^[25] Such a quantitative parallel photoreaction guided by folding is remarkable. It reflects not only that the anti-parallel aromatic β -sheet is disfavored, but also that its conformation is not conducive of a photoreaction (Figure S16). As expected, the reaction was shown to be thermally reversible: in $C_2D_2Cl_4$, **2** was stable at 328K but quantitatively converted back into **1** upon heating at 393K for 15h (Figure S3-S4).

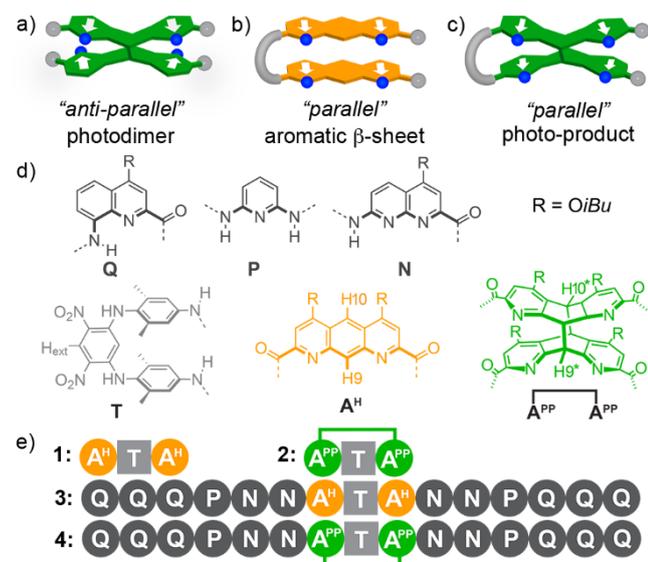


Figure 1. Cartoon representations of: (a) an antiparallel diazaanthracene photodimer; (b) a parallel arrangement of strands in a diazaanthracene β -sheet and (c) a parallel diazaanthracene photo-product in an aromatic β -sheet. In (a,b,c) white arrows indicate local dipole orientation and blue spheres 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 photo-products of **1** and **3**, respectively. The terminal A^H and Q units of these sequences have a methyl ester group and an 8-nitro group (instead of an 8-amino function), respectively.

We then planned to test this photoreaction within a larger foldamer structure. Sequence **3** comprising two conical Q₃PN₂ helical hexameric segments attached on both sides of a central A^HTA^H sheet was designed and synthesized (Scheme S2-S3). We have previously 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.^[18] 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*)-s3 (see energy minimized models in Figure 2e and S17). In line with earlier observations,^[18] the ¹H NMR spectrum of **3** in *d*₆-acetone shows one set of sharp lines whose multiplicity is consistent with an overall symmetrical (*M,P*)-s3 structure (Figures 2a and S6). However, the ¹H NMR spectrum of **3** in CDCl₃ 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 CDCl₃ down to 233K, the proportion of this species increased to exceed 50% and signals remained somewhat broad (Figure 2c and S7-S8). In CD₂Cl₂, the signals sharpened at 243K and below (Figure S10

and revealed a number of amide resonances compatible with a dissymmetrical structure (Figure 2d and S10).

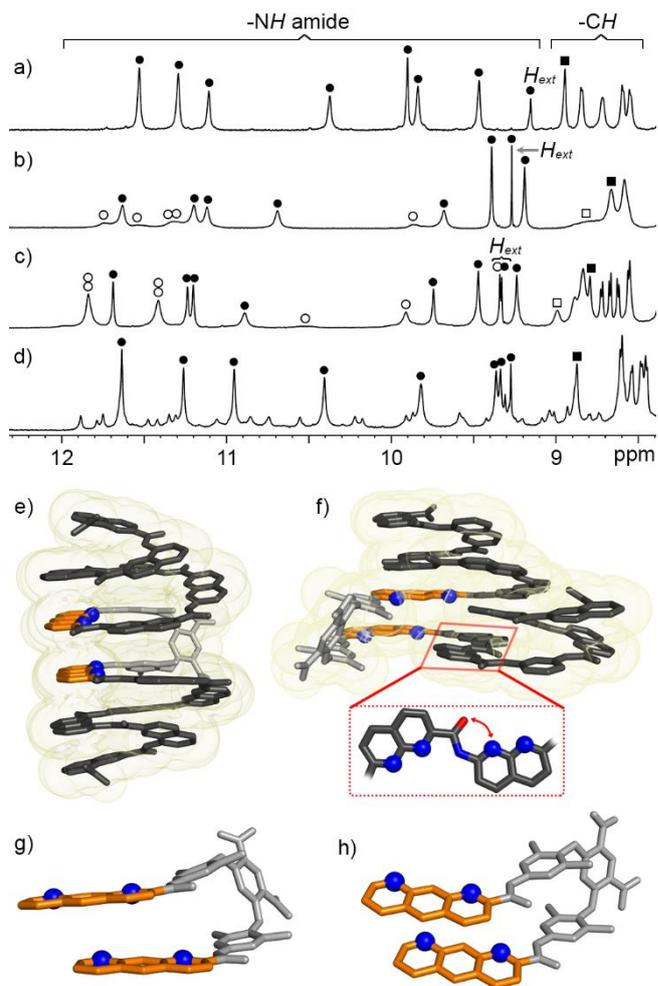


Figure 2. Part of the 700 MHz ¹H NMR spectra of **3** (1 mM) at: (a) 298K in *d*₆-acetone; (b) 298K in CDCl₃; (c) 233K in CDCl₃ and (d) 213K in CD₂Cl₂. Signals assigned to symmetrical (*M,P*)-s3 and unsymmetrical (*M,P*)-u3 are marked with black (●) and empty (○) circles, respectively. The black and empty squares denote the amino protons of the turn unit for (*M,P*)-s3 and (*M,P*)-u3; respectively. (e) Side view of the energy-minimized molecular model using Merck Molecular Force Field static (MMFFS) of plane symmetrical (*M,P*)-s3. (f) Front view of the structure in the solid state of unsymmetrical (*M,P*)-u3. 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*)-s3 (from e) and (*M,P*)-u3 (from f), respectively. The model and X-ray structures are shown in tube representation with color coded monomers as in Fig. 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.

Solid state investigations shed light on the conformational behavior of **3**. X-ray quality single crystals were grown by slow diffusion of hexane into a chloroform solution. 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 2e), and to which the dissymmetrical species observed in solution may tentatively be assigned. 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 β -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 2e). This 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 (Figure S14). These contacts would not occur for β -sheets with three or more aromatic strands, hence the absence of unsymmetrical conformer for longer parent sequences.^[18] Conformation $u3$ in principle exists as a mixture of two degenerate (M,P) and (P,M) states. The mechanism of their interconversion is unclear, and in particular whether or not it must transit through $s3$ (equilibria 1 & 2 in Figure 3).

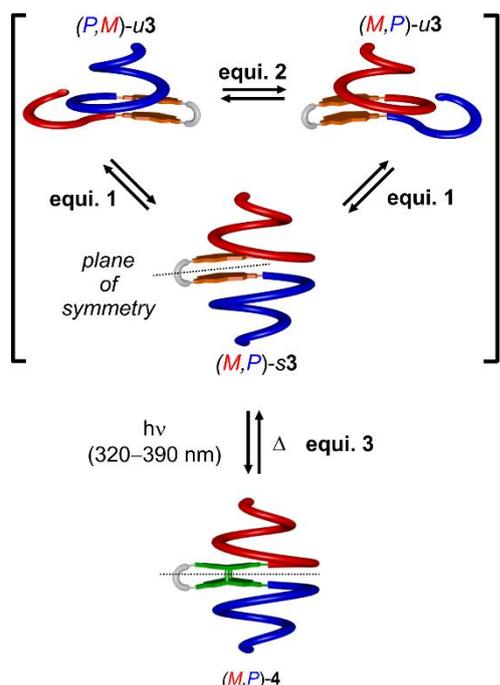


Figure 3. Schematic representation of the equilibria involved in the switching process. Equilibria 1 and 2 do not require helix handedness inversion. Yet the ensemble of $u3$ and $s3$ species is at slow equilibrium with another mirror-imaged (thus degenerate) ensemble obtained through handedness reversal of both helical segments. The thermally reversible photoreaction of the two parallel A^H units (equi. 3) locks the conformation in a plane symmetrical state. P and M helices are shown as blue and red tubes, respectively. The diazaanthracene β -sheet and its photo-product are color-coded in orange/grey and green/grey, respectively.

In both the crystal structure of $u3$ and the energy minimized model of $s3$, the two A^H units have a parallel orientation but are significantly offset (Figure 2f,g) and not ideally preorganized for a [4+4] cycloaddition. Photoirradiation of 3 in $CDCl_3$ was nonetheless performed. Thus, a 1 mM solution was irradiated under an argon atmosphere and a photoreaction took place, albeit at a slower rate than with 1 . As followed by 1H NMR, 80% of the starting oligomer 3 was converted into its photoproduct 4 after 1h of irradiation (Figure 4b). Complete conversion was reached within 4h (Figure 4c,e). The slower kinetics may be assigned to the not-ideal conformation mentioned above and to favorable interactions within $u3$ and $s3$ that must be disrupted for the reaction to take place. The parallel arrangement of the photoproduct was again ascertained by the emergence of two

singlets at 4.8 and 5.5 ppm assigned to $H10^*$ and $H9^*$, respectively. In addition, the 1H NMR spectrum of 4 shows a single set of signals and indicates a symmetrical structure.

The symmetrical conformation with a P and an M helices, and the parallel arrangement of the photoproduct were confirmed by a solid state structure of 4 . Crystals grew upon slowly diffusing methanol in a chloroform solution. The structure was solved in the P-1 space group and revealed that the helices remain above and below the butterfly-shaped photoreacted β -sheet in a canonical structure even though proper stacking onto the A^H units is no longer possible. Thus, 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 (Figure 4f-h).

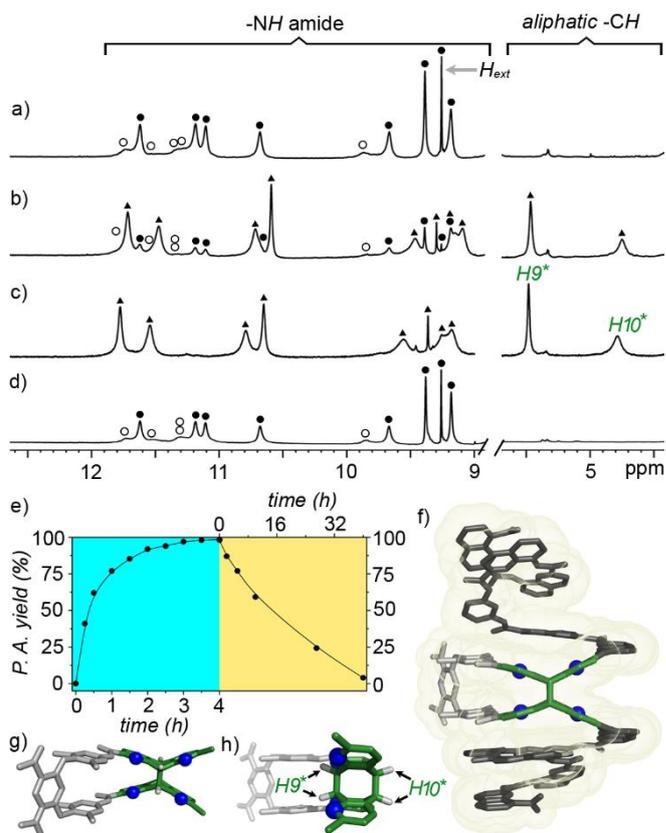


Figure 4. Part of the 700 MHz 1H NMR spectra of at 298K of 3 (1 mM in $CDCl_3$) under photoirradiation after (a) 0 min.; (b) 60 min.; (c) 4 h. (d) Evolution after incubating sample (c) at 328K for 40 h. Signals of $s3$ and $u3$ are denoted with black (\bullet) and white (\circ) circles, respectively. Black triangles indicate signals of photo-product 4 . (e) Kinetic monitoring (1H NMR) of: (left) the photoreaction of 3 yielding 4 and (right) the thermolysis of 4 back into 3 . (f) Crystal structure of 4 . (g,h) Front and side views of the photoreacted β -sheet highlighting the parallel arrangement. The structure is shown in tube representation and the monomers are color coded as in Fig. 1. Blue balls denote endocyclic nitrogen atoms. Side chains, solvent molecules and hydrogen atoms are not shown for clarity.

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^H units is selective: cross-reaction with other heterocycles in the structure is avoided.^[26] Furthermore, the photoproduct can be thermally reverted to the mixture of $u3$ and

s3. Heating **4** in CDCl₃ at 328K led to ~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 and anyway much faster than for photo-product **2** which is stable at this temperature. The lower stability of **4** possibly reflects a higher strain imposed by folding.

In summary, we have discovered an unanticipated unsymmetrical conformer in helix-sheet-helix foldamers, and found that the quantitative parallel photoreaction of diaza-anthracenes within aromatic β -sheets exclusively and reversibly produces symmetrical conformers. The cleanness 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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Keywords: foldamer • photochemistry • molecular switch • aromatic oligoamide • X-ray crystallography

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