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## COMMUNICATION

## Self-Assembling Figure-of-Eight and Pseudoplectoneme Aromatic Oligoamide Ribbons

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**Two oligoamide macrocycles composed of eight and twelve 7-amino-8-fluoro-2-quinolinecarboxylic acid monomers were synthesised despite the propensity of their acyclic precursors to fold and self-assemble into double helices. Macrocyclisations were made possible through the transient use of helicity disruptors. The resulting macrocyclic ribbons were found to adopt figure-of-eight and pseudoplectoneme shapes that maintain an ability to self-assemble.**

Macrocycles derived from frustrated foldamer helices<sup>‡</sup> are molecules that would adopt a helical conformation upon ring-opening and whose inherent conformational preferences can't all be fulfilled in the cyclic form. The constraints that derive from conformational frustration often lead to molecular shapes not reachable by others means.<sup>1</sup> Besides, without conformational frustration, a helical foldamer would not macrocyclise as its two ends diverge from each other. The strain induced by the macrocyclisation decreases conformational freedom, gives access to unusual conformations and, more often than not, reveals peculiar properties and reactivities. Macrocycles derived from frustrated foldamer helices can thus in many ways be compared to other types of strained macrocycles including hydrocarbon belts,<sup>2</sup> infinitene,<sup>3</sup> cycloparaphenylenes,<sup>4</sup> macrocycles bearing angle-strained alkynes,<sup>5</sup> expanded porphyrinoids.<sup>6</sup> In this study, we report on the conformational frustration of aromatic oligoamide sequences that form stable double helices in solution. Previously, we demonstrated that the macrocyclisation of stable single helices of 8-amino-2-quinolinecarboxylic Q (2.5 units/turn), ranging from 5 to 7 units,

was made possible by the transient use of local disruptor of helicity.<sup>1b,c</sup> Specifically, using acid labile dimethoxybenzyl (DMB) groups for the alkylation of secondary amide functions led to the destabilisation of the canonical folding of aromatic oligoamide helices and allowed for their macrocyclisation.

Besides single helices, some aromatic oligoamide sequences have a strong propensity to self-assemble into double helical dimers. This applies in particular to monomers coding for a wide diameter because of the lower energy cost of spring-like extension associated with double helix formation (Figure 1a, top right).<sup>7</sup> In the case of oligoamides of 7-amino-8-fluoro-2-quinolinecarboxylic acid (Q<sup>F</sup>), the predicted curvature is *ca.* 4 units per turn. Q<sup>F</sup><sub>8</sub>, an oligomer that spans about two turns, revealed a high dimerisation constant ( $K_{dim}$ ) of almost 10<sup>6</sup> L mol<sup>-1</sup> in chloroform. Elongating a sequence beyond eight units is low yielding because of the steric hindrance at the strand termini associated with folding and double helix formation. Notwithstanding elongation, the direct cyclisation of long fluoroquinoline oligoamides is simply impossible. We devised that the alkylation with DMB groups of few secondary amide functions of Q<sup>F</sup> oligomers might perturb simultaneously the folding of the helical strands as well as their propensity to self-assemble so as to allow macrocyclisation (Figure 1a, top left). Indeed, the use of DMB groups has been validated before to prevent aggregation of aromatic oligoamides rods<sup>8</sup> and to decrease hindrance in single helices.<sup>9</sup>

Octameric and dodecameric macrocycles **1b** and **2b** (Figure 1b) were synthesised following a convergent strategy as described in detail in the supporting information. We assumed that one DMB tertiary amide bond per helix turn would be sufficient to prevent correct folding. Thus, an octamer would be alkylated twice whereas a dodecamer would contain three DMB groups. The DMB-containing cyclo-octamer **1a** and cyclo-dodecamer **2a** were obtained from their respective acyclic amino acid precursors using in situ acid chloride activation with Cl<sub>3</sub>CCN/PPh<sub>3</sub> (Figure S3-S4, ESI<sup>†</sup>).<sup>1b,c</sup> A two-step purification of the cyclic products was required using first silica gel chromatography to remove the unreacted amino acid precursor

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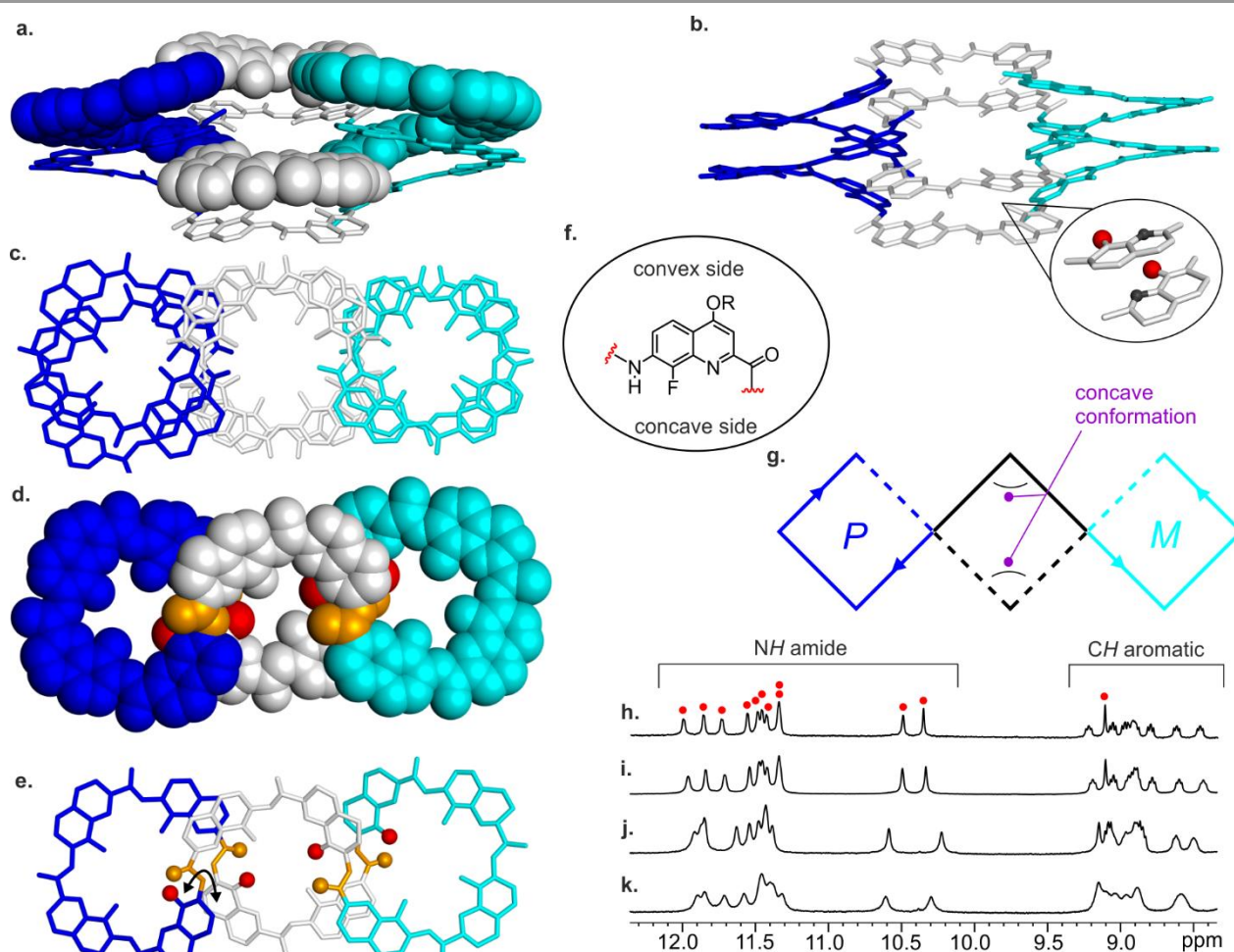
<sup>‡</sup> Footnotes relating to the title and/or authors should appear here.

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of similar handedness intertwine via the intercalation of one their loops (Figure 2b) forming a triangular shape dimer ( $\mathbf{1b}$ )<sub>2</sub>. Then, two enantiomeric triangular dimers ( $\mathbf{1b}$ )<sub>2</sub> that is (*P,P*).(P,P) and (*M,M*).(M,M) can interdigitate to form a well-defined quaternary assembly ( $\mathbf{1b}$ )<sub>4</sub> of imbricated figure-of-eight macrocycles (Figure 2f). The interdigitation seems to be directly

inherited from the propensity of the noncyclic sequences to form double helices and is associated to the low energy cost of increasing the helix pitch of Q<sup>F</sup> oligomers (see above). Additionally, penetration of some isobutoxy side chains into neighbouring helix cavities further enhance intermolecular contacts (Figure 2h,2i, yellow).



**Figure 3.** X-ray structure of ( $\mathbf{2b}$ )<sub>2</sub>: a) front view showing one strand in space filling representation whereas the second one is shown in tube representation; b) front view in tube representation and zoom of two Q<sup>F</sup> monomers in antiparallel arrangement; c) top view in tube representation. d,e) top view of a single strand of ( $\mathbf{2b}$ )<sub>2</sub> shown in space filling and tube representation, respectively. The black double-headed arrow in e) denotes the rotation about the fluorobenzene/nitrogen amide bond. In a-e) the *P* and *M* helical segments are shown in blue and light blue, respectively, whereas the central flipped Q<sup>F</sup><sub>2</sub> segments are shown in white. Some fluorine atoms are shown as red balls whereas flipped carbonyl are represented as golden balls. Isobutoxy side chains (O*i*Bu) and included solvent molecules have been removed for clarity. f) Definition of the convex and concave side of a Q<sup>F</sup> unit. g) Schematic representation of  $\mathbf{2b}$  highlighting the *P,M* helicity and the concave conformations. Part of the 400 MHz <sup>1</sup>H NMR spectra of  $\mathbf{2b}$  at: h) 0.1 mM, 298 K, in CDCl<sub>3</sub>; i) 3.2 mM, 298 K, in CDCl<sub>3</sub>; j) 0.5 mM, 298 K, in C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>; k) 0.5 mM, 353 K, in C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>. The red circles denote the 12 amide protons.

Single crystals of  $\mathbf{2b}$  were also obtained from the diffusion of hexane in a chloroform solution of the dodecameric macrocycle and its solid state structure was solved in the *P*-1 space group. The crystalline structure revealed an unprecedented ( $\mathbf{2b}$ )<sub>2</sub> architecture composed of two intercalated aromatic ribbons (Figure 3a-c). Each dodecameric cyclic strand displayed four twisted Q<sup>F</sup> units coloured in white in Figure 3. By analogy with the convention established for porphyrinoids,<sup>10</sup> macrocycle  $\mathbf{2b}$  possesses a quadricconcave conformation (Figure 3d-g). Each concave conformation occurs at a Q<sup>F</sup> unit that is flipped with respect to the naturally convex

curvature of the macrocycle (see Ref 10 for a detailed presentation). A pair of flipped units generates a crossing so the structure has two crossings (Figure 3 d,e). One can note that, as for  $\mathbf{1b}$  and contrarily to some Q macrocycles,<sup>1b,c</sup> no *cis* amide conformation is involved. Instead, Q<sup>F</sup> units rotate about 180° about the bond linking their fluorobenzene ring and the neighbouring amide NH (Figure 3e, black double-headed arrow). Overall, the resulting macrocycle structure has two full helical turns (*i.e.* each comprised of four Q<sup>F</sup> units) with opposite *P* and *M* handedness connected by two concave bridges, one above and one below the median plane of the macrocycle

(Figure 3d, e and g). Swapping the above/below position of the two bridges would lead to the inversion of both helices. Like some *meso* helices,<sup>11</sup> this macrocycle possesses a centre of symmetry. As the macrocycle contains an even number (2) of crossings the macrocyclic architecture can be termed pseudoplectoneme by analogy with plectonemic conformations of DNA.<sup>10</sup> It should be emphasized that the ribbon is not twisted in contrary to the figure-of-eight shape of **1b**.

The propensity of Q<sup>F</sup> oligomers to self-assemble is expressed in the structure of **2b** under the form of discrete dimers. A doubling of helix pitch is required to form a double helix from two single helices in acyclic oligomers. The same extension of a cyclic ribbon enables the intercalation of a second strand without alteration of the overall shape (Figure 1a, bottom left). The dimer shows extensive intermolecular aromatic stacking. Electrostatics probably drive the opposite N-to-C orientation of the two cyclic ribbons within the dimer (Figure 3b, zoom). Within the dimeric assembly, the two macrocycles are equivalent. However, the assembly results in a loss of symmetry: within each macrocycle, all twelve Q<sup>F</sup> units are distinct. Such loss of symmetry has been reported in other large homomeric macrocycles.<sup>12</sup> Furthermore, contrary to the individual achiral *C*<sub>i</sub> symmetrical monomers, the dimeric assembly is chiral with an overall axial *C*<sub>2</sub> symmetry (Figure S16, ESI<sup>†</sup>). Chirality can be reverted by taking the macrocycle “below” within the stack, and translating it “above” without any rotation.

The structure and aggregation properties of **2b** in solution were probed by NMR. The <sup>1</sup>H NMR of the dodecameric macrocycle in CDCl<sub>3</sub> revealed a single set of 12 sharp amide resonances (Figure 3f), a number that is twice as large as the theoretical six resonances than can be expected for the *C*<sub>i</sub> symmetry of the single stranded **2b** but that corresponds exactly to *C*<sub>2</sub>-symmetrical dimer (**2b**)<sub>2</sub>. The twelve fluorine resonances detected by <sup>19</sup>F NMR also confirmed that the dimer form is the prevalent species in solution. Diluting a solution of (**2b**)<sub>2</sub> in CDCl<sub>3</sub> or tetrachloroethane-d<sub>2</sub> did not reveal any traceable amount of single stranded macrocycle. No significant changes can be observed neither upon heating the same sample at 353K (Figure 3i). These experiments gave a minimal estimate of the dimerization constants (*K*<sub>dim</sub>) of 10<sup>8</sup> L mol<sup>-1</sup>. They also indicate that fluxionality within the macrocycle is slow on the NMR timescale at this temperature.

## Conclusion

We have shown that macrocyclisation of Q<sup>F</sup> oligomers lead to new expressions of their propensity to fold into helices and to assemble into double-stranded dimers. One may speculate that other cyclo-Q<sup>F</sup><sub>n</sub> oligomers may form shapes similar to those of cyclo-Q<sup>F</sup><sub>8</sub> and cyclo-Q<sup>F</sup><sub>16</sub> by combining twisted and pseudoplectoneme motifs. The self-assembly of macrocycles by strand intercalation is novel and contrasts with the more classical stacking of flat shape-persistent rings.<sup>13-16</sup>

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

‡ Frustrated foldamer helices can be defined as foldamers whose helical folding propensity is frustrated, *e.g.* by macrocyclization, preventing the fulfilment of some conformational preferences.

‡‡ Single crystals suitable for X-ray diffraction analysis were obtained by slow liquid-liquid diffusion. **1b** (CCDC #2160708); (**2b**)<sub>2</sub> (CCDC #2161479). See the ESI for details about crystallographic methods and data.

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