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Selective and Cooperative Photocycloadditions within Multistranded Aromatic Sheets

Bappaditya Gole,[§,†] Brice Kauffmann,[‡] Arnaud Tron,[¶] Victor Maurizot,[§] Nathan McClenaghan,[¶] Ivan Huc,[#,‖,*] Yann Ferrand,[§,*]

[§] Univ. Bordeaux, CNRS, Bordeaux Institut National Polytechnique, CBMN (UMR 5248), 2 rue Escarpit 33600 Pessac (France)

[‡] Univ. Bordeaux, CNRS, INSERM, Institut Européen de Chimie Biologie (UMS3033/US001), 2 rue Escarpit 33600 Pessac (France)

[¶] Univ. Bordeaux, CNRS, Institut des Sciences Moléculaires (UMR5255), 351 cours de la Libération, 33405 Talence cedex (France)

Department of Pharmacy, Ludwig-Maximilians-University, Butenandtstr. 5–13, 81377 Munich (Germany)

‖ Cluster of Excellence e-conversion, 85748 Garching (Germany)

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ABSTRACT: A series of aromatic helix-sheet-helix oligoamide foldamers composed of several different photosensitive diazaanthracene units have been designed and synthesized. Molecular objects up to 7 kDa were straightforwardly produced on a 100 mg scale. NMR and crystallographic investigations revealed that helix-sheet-helix architectures can adopt one or two distinct conformations. Sequences composed of an even number of turn units were found to fold in a canonical symmetrical conformation with two helices of identical handedness stacked above and below the sheet segment. Sequences composed of an odd number of turns revealed a coexistence between a canonical fold with helices of opposite handedness, and an alternate fold with a twist within the sheet and two helices of identical handedness. The proportions between these species could be manipulated, in some cases quantitatively, being dependent on solvent, temperature and absolute control of helix handedness. Diazaanthracene units were shown to display distinct reactivity towards 4+4 photocycloadditions according to the substituent in the 9 position. Their organization within the sequences was programmed to allow photoreactions to take place in a specific order. Reaction pathways and kinetics were deciphered and products characterized, demonstrating the possibility to orchestrate successive photoreactions so as to avoid orphan units, or to deliberately produce orphan units at precise locations. Strong cooperative effects were observed in which the photoreaction rate was influenced by the presence (or absence) of photoadducts in the structure. Multiple photoreactions within the aromatic sheet eventually lead to the structure lengthening and stiffening, locking conformational equilibria. Photoproducts could be thermally reverted.

INTRODUCTION

Face-to-face π-π stacking[1] promotes both defined molecular or supramolecular structures, and specific electronic properties, in systems as diverse as nucleic acids,[2] organic reactions,[3] dye assemblies[4] and solids for organic electronics.[5] Molecules or assemblies that possess a discrete number of stacked aromatic rings bear special interest because they provide an entry into the understanding and tailoring of their physical properties. Over the years, multiple strategies have been developed to control the well-ordered stacking of a defined number of aromatic rings, either all identical, or different:[6] rigid polycyclophanes,[7] coordination cages,[8] and catenanes[9] represent conceptually distinct, yet successful approaches; flat, shape-persistent macrocycles may also be programmed to form finite aggregates with or without the assistance of a template;[10] rigid rods with hanging aromatic units may interdigitate to produce well-defined assemblies.[11] Compared to the approaches above, the folding of oligomers comprised of various aromatic monomers present the advantage of unequivocal sequence control. Thus aromatic foldamers, *i.e.* foldamers with aromatic rings in their main chain, have been designed to adopt well-defined multi-turn helical conformations involving face-to-face stacking.[12] Foldamers containing strongly dipolar aromatics, or alternating electron rich and electron poor aromatics, may form pillar-like architectures driven by favorable interactions between stacked rings.[13] Aromatic foldamer sheets have also been designed using turns that promote face-to-face arrangements of adjacent units.[3b,14,15] Several reports have evidenced remarkable charge transport within discrete aromatic stacks, probably due to charge hopping between adjacent rings, *i.e.* not just through bond but also through space.[16]

The examples cited above highlight that the control of stacked aromatic architectures is a well-developed area of research. Beyond the control of the structure lies the challenge of addressing these rings specifically so as to tune physical properties. As exemplified in rotaxanes[17] and helical foldamers[18] redox responsive units allows for the injection or withdrawal of electrons which eventually results in structural

rearrangements. Photoresponsive monomers, typically azobenzenes or diarylethenes,[19] and more rarely photocycloaddition precursors,[15e,20] have also been exploited to alter aromatic foldamer folding and their ability to bind to guest molecules. However, these systems often feature one photo- or electroresponsive aromatic unit, or multiple copies of the same unit that all respond in the same manner and amplify the effect.

In contrast, we introduce herein the possibility to involve multiple photoresponsive units with distinct reactivity, thus allowing different photoreactions to take place in a certain order within a stack of aromatic rings produced by folding of an oligomer into a sheet structure. We use the classical photoinduced anthracene [4+4] cycloaddition reaction[21] to disrupt face-to-face stacking of anthracenes through the dearomatization of their central benzenic rings (Figure 1A,B). We demonstrate that photocycloaddition rates may be tuned by placing substituents in the 9 position of the anthracene rings. Depending on the electronic and steric properties of the substituents, we show that it is possible to program photocycloadditions within a stack of anthracene rings in such a way that products having orphan anthracenes are avoided or, on the contrary, that products with orphan anthracenes at defined positions are generated (Figure 1C). The photoreactions eventually extend the sheet length and rigidify the overall architecture. We also present the unexpected discovery that photoreactions of anthracene units within a stack sometimes show positive cooperativity. In other words, that the rate of a photoreaction may be influenced by the fact that another photoreaction has taken place or not.

RESULTS AND DISCUSSION

Tuning photocycloaddition kinetics in model systems. The reversible [4+4] cycloaddition leading to the dimerization of anthracene under photoirradiation is one of the most studied photochemical reactions,[21] and has been extensively exploited in supramolecular systems.[22] In the case of substituted anthracenes, parallel and antiparallel (*i.e.* head-to-head and head-to-tail) isomeric photodimers may form. However, dipolar repulsions generally favor antiparallel isomers,[24] unless molecular or supramolecular constrains are imposed.[22,23] For example, 1,8-diazaanthracenes (*i.e.*, pyrido-[3,2-g] quinolines) undergo quantitative regioselective photodimerization in an antiparallel manner (Figure 1A) due to dipolar interactions between pyridine rings.[24c]

In the context of our studies on aromatic sheet foldamers,[15] we have introduced turn units such as dinitro-diamino-benzene T (Figure 2A), that favor a parallel orientation of appended diazaanthracene units. In these systems, photocycloadditions were shown to yield the parallel photoproduct quantitatively (Figure 1B).[15e] This observation led us to consider the effect of substitutions at the 9 position of the diazaanthracenes as a possible means to tune the efficiency of the [4+4] photocycloaddition. Herein, each diazaanthracene is noted A^X where X can be a hydrogen atom (H), a fluorine atom (F), a methyl (Me) or a methoxy (OMe) group in the 9 position (Figure 2A). To assess the effect of the substituent in the 9 position, we prepared aromatic sheet models **1**–**7** (Figures 2B and 3A) comprised of two identical or different A^X units linked by a turn T (Scheme S1-S6). Synthetic procedures and characterization of all compounds are described in the Supporting Information (SI).

Each A^X-T-A^X sheet was irradiated in degassed $CHCl_3$ using UV light (λ=320–390 nm) under anaerobic conditions using a 50 W portable mercury lamp. The occurrence of photocycloadditions was visible by the naked eye, the yellow color of the solutions becoming less intense (Figure S14). Reactions were monitored in parallel by ^{1}H-NMR and electronic absorption spectroscopy. The latter methodology, utilizing monochromatic light (λ = 365 nm) and a chemical actinometer reference, afforded accurate photoreaction quantum yields (vide

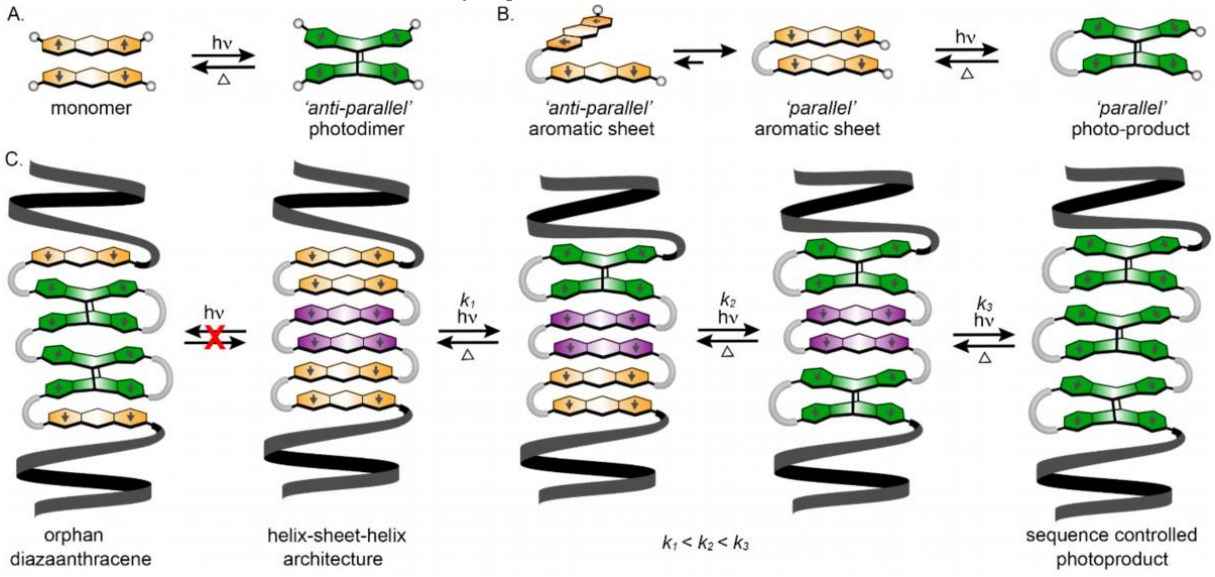


Figure 1. Schematic representation of: (A) intermolecular and (B,C) intramolecular [4+4] 1,8-diazaanthracenes photocycloadditions. Arrows shown in the aromatic rings represent local dipole orientations. (A) Intermolecular anti-parallel photocycloaddition of diazaanthracenes directed by dipole moments. (B) Anti-parallel and parallel arrangement of diazaanthracenes in an aromatic sheet. Photocycloaddition only occurs when the sheet is in its parallel configuration. (C) Cartoon representation of helix-multi-stranded sheet-helix architectures designed to undergo sequence specific intramolecular photocycloadditions. The photoproduct reverts to the starting material upon heating.

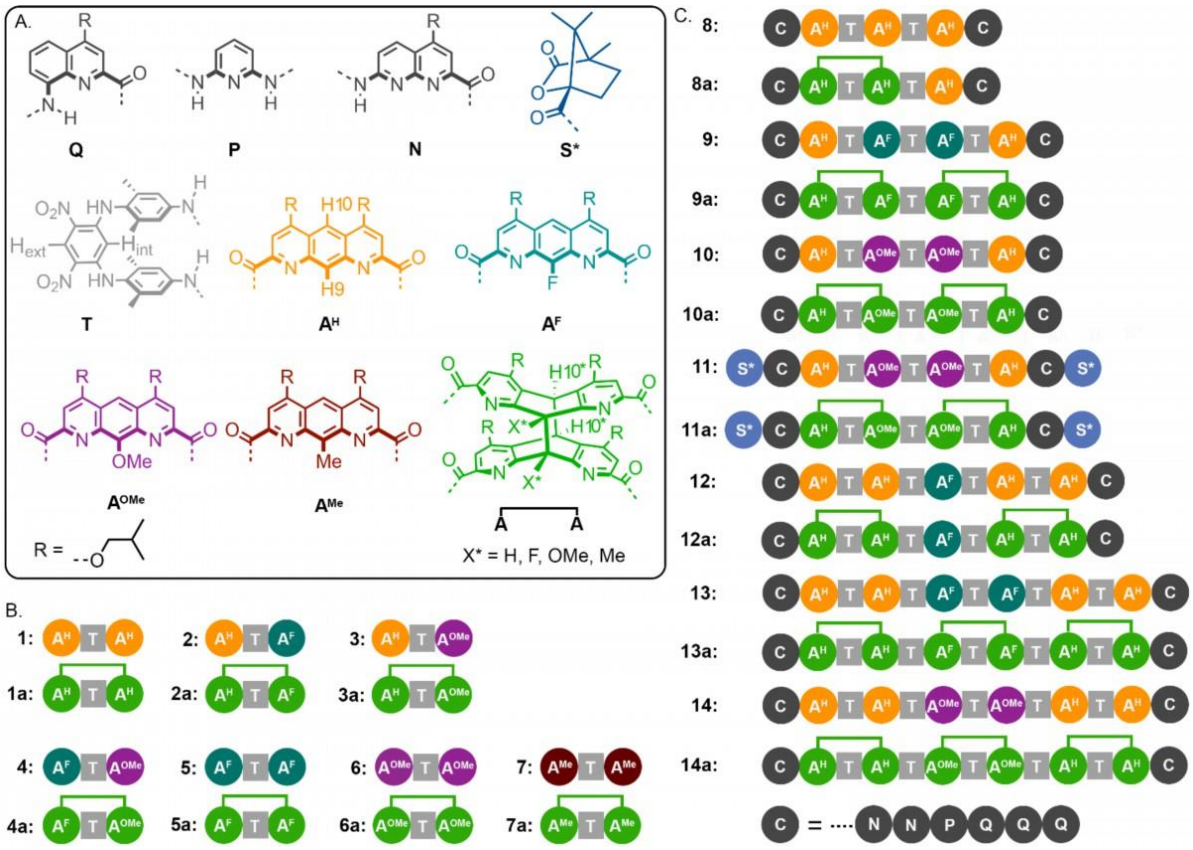


Figure 2. (A) Color coded formula and corresponding abbreviations of amino acid, diamino, and diacid monomers. (B) Sequences **1**–**7** are aromatic sheets comprised of two diazaanthracene units having various groups in the 9 position and **1a**–**7a** are their corresponding photocycloadducts. (C) **8**–**14** and **8a**–**14a** are helix-sheet-helix oligoamide sequences and their photoproducts, respectively. Terminal diazaanthracene and quinoline units bear a methyl ester group and an 8–nitro group (instead of an 8–amino function), respectively.

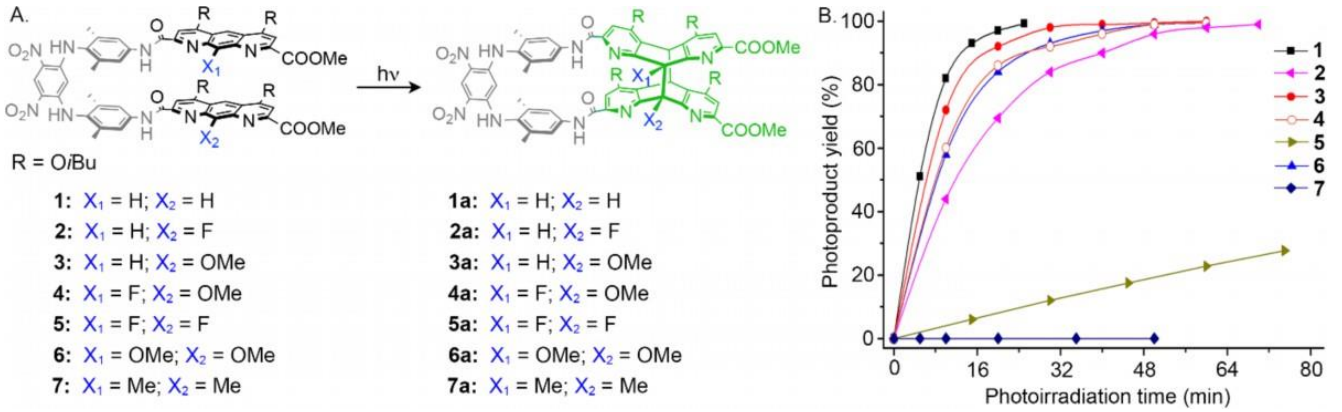


Figure 3. (A) Photocycloadduct formation from diazaanthracene sheets **1**-**7** (1 mM solution in $CHCl_3$) bearing varying substituents upon irradiation with λ = 320–390 nm under anaerobic condition. (B) Time traces showing photocycloadduct yield as a function of photoirradiation time.

infra). Results from ^{1}H-NMR monitoring are summarized in Figure 3B and show large variations of reaction rates depending on substituents. A^H-T-A^H sheet **1** reacted most efficiently (>82% completion after 10 minutes, Figure 3B) under the conditions used (Figure 2). The A^{OMe}-T-A^{OMe} sheet **6** was only slightly slower (>60% completion after 10 minutes). In contrast, the A^F-T-A^F sheet **5** underwent only 30% conversion after 75 minutes, and the A^{Me}-T-A^{Me} sheet **7** did not yield any traceable photoproduct. Nonetheless, all photocycloadditions, with the exception of A^{Me}-T-A^{Me},[25] were brought to completion and yielded a single photoproduct. Aromatic sheets composed of two different A^X moieties, for example a slow and a fast reacting unit as in A^H-T-A^F, displayed intermediate reaction kinetics (Figure 3B).

In total, seven different aromatic sheets were prepared and each exhibited different rates of photocycloaddition. Electronic absorption spectroscopy corroborated these results (see the supporting information). The photocycloaddition quantum yields for all aromatic sheets ($\Phi_{photodimer}$) have been calculated and the trends match well with the results of NMR spectroscopy studies (Table 1). In short, the results highlight that electronic factors and steric effects operate simultaneously, and may act antagonistically on the photocycloaddition efficiency. Thus, an electron-donating group such as OMe promotes the [4+4] cycloaddition, whereas a bulky Me group induces an opposite effect due steric hindrance. As expected, the photoreaction is thermally reversible in 30 h at 333 K in $CHCl_3$ (Figures S2–S12). Attempts to revert the reaction using light irradiation at 254 nm were not successful.[26]

Table 1. Photoluminescence quantum yield (Φ_{Lum}) and lifetime (τ) of substituted aromatic sheets are given along with their corresponding photoproduct formation quantum yield ($\Phi_{photodimer}$).

Oligomers	Φ_{Lum}[a]	τ[b] (ns)	$\Phi_{photodimer}$[c]
1	2.0×10^{-3} (2.9×10^{-3})	< 1	6.7×10^{-3}
2	0.1×10^{-3} (0.2×10^{-3})	< 1	2.8×10^{-3}
3	4.5×10^{-3} (6.8×10^{-3})	< 1	6.0×10^{-3}
4	6.1×10^{-3} (9.2×10^{-3})	< 1	3.4×10^{-3}
5	0.4×10^{-3} (0.6×10^{-3})	< 1	0.2×10^{-3}
6	5.3×10^{-3} (9.2×10^{-3})	< 1	3.2×10^{-3}
7	1.6×10^{-3} (2.4×10^{-3})	< 1	1.4×10^{-5}

[a] optically dilute CH_2Cl_2 solution in aerobic and anaerobic (in parentheses) conditions. [b] measured in anaerobic CH_2Cl_2. [c] measured in $CHCl_3$ (30 μM) in anaerobic condition.

Helix-sheet-helix design and synthesis. Encouraged by these results, we surmised that appropriate combinations of A^X units in a multistranded aromatic oligoamide helix-sheet-helix sequence would potentially give rise to selective and sequential intramolecular photocycloadditions, via a precise control of the photoproduct formation efficiency. We previously studied the folding of bent aromatic sheets flanked by two helices.[15d,e] Here, we have extended this design so as to incorporate up to six stacked A^X units in the central sheet segment. In our earlier work, only up to three A^{Me} units, *i.e.* units unreactive under photoirradiation, had been incorporated. Sequences **8-14** (Figure 2C) were thus synthesized and characterized (see supporting information). All comprise a central $A^x(TA^x)_n$ sheet ($2 \le n \le 5$) flanked with two terminal Q_3PN_2 helical segments. The helices have a conical shape because Q, P and N monomers (in that order) code for an increasingly large helix diameter. These helical cones are abbreviated C in the sequences (Figure 2C).

To access a large number of sequences we opted for a modular synthetic approach coupled with a convergent strategy. Practically, helical and sheet modules were prepared separately. For all the target sequences (**8-14**), we decided to use a unique hexameric helical segment Q_3PN_2 whose synthesis is fully mastered on the dozen gram scale.[15d] In parallel, the different dissymmetrical turn units A^XT were also prepared on gram scales. The helical segment was then elongated with one or two AT turns using PyBOP as a coupling agent to yield an intermediate helix-sheet segment. Finally, after a Boc deprotection of its amino function the latter was coupled twice to either an anthracene A^X diacid or an A^X-T-A^X turn diacid to produce the desired helix-sheet-helix comprising 2, 3, 4, or 5 turn units (Schemes S8-S15). One should mention that the final couplings have not been optimized, yet the coupling reactions proved to be well behaved. The targeted large folded macromolecules (up to 7 kDa) could be obtained on scales larger than 100 mg quite straightforwardly.

Depending on the sequences, the nature of the A^X units involved was varied so that contiguous units in the stack may be identical or different. Thus, the rates of photocycloaddition with one neighbor or the other may vary as well. Based on prior knowledge,[15] we initially expected that $A^x(TA^x)_n$ sheets would place all A^X units in a parallel orientation. In the following, we show deviations from this pattern. Yet these deviations did not hamper the programming of pairwise photocycloadditions within large aromatic stacks. Nevertheless, before investigating photoreactions, we ascertained the conformations of theses sequences.

Helix-sheet-helix folds with odd numbers of A^X. Sequence **8,** integrating a central A^H-T-A^H-T-A^H segment, was first prepared and its folding was evaluated in solution and in the solid state. In solution, ^{1}H-NMR spectra in $CDCl_3$ revealed a single set of sharp and well spread resonances (Figures 4A and S15) indicative of folding into a well-defined species. Chemical shift values were found to vary negligibly between 233 K and 308 K (Figure S18). The number of amide resonances (eight) and the presence of a single H_{ext} signal (as defined in Figure 2A) indicated an overall symmetry of the molecule which, considering its sequence, can only be C_2 symmetry. A crystal structure of **8** confirmed the symmetry and the predicted folding (Figure 4C-E). The three diazaanthracene rings stacked with their local dipoles parallel, and the two conical Q_3PN_2 segments have the same helix handedness. This helix-sheet-helix structure can be seen as a basket-like object with central aperture of 17.5 Å. In this design, a photocycloaddition can only involve the central and one of the peripheral $\mathbf{A^H}$ units (see below).

Sequence **12**, an evolution of **8** with a five-anthracene stack was then considered (Figure 2C). An odd number of anthracenes should preserve the C_2 symmetry and thus the same handedness of the two terminal helical segments. In contrast, an even number of anthracenes leads to plane symmetrical objects and thus to a reversal of helical handedness. Unlike for **8**, growing single crystals of **12** was not successful. ^{1}H-NMR in $CDCl_3$ and d_6-acetone showed one set of sharp resonances (Figure 4B and S19) and a global pattern that was very similar to that of **8**. Similarly, changing temperature from 238 to 318 K did not alter the spectrum (Figure S20). As for **8**, the number of amide signals (10) and the presence of two H_{ext} resonances, each integrating for two protons, was indicative of an average C_2 symmetry. Based on this information an energy minimized molecular model was built (Figure 4F-H). Within such an object, photocycloadditions may in principle yield diverse products. However, if the central A^F unit reacts slower than the two peripheral pairs of A^H units, than the latter would react first and a single product may be expected with an orphan central A^F unit.

Helix-sheet-helix folds with even numbers of A^X. Stacks comprised of an even number of A^X units are attractive because,

under ideal conditions, all A^X units may undergo an intramolecular photocycloaddition. Sequences **9**, and **10** (each with four units), and **13** and **14** (each with six units) feature different combinations such that contiguous A^X units within the stack may be identical or different, and thus potentially have different reactivity with their immediate neighbors. Unlike for sequences with an odd number of A^X units, the ^{1}H-NMR spectra of **9** or **10** in $CDCl_3$ revealed not one but two sets of sharp resonances of different intensity, hinting at the presence of two conformations exchanging slowly on the NMR timescale (Figure 5, Figure S22). Each set of signals shows nine -N*H* resonances, indicating that both species are symmetrical. In other solvents such as CD_2Cl_2, d_6-acetone, d_3-acetonitrile and d_2-tetrachloroethane, noticeable variations of the proportion of the two species were observed (Figure S22 and S25). For example, the spectra of **9** showed one highly prevalent species (>95%, Figure S22) in d_3-acetonitrile and a 60/40 mixture in d_2-tetrachloroethane. The proportions between the species were found to also vary considerably with temperature: upon cooling a solution of **10** in $CDCl_3$ to 238 K, a unique conformation is stabilized (Figure 5A,B and S26). However, proportions did not change with concentration and DOSY experiments showed that they have the same hydrodynamic radius.

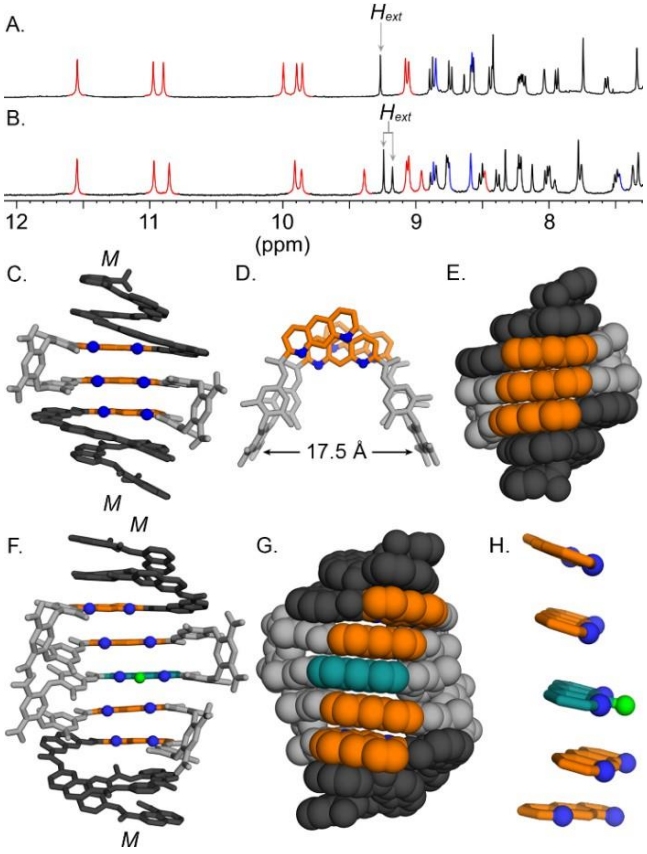


Figure 4. Part of the 400 MHz ^{1}H-NMR spectra of **8** (A) and **12** (B) in 1 mM $CDCl_3$ solutions at 298 K. The amide and amine signals are highlighted in red and blue, respectively. (C-E) Views of the crystal structure of **8** shown in tube or space filling representations. In (D) only the central sheet segment is shown; conical segments are omitted for clarity. (F) Front view of the energy-minimized molecular model of **12** using the Merck Molecular Force Field static (MMFFs) shown in tube representation. (G) Back view of the same in space filling representation. (H) Parallel arrangement of the diazaanthracene in the model of **12**. The structures are shown with color-coded monomers as defined in Figure 2. Blue balls depict endocyclic nitrogen atoms. Hydrogen atoms, side chains and solvent molecules are omitted for clarity.

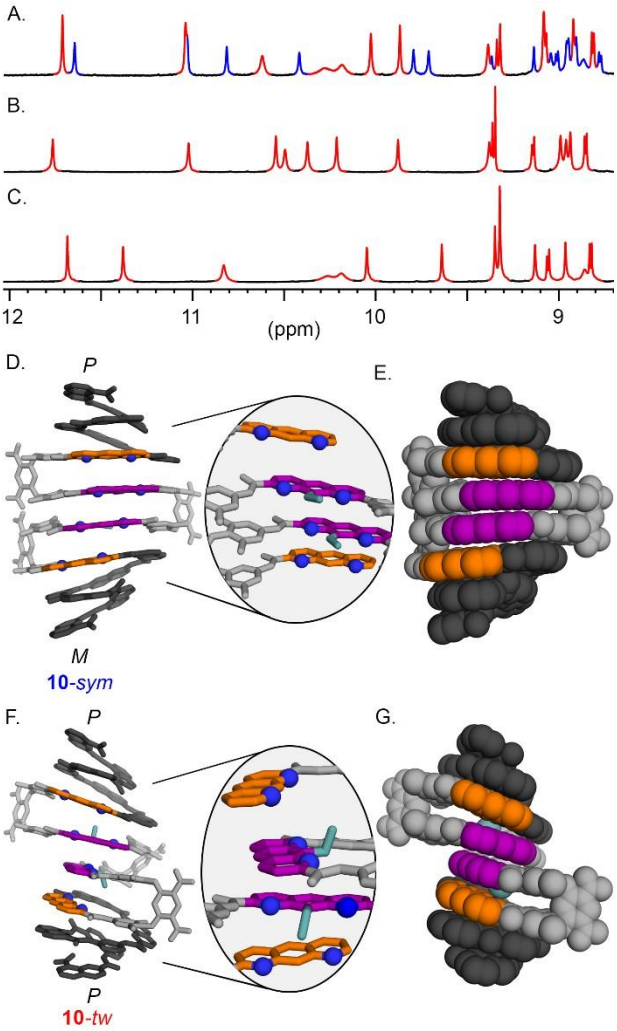


Figure 5. Part of the 700 MHz ^{1}H-NMR spectra of **10** (1 mM) at: (A) 298 K and; (B) 238 K in $CDCl_3$. (C) Part of the 700 MHz ^{1}H-NMR spectrum of **11** (1 mM) at 298 K in $CDCl_3$. Signals assigned to conformers **10**-*tw* and **10**-*sym* are highlighted in red and blue. (D,E) Views of an energy-minimized molecular model (MMFFs) of **10**-*sym* in tube and space-filling representations. The relative arrangement of diazaanthracene units is shown in the inset. (F,G) Views of the crystal structure of conformer **10**-*tw* in tube and CPK representation. The structures are shown with color-coded monomers as defined in Figure 2. Blue balls indicate endocyclic nitrogen atoms. Hydrogen atoms, side chains and solvent molecules are omitted for clarity.

We first tried to predict the folding mode of sequences **9** and **10** using molecular modelling. The energy-minimized (MMFFs) canonical conformation of **10** is shown in Figure 5D, 5E. The model displays the expected stack of four parallel diazaanthracenes. The structure has an average plane of symmetry. Thus, the terminal helices possess opposite *P* and *M* handedness. This conformer was named **10**-*sym* (respectively **9**-*sym*) and is expected to be one of the two conformers observed in solution. Solid-state investigations shed light on the other conformer. Single crystals of **10** were obtained from the slow

diffusion of *n*-hexane into 1 mM $CHCl_3$ solution at 253 K, a temperature at which one of the two conformations is predominant. The solid-state structure revealed an unanticipated C_2-symmetrical conformation. Half of the foldamer had undergone a 180 ° rotation about a single aryl-amide bond between one xylyl group of the central T unit and its adjacent diazaanthracene unit (Figure 5F,G). Furthermore, the handedness of the corresponding helical segment had inverted. It follows that the central two A^{OMe} units are in an antiparallel arrangement, which gives the molecule a twisted shape. We termed this conformer **10**-*tw*. Antiparallel sheet conformations have been observed in other systems.[14g] Nevertheless, why they occur in **9** and **10** and also in **13** and **14** (see below), but not in **8** and **12**, is unclear. That the proportions of **10**-*sym* compared to that of **10**-*tw* depends strongly on temperature highlights a significant entropic contribution in this equilibrium, but its origin also remains unclear.Measuring an NMR spectrum immediately after dissolving a single crystal of **10**-*tw* did not allow us to assign this conformer to one set of signals or the other. Indeed, the spectrum already showed both sets of signals indicating that equilibrium had been quickly reached. Therefore, we prepared sequence **11** as a variant of **10** in which the helical segments are terminated by (1*S*)-(−)-camphanyl groups (**S*** in Figure 2). The effect of the **S*** groups is to quantitatively bias handedness towards *M* helicity.[27] It follows that the conformation of **11** should predominantly be **11**-*tw* because **11**-*sym* would require one *P* helix. As expected, the ^{1}H-NMR spectrum of **11** shows only one set of signals (Figure 5C, Figure S32) and this does not change with temperature (Figure S34). The spectrum of **11**-*tw* has analogies with the conformer of **10** that predominates at low temperature. This, together with the fact that **10**-*tw* crystallized at low temperature suggests that **10**-*tw* is the conformer favored at low temperature. The two conformers of **10** have thus been identified and changing temperature and solvent polarity provides conditions under which either the *tw* or the *sym* conformer prevails.

The folding **13** and **14**, which possess a six-stranded sheet that combines A^H and A^F, or A^H and A^{OMe}, respectively, was investigated by ^{1}H and ^{19}F NMR. As for **9** and **10**, the spectra of **13** and **14** revealed two sets of resonances (Figure 6 and Figures S34 and S38) indicating the presence of two species under slow exchange on the NMR time scale. However, this time, the number of resonances shows that one species has an overall symmetry but not the other: ^{1}H-^{15}N HSQC spectra clearly show eleven N*H* resonances for one species and twenty two for the other (Figures S36, S39). Conversely, ^{19}F-NMR spectra of **13**, which has two central A^F units, show a single fluorine resonance at –132.6 ppm for the symmetrical species, and two resonances at –130.8 ppm and –131.2 ppm for the dissymmetrical species (Figure 6a-d). The species were assigned to two conformers termed **13**-*sym* and **13**-a*sym*, and **14**-*sym* and **14**-a*sym*. The proportions between the *sym* and *asym* conformers was again shown to vary with temperature and solvent (Figure 6, Figures S35 and S38), but not with concentration. For instance, as for **9** and **10**, **14**-*sym* was the prevalent species in CD_3CN (Figure S38), and *asym* conformers were favored at low temperature (Figure 6D).

Solid-state investigations allowed us to decipher the folding modes of these large multi-stranded helix-sheet-helix architectures. X-ray quality single crystals of **13**-*sym* were obtained by the slow diffusion of *n*-hexane in $CHCl_3$ solution (Figure 7A-D). The structure was solved and revealed an approximately plane-symmetrical (albeit tilted) six-stranded aromatic sheet with all A^X units in a parallel arrangement. Thus, as for **10**-*sym* (Figure 5D,E). The two terminal C segments have opposite helix handedness. Differences between the two structures are minor. The resulting overall shape is that of a 3 nm long and almost 2 nm wide basket, with all the X group of the A^X units lining the bottom of the cavity. An energy-minimized molecular model of **14**-*sym* based on the canonical structure of **13**-*sym* was calculated and is shown in Figure S62.

The structure of **14**-*asym* was also confirmed from crystals obtained by slow evaporation of an acetone solution (Figure 7E-H). The structure revealed the flip of a large part of the molecule due to the presence of one pair of antiparallel A^X units. This motif is similar to that observed in the structure of **10**-*tw* (Figure 5F,G). However, unlike in **10**-*tw*, it does not occur in the middle of the sequence between two A^{OMe} units, but side-wise between an A^H and an A^{OMe}. We inferred that **13**-*asym* has a similar conformation to **14**-*asym*. NMR spectra unambiguously showed that the twist occurs at a single site and occurs only once. Yet, in the structures of **13** and **14**, multiple possibilities exist for such twists to occur at other sites or to occur more than once. The reasons why this is not the case are not clear. Spontaneous desymmetrization is not a common phenomenon. Clearly, the conformation of one part of the molecule must influence the conformation of the other part despite the large distances involved.

In summary the in-depth conformational analysis of the new helix-sheet-helix foldamers allowed us to decipher their folding behavior. When the sheet contains an odd number of strands, only canonical folding is observed. If this number is even, then we observed two and only two conformers: one canonical and the other having one pair of anti-parallel AX units.

Cooperative photocycloadditions within multi-stranded helix-sheet-helix architectures. Motivated by the efficient conversion of aromatic sheet models **1**-**6** to their respective photoproducts **1a**-**6a**, photoirradiations were performed on longer sequences following similar protocols. All

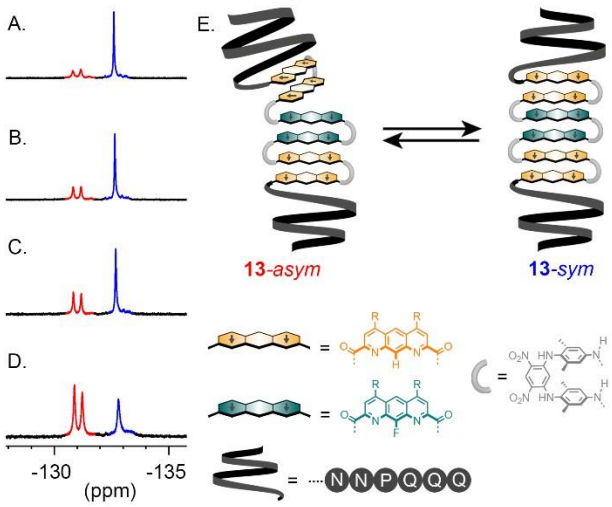


Figure 6. ^{19}F NMR spectra (376 MHz) of **13** (1 mM) at: (A) 298 K; (B) 278 K; (C) 258 K; and (D) 248 K in d_6-acetone. Signals assigned to two conformers **13**-*sym* and **13**-*asym* are highlighted in blue and red, respectively. (E) Schematic representation of the dynamic exchange between the two conformers. Letter and color codes are defined in Figure 2.

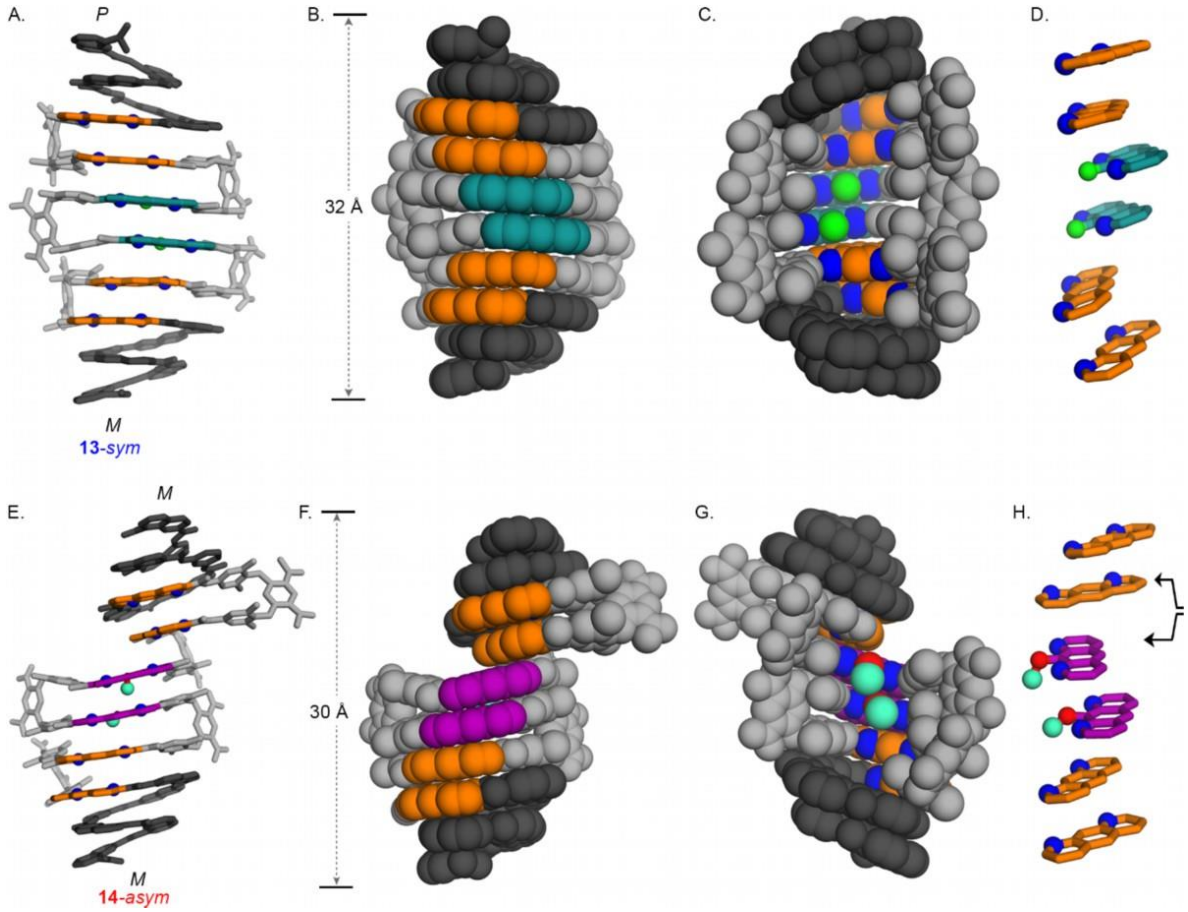


Figure 7. (A,B) Back views of the solid-state structure of **13**-*sym* in tube and space-filling representations, respectively. (C) Front view of **13**-*sym* in space-filling representation revealing the large cavity of the basket-like foldamer. (D) Orientation of the diazaanthracene units in **13**-*sym*. (E,F) Back views of the solid-state structure of **14**-*asym* in tube and space-filling representations, respectively. (G) Front view of **14**-*asym* in space-filling representation. (H) Orientation of the diazaanthracene units in **14**-*asym*. Arrows indicate the only pair of antiparallel diazaanthracene units. Color coding of monomers is defined in Figure 2. Blue balls indicate endocyclic nitrogen atoms. Hydrogen atoms, side chains and solvent molecules are omitted for clarity.

photoirradiation experiments were carried out in NMR tubes using millimolar solutions of oligomers in different solvents under anaerobic condition (see supporting information). First, we tested the photoirradiation of oligomers with three (**8**) or five (**12**) A^X units. We have shown above that these exist as a unique basket-like conformer in which all A^X are stacked parallel to one another. Oligomer **8** possesses three A^H units and may thus undergo one photocycloaddition. Upon irradiation, a 95% conversion to photoproduct **8a** after 90 min of irradiation was observed by ^{1}H-NMR (Figure S41). This reaction results in a loss of the initial C_2 symmetry and in the doubling of the number of proton resonances. The parallel configuration of the photoproduct was ascertained by characteristic resonances in the ^{1}H-NMR spectrum: (i) a broad resonance at 4.67 ppm corresponding to the two H10* protons (as defined in Figure 2), (ii) two doublets at 5.03 ppm and 5.17 ppm assigned to the coupled non-equivalent H9* protons. An energy minimized structure was obtained using MMFFs, highlighting that a canonical folding is preserved in spite of the butterfly-like shape of the photoadduct (Figure S60). We also note that the phootreaction of **8** is somewhat slower than that of simple sheet **1**. This trend was general for all sequences and hints at a photo-shielding effect of the helical cones that flank the central sheet. The reverse reaction to **8** was achieved quantitatively by heating a solution of **8a** at 333 K for 36 hours (Figure S42).

Sequence **12** possesses five A^X units and may in principle yield multiple photoproducts. However, the presence of the central A^F and the faster photoreaction of A^H units hinted at the possible selective pairwise reaction of the latter, leaving an orphan A^F in the middle of a unique symmetrical photoproduct. This, however, proved not to be straightforward. Irradiating **12** for 5 hours in $CDCl_3$ or in d_6-acetone resulted in the emergence of more than one species with unresolved (*i.e.* broad) ^{1}H NMR signals (Figure S54). ^{19}F NMR spectra suggests a two-step process: a first mono photocycloaddition after 1 hour followed, after 5 hours of irradiation, by a second photocycloaddition (Fig S55). Because all other photoreactions could be monitored and the products identified thanks to sharp NMR spectra, and because the discrimination between A^H/A^H and A^H/A^F pairs was evidenced in other sequences, the investigation of **12** was not pursued further. We instead focused on multi-stranded oligomers with an even number of A^X units. Due to their bimodal folding modes, we anticipated more complex analysis but, on the contrary, experiments instead showed remarkably selective conversions.

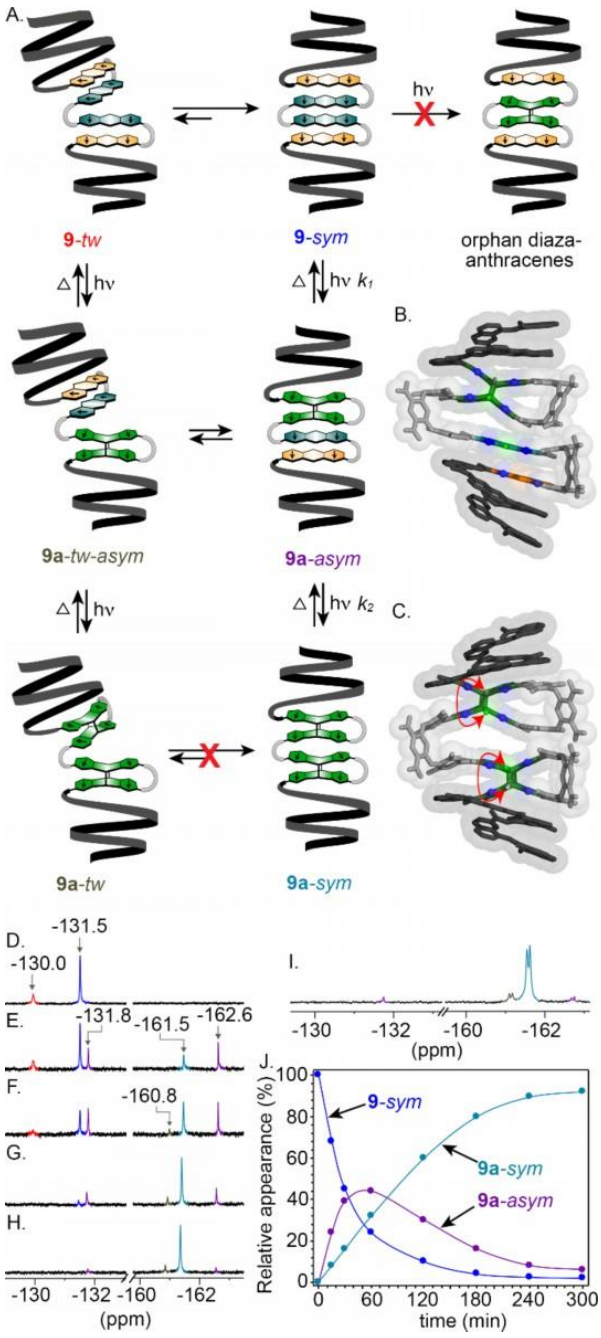


Figure 8. (A) Schematic illustration of stepwise photoadduct formation of **9**. Initially two conformers, **9**-*tw* and **9**-*sym*, are at equilibrium at room temperature. Both may undergo stepwise photoreactions giving final products **9a**-*tw* and **9a**-*sym*, respectively. Photoreaction between the two central $\mathbf{A^F}$ units is much slower. (B,C) Energy-minimized molecular models (MMFFs) of **9a**-a*sym* and **9a**-*sym* in tube representation. Monomers are color-coded as in Figure 2. Blue balls indicate endocyclic nitrogen atoms. Hydrogen atoms and side chains are not shown for clarity. Red double headed arrows indicate scalar coupling between F9* and H9* as reflected in (I) The 376 MHz $^{19}F\{^1H\}$ NMR spectra of **9** (1 mM in d_6-acetone) at 298 K after (D) 0 min; (E) 30 min; (F) 1 h; (G) 2 h; and (H) 5 h of photoirradiation. (I) The ^{19}F NMR spectra after 5 h irradiation. Signals assigned to individual species are highlighted with colors as in (A). j) Plot showing the time course of the proportions of **9**-*sym*, **9a**-*sym* and **9a**-*asym* during the reaction. The usual color code is maintained throughout.

Sequences **9** and **10** were designed with four-stranded sheets so that the central pair of $\mathbf{A^X}$ units react slower than the peripheral pairs. As depicted in Figure 8A, the photocycloaddition of the two central A^F units of **9**-*sym* would produce two orphan peripheral A^H units. However, we have seen above (Figure 3B) that the photocycloaddition of an A^F/A^F pair is much slower than that of A^F/A^H. The difference is lesser in the case of the A^{OMe}/A^{OMe} and A^{OMe}/A^H pairs found in compound **10**, and selectivity may be more difficult to achieve in this case. Photoirradiation was carried out on both **9** and **10** in d_6-acetone and monitored by ^1H and ^{19}F NMR. Photoconversion was essentially complete after five hours and one hour, respectively. The overall reactions rates thus reflect well the higher photoreactivity of A^{OMe} than of A^F. The final spectra revealed the presence of two products and showed no orphan A^H unit (Figure 8, Figures S42, S45). Thus selective cyclo-additions are achieved in both cases; even A^{OMe} and A^H react preferentially. In the case of **9**, proof that the products consist of photocycloadditions between A^H and A^F units came from the observation of doublets in proton-coupled ^{19}F-NMR (Figure 8J). These doublets originate from the scalar coupling between the H9* and the F9* atoms in the cyclo-addition products (Figure 8C, see Figure 2A for the definition of H9* and F9*).

The photoreaction of **9** in d_6-acetone could be monitored in detail by both $^{19}F\{^1H\}$ (*i.e.* proton decoupled, Figure 8 D-H) and ^1H-NMR (Figure S43). After thirty minutes of photoirradiation of the initial **9**-*sym*:**9**-*tw* mixture (3:1 ratio), two new species emerged (Figure 8E). One species shows a single ^{19}F resonance at –161.5 ppm and proved to be a final product. The other displays two ^{19}F resonances at –131.8 and –162.6 ppm. It is thus dissymmetrical, and it disappears, after reaching a maximum, as the reaction continues (Figure 8J). At the end of the reaction, two products have appeared (at –161.5 and –160.8 ppm), and traces of the intermediate remain (Figure 8H). These two products can reasonably be assigned to **9a**-*sym* and **9a**-*tw* and the intermediate to **9a**-*asym*. Non-linear fitting of the observed ^1H NMR resonance intensity change of each species during the photoreaction, considering two sequential photodimerization reactions yielded apparent kinetic constants $k_1 = 4.4 \times 10^{-4}$ s^{-1} and $k_2 = 2.0 \times 10^{-4}$ s^{-1} (Figure 8A). While the magnitude of these observed values depends on the irradiation conditions, the ratio of these values, k_1:k_2, corresponds to the relative efficiency of the photodimerization reactions. When taking into account the changing absorption/removal of one of two pairs of reactive anthracenes accompanying the initial photodimerization reaction, within experimental error, the second photodimerization reaction is seen to proceed similarly and is thus unimpeded by the first. As anticipated **9a**-*tw* and **9a**-*sym* (as well as **10a**-*tw* and **10a**-*sym*) do not interconvert upon changing temperature (Figure S48) or solvent (Figure S49). Therefore, photocycloadditions have locked the respective conformers and prevent exchanges.

The complete absence of orphan unit in the photoproducts is remarkable in the case of **10** because the rates of photo-cycloadditions within A^H-T-A^H (**1**), A^H-T-A^{OMe} (**3**) and A^{OMe}-T-A^{OMe} (**6**) do not differ to a great extent (Figure 3). One may comment that the existence of *tw* conformers should favor this outcome but the abundance of a **10a**-*sym* suggests that other effects are at play and that the reaction selectivity is further enhanced in the multistranded sheets.

Remarkably, the final **9a**-*sym*:**9a**-*tw* ratio (10:1) differs from the initial **9**-*sym*:**9**-*tw* ratio. Photoirradiation of compound **10** in d_6-acetone also led to a **10a**-*sym*:**10a**-*tw* ratio significantly larger than the initial **10**-*sym*:**10**-*tw* ration (Figure S47). In contrast, when photoirradiation was performed in $CDCl_3$, the initial **10**-*sym*:**10**-*tw* ratio (1:2) was reflected in the proportion of products (Figure S46). A plausible mechanism for the stepwise photocycloaddition is presented in Figure 8A and models are shown in Figure 8B,C and Figure S64. The prevalence of product **9a**-*sym* can be interpreted in several ways. For example, if intermediate **9a**-*tw-asym* is less stable than intermediate **9a**-*asym*, a conformational rearrangement may occur between the two before **9a**-*tw-asym* is converted in the final **9a**-*tw*. Another reason may be that **9**-*sym* undergoes a first photocycloaddition much faster than **9**-*tw*. Both hypotheses would explain that the **9a**-*tw-asym* intermediate remained below detection levels.

Complementary information came from the photoreaction of chiral sequence **11**, which, as we have seen, exists as an exclusive **11**-*tw* conformer. This compound undergoes a clean conversion to a single photoproduct, **11a**-*tw* (Figure S51). Remarkably, this conversion occurs without any detectable **11a**-*tw-asym* intermediate, indicating a very strong cooperativity: the photoreaction of **11**-*tw* must be much slower than that of **11a**-*tw-asym*, which does not accumulate. These results are in agreement with the hypothesis that the initial *tw* species are the least reactive of all and reveal an intriguing interplay between conformations and successive photoreactions that result in remarkable selectivity. Additionally, it is worth noting that eight stereogenic centers are generated simply by irradiating the sequence with light. Indeed, a careful examination of the NMR spectrum of **11a** (Figure S53) revealed the existence of a single set of amide resonances which indicates a full control of the stereogenicity of the eight new asymmetric centers. The outcome of this photoreaction is that folding combined with camphanyl moieties that are positioned several angstrom away from diazaanthracenes can fully control the stereoselectivity of the photoreaction.

Finally, we demonstrated the orchestration of three consecutive photocycloadditions within 7 kDa helix-sheet-helix foldamers **13** and **14**. In both compounds, sheet segments are composed of two peripheral pairs of A^H units and a central pair of A^F or A^{OMe} units. Based on the results shown in Figure 3, we envisaged that the pairs of A^H monomers would photoreact first, followed by the pairs of A^F or A^{OMe} units, while anticipating that reaction completion may be hard to reach with a pair of A^F units. Such a pathway would exclude orphan A^X units in the final products. Since **13** and **14** each exist as two *asym* and *sym* conformers (Figures 6 and 7) different intermediates and two final products can be envisaged (Figure 9A).

Photoirradiation of **13** was first monitored in d_6-acetone by ^{1}H- and ^{19}F-NMR. Despite the presence of two initial *asym* and *sym* conformers, $^{19}F\{^1H\}$-NMR spectroscopy clearly showed the formation of a single dissymmetrical intermediate followed by a single symmetrical product (Figure S56). The absence of ^{19}F signals near –162 ppm indicated that none of these species resulted from a cycloaddition of an A^F unit, which have thus remained intact. The intermediate was therefore assigned to **13a**-*sym-mono* and the final product to **13a**-*sym-di*. In summary, selective photoreaction of A^H units was achieved, *asym* photoproducts were not observed, no orphan A^X units were produced, but the pair of A^F units did not react after 12h.

In the case of **14** (Figure 9B-G), two main intermediates, one dissymmetrical and one symmetrical were observed as well as a main photoproduct, which were assigned to **14a**-*sym-mono* and **14a**-*sym-di* and **14a**-*sym*, respectively (Figure 9A). ^{1}H NMR confirmed that all A^X units of **14a**-*sym* could react, including the central pair of A^{OMe}, and that no orphan $\mathbf{A^X}$ unit was formed. Isolation of the final product by slow precipitation in acetone revealed that it contains a small amount (~15 %) of a dissymmetrical species that we interpreted as being **14a**-*asym*. Intermediates toward that species were not seen because their proportion remained minor throughout the reaction. Changing solvent or temperature did not alter the **14a**-*sym*/**14a**-*asym* ratio, confirming that the structures are locked by intramolecular cycloadditions (Figures S56 and S57). Molecular models of **14a**-*sym* revealed that the three intramolecular cycloadditions resulted in an extension of molecular length of 0.8 nm compared to **14**-*sym* (3.9 vs 3.1 nm) (Figure S67).

CONCLUSION

In summary, we have designed and synthesized high molecular weight abiotic helix-sheet-helix architectures comprised of multiple functional diazaanthracene units that can be selectively modified upon light irradiation. The modular and oligomeric nature of the helix-sheet-helix backbones allowed us to access straightforwardly to seven different sequences using convergent synthetic schemes. Both the number of aromatic turns and the nature of the photoreactive units may be conveniently varied. We first deciphered the folding behavior of these macromolecules and found that folding depends on the number of turn units. An even number of aromatic turns systemically led to a unique folded species with a canonical sheet folding and two helices of identical handedness. In contrast, an odd number of turn units led to an equilibrium between a symmetrical canonical sheet and a dissymmetrical twisted sheet whose proportions where found to vary significantly with solvent and temperature. This equilibrium may in principle be quantitatively shifted in favor of one or the other species by controlling the handedness of the terminal helical segments – canonical species have helices of opposite handedness and twisted species have helices of opposite handedness – though this was implemented only in the case of one dissymmetrical species.

We also found that the photoreactivity of the diazaanthracene monomers was finely tunable upon introducing various substituents in the 9 position. We thus introduced different diazaanthracene units at defined position of the helix-sheet-helix sequences to implement multiple selective 4+4 photocycloadditions and trigger photomodifications of the aromatic backbones at precise locations, avoiding orphan units or, on the contrary programming the formation of orphan units. Monitoring the photoreactions revealed that they were not only influenced by the nature of the diazaanthracene substituents. The canonical (symmetrical) or twisted (dissymmetrical) conformation of the foldamer also influences reaction rates as well as the presence or not of an intermediate photoadduct in the structure. In some cases, this led to strongly cooperative photoreactions in which the fully photoreacted product was generated without any detectable amounts of partly reacted intermediates. Up to three distinct photocycloadditions were implemented in the same helix-turn-helix architecture leading to the stiffening of the backbone, and to a length extension of the sheet segment. This lengthening of the sheet is reminiscent of previous work on helix extension by the groups of Aida[18a]

and of Yashima.[28] The predictability of the folding of the aromatic helix-sheet-helix structures and the fine tuning of the photoreactions may find applications in photocontrolled guest release, or for the photocontrol of charge transport properties through selective disruption of face-to-face π stacking interactions.[16e,f] Efforts toward these objectives are currently in progress in our laboratories and will be reported in due course.

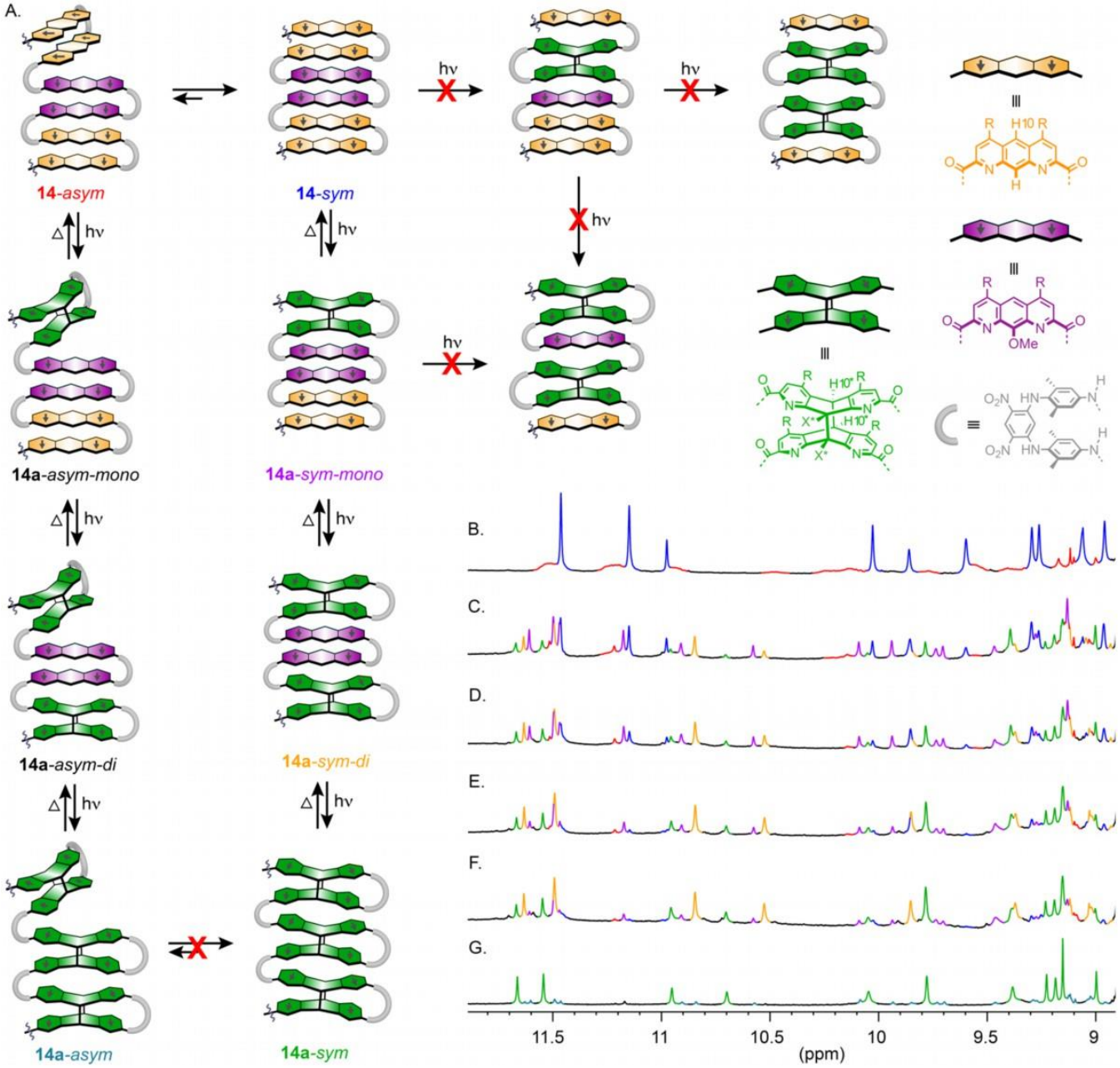


Figure 9. (A) Schematic illustration of stepwise photoreactions of **14**. Initially two conformers: **14**-*asym* and **14**-*sym*, are in equilibrium at room temperature. Both may undergo stepwise photoreactions to produce **14a**-*asym* and **14a**-*sym*, respectively. Pathways that would yield orphan A^X units were not observed. Terminal helices have been omitted for clarity. Part of the 700 MHz ^{1}H NMR spectra of **14** (1 mM in d_6-acetone) at 298 K under photoirradiation after (B) 0 h; (C) 2 h; (D) 3 h; (E) 5 h; (F) 7 h; and (G) 10 h after isolation of the products by precipitation. Signals assigned to individual species (**14a**-*sym*, **14a**-*asym*, **14a**-*sym-mono*, **14a**-*sym-di*, **14a**-*asym*, **14a**-*sym*) are highlighted with color as depicted in (A).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Details on the synthesis and structural characterizations of compounds, NMR spectra, UV-vis spectra, crystallographic and molecular mechanics data including Schemes S1-S15, Figures S1-S66 and Tables S1-S4 (PDF).

Accession Codes

CCDC 2144667, 2144666, 2144663 and 2144662 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*yann.ferrand@u-bordeaux.fr
*ivan.huc@cup.lmu.de

Current Address

† Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Gautam Buddha Nagar, UP 201314, India.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(26) The pyridine photo-products can be excited at shorter wavelengths. At these wavelengths, all other aromatic moieties of the oligomers also absorb, making the fraction of light available to the photodimer to regenerate the starting material extremely small. This is compounded by the possibility of electronic energy transfer from the excited photodimer to the neighboring aromatic units, effectively de-exciting the photodimer and impeding the photoreversion.

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SYNOPSIS TOC

