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Design of an Inversion Center between Two Helical Segments

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Abstract: A new strategy is proposed to control the relative orientation of two folded helical oligomers in such a way that they diverge from an aromatic linker and have opposite helical handedness. Mutual steric exclusion between the two helices results from the fact that they cannot be at the same time folded and on the same side of the linker. The concept is validated using the helical conformations of oligoamides of 8-amino-2-quinolinecarboxylic acid, but it should be applicable to many families of oligomers and leads to the first designed *meso*-helices.

Introduction

Much attention is devoted to synthetic aliphatic and aromatic oligoamides that fold into well-defined helical and linear secondary structures.[1,2] They mimic the conformations and potentially the functions of naturally occurring a-peptidic chains and have shown promising activities as, e.g., amphipathic cytotoxic agents[3] and as scaffolds for the recognition of protein surfaces.[4] An important challenge in this area is the design of highly organized protein-like tertiary motifs from the assembly of several secondary elements. To reach this goal, strategies need to be developed to control the relative orientation of secondary building blocks within a tertiary fold. Several approaches have been proposed to assemble α-peptidic segments. For example, one may rely on flexible linkers and on specific interactions between secondary elements such as hydrogen bonding[5a−c] and hydrophobic contacts.[5d,e] Less commonly, rigid linkers have been designed to locally set the relative orientation of the secondary elements.[6] In particular, coordination of histidine and cysteine residues to metal ions has proven to be very efficient at rigidly connecting α-helical peptides.[6] In this paper, we describe a strategy based on mutual steric exclusion to orient two helical segments in opposite directions and simultaneously impose an inversion of helix handedness between them. The concept is validated using the helical conformations of aromatic oligoamides (AOAs) of 8-amino-2-quinolinecarboxylic acid.[7] Nevertheless, a similar approach may be proposed for many other classes of nonchiral helical aromatic or aliphatic oligomers.

Results and Discussion

Design Principles. The helices of AOAs are held by a network of hydrogen bonds between amide protons and adjacent quinoline nitrogens and by extensive intramolecular aromatic stacking. We reasoned that a rigid linker such as 1,5-diaminoanthraquinone may be inserted between two helices at the C terminus without disrupting the continuity of the hydrogen bond network and of $\pi-\pi$ interactions (Figure 1a). Rotations about the amide nitrogen−aryl linkages at the 1 and 5 positions of the anthraquinone should be restricted by NH−O═C hydrogen bonds, leading to a planar structure of the shorter derivative

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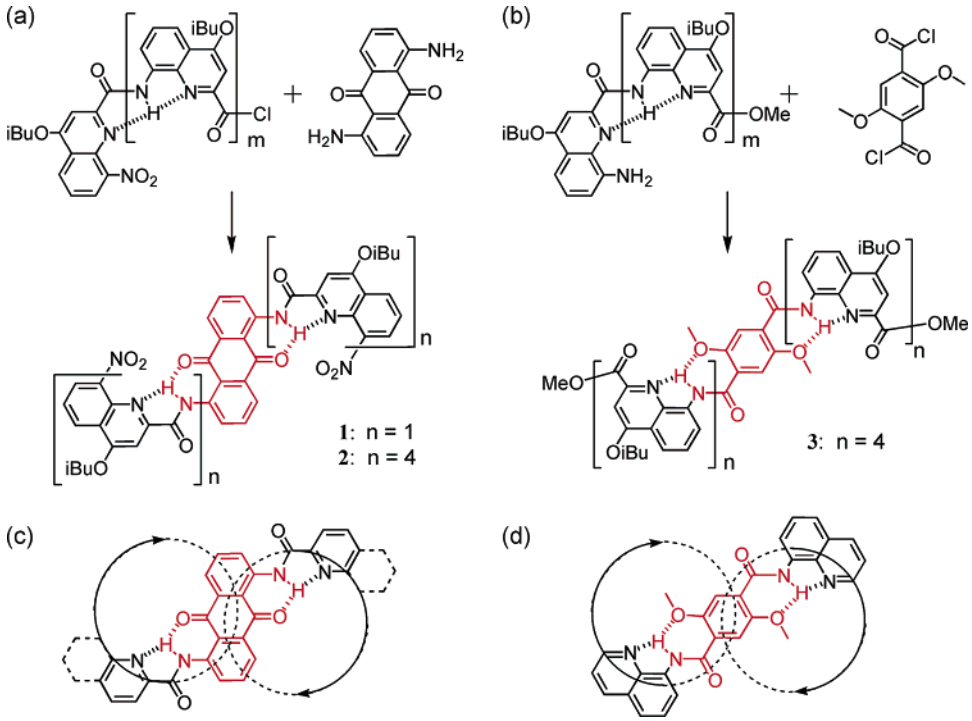

Figure 1. Structures and synthetic schemes of compounds **1** and **2** (a) and **3** (b). Schematic representation of the projection of the two helical oligoquinolinecarboxamide segments of **2** in the plane of the diaminoanthraquinone spacer (c), and of **3** in the plane of the dimethoxyterephthaloyl spacer (d). In both **2** and **3**, the surfaces covered by the two helical segments (circles) partly overlap, indicating steric hindrance if the helices extend on the same side of the spacer. The arrows indicate the direction in which each oligomeric segment extends from the spacer. For a given compound, that both arrows turn in the same direction (clockwise) indicates that the two helical segments have the same handedness if they extend on the same side of the spacer, and opposite handedness if they extend on opposite sides.

1.[1a] In the longer oligomer **2**, two tetrameric quinolinecarboxamide segments should give rise to two helices of more than one and a half turns. The helices may, in principle, extend either on the same side or on opposite sides of the plane of the anthraquinone moiety. However, the former possibility is expected to result in steric hindrance between the helices (Figure 1c) and may not be possible without significant perturbations of the hydrogen bonds and $\pi-\pi$ interactions. Moreover, the centrosymmetric nature of the anthraquinone linker should have a major consequence on the handedness of the two helical segments. The helices should be both right-handed (P−P) or both left-handed (M−M) if they extend on the same side of the anthraquinone, and they should have opposite handedness (P−M) if they extend on opposite sides.

A similar reasoning could be applied for linking two helices at the N-terminus using a 2,5-dimethoxyterephthaloyl linker (Figure 1b). In this case, rotations about the aryl−carbonyl bonds of the linker should be restricted by hydrogen bonds between each ether oxygen and the neighbor amide proton, and also by repulsions between each ether oxygen and the neighbor amide oxygen.[1a] Again, steric hindrance is expected to prevent the two helical segments from extending on the same side of the linker, and their extension on opposite sides of the linker should result in an inversion of helical handedness.

As shown in Figure 1a, oligomers **1** and **2** were prepared from the commercially available 1,5-diaminoanthraquinone and the corresponding acid chlorides.[7] Similarly, oligomer **3** was prepared from 2 equiv of a tetrameric amino ester oligomer[7] and 2,5-dimethoxyterephthaloyl dichloride[8] (see the Supporting Information).

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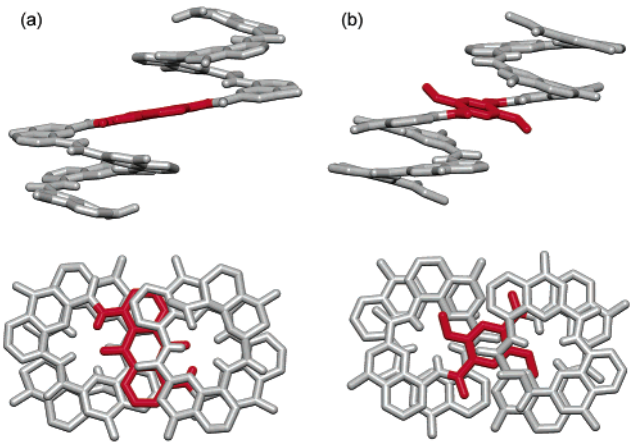

Figure 2. Side views (top) and top views (bottom) of stick representations of the crystal structure of **2** (a) and of the crystal structure of **3** (b). The diaminoanthraquinone moiety in **2** and the dimethoxyterephthalic unit in **3** are shown in red. Included solvent molecules, isobutyl groups, and carbon hydrogens have been omitted for clarity.

Solid-State Structural Studies. The concept was first validated in the solid state by the structure of **2** (Figure 2a) obtained by single-crystal X-ray diffraction analysis (Table 1).[9] The first quinoline group at the C-terminus of each tetrameric quinolinecarboxamide segment is almost coplanar with the anthraquinone ring, and the network of intramolecular hydrogen bonds sets the conformation of each rotatable bond over the entire strand. Tight hydrogen bonds are established between the anthraquinone oxygens and the neighbor amide protons

(9) The poor quality of this structure is due to weak diffraction intensity and strong disorganization of isobutyl side chains and included solvent molecules, some of which show partial occupancy factors.

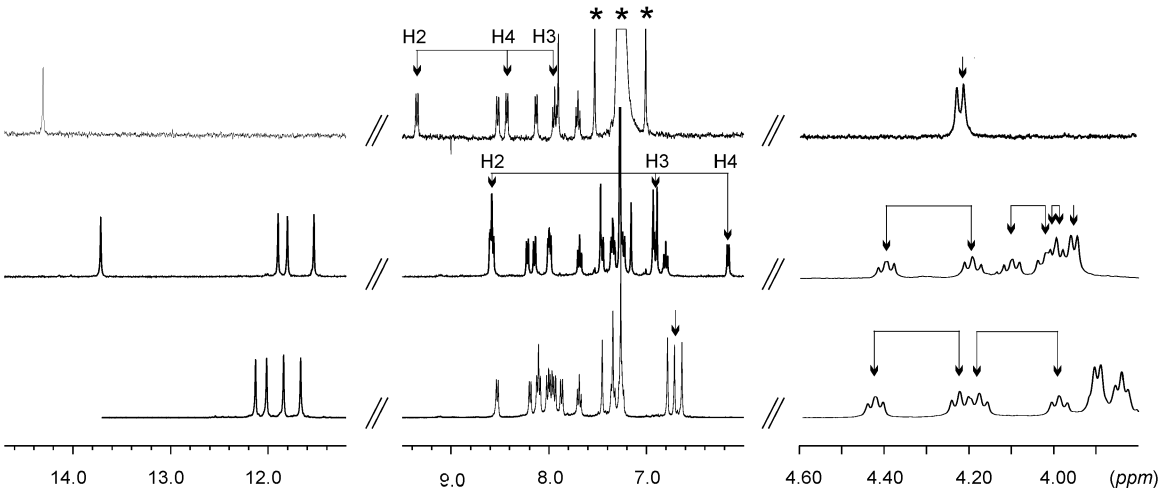

Figure 3. Part of the 400 MHz ^{1}H NMR spectra of **1** (top), **2** (middle), and **3** (bottom) in $CDCl_3$ showing the signals of amide (11−15 ppm), aromatic (6−9.5 ppm), and methylene (3.8−4.6 ppm) protons. The arrows in the aromatic region indicate the signals of anthraquinone (**1** and **2**) and of terephthaloyl (**3**) protons assigned from COSY and HMBC experiments. The arrows in the methylene region indicate the signals of pairs of diastereotopic protons. The asterisks mark signals of residual $CHCl_3$.

Table 1. Crystallographic Data

	2	**3**
solvent/precipitant	$(CH_2Cl)_2$/hexane	$CHCl_3$/pentane
aspect	orange prisms	yellow prisms
radiation type	Cu Kα	Mo Kα
formula	$C_{63}H_{59}N_9O_{11}\,(CH_2Cl)_2$-$(H_2O)_6$	$C_{62}H_{63}N_8O_{11}\,(C_5H_{12})$-$(CHCl_3)_2$
fw	1325.24	1407.09
cryst syst	monoclinic	monoclinic
space group	*P*21/*c*	*P*21/*n*
unit cell params		
a (Å)	13.9715(1)	18.8887(11)
b (Å)	27.4987(1)	19.0940(12)
c (Å)	17.0704(1)	19.6816(15)
β (deg)	97.856(1)	98.967(3)
temp (K)	173(2)	150(2)
Z	4	4
R_1 ($I > 2\sigma(I)$)	0.1708	0.0814
wR_2 (all data)	0.4759	0.2625
GOF	1.128	1.030

(d_{N-O} = 2.56 Å; ∠(N−H−O) = 140°). The helical segments are found on opposite sides of the anthraquinone. The top view of the structure clearly shows that the two helices would bump into each other if they were located on the same side. The structure possesses a center of symmetry in the middle of the anthraquinone ring, and the asymmetric unit contains only half a molecule. The two helices thus have opposite handedness, giving rise to *meso*-helicity.

The structure of **3** was also characterized in the solid state (Figure 2b) by single-crystal X-ray diffraction analysis (Table 1). It is strongly related to that of **2**. As expected, rotations about the aryl−carbonyl bonds of the linker are restricted by NH−O hydrogen bonds (d_{N-O} = 2.66 Å; ∠(N−H−O) = 127°) and add to the network of conformational restrictions that holds the entire structure. Thus, the linker belongs to both helical segments. This time, it is slightly tilted (25°) out of the plane of the two adjacent quinoline rings. It lies parallel to the next two quinoline rings in the sequence between which it is sandwiched. As for **2**, the two helical segments of **3** are found on opposite sides of the linker, leading to a centrosymmetric, *meso*-helical structure. Supramolecular *meso*-helices have occasionally been encountered in the solid state.[10] But to the best of our knowledge, the structures of **2** and **3** represent the first examples of rationally designed *meso*-helices.

Solution Studies. In solution, ^{1}H NMR spectra of **2** and **3** strongly resemble the sharp NMR spectra of the AOA helices that we previously characterized.[7] The signals of aromatic protons are strongly shifted upfield from their positions in the spectra of **1**, indicating extensive intramolecular π−π stacking (Figure 3). For example, in compound **1**, the signals of anthraquinone protons H2, H3, and H4 are found at 9.35, 7.94, and 8.43 ppm, respectively, whereas they are found at 8.58, 6.92, and 6.16 ppm, respectively, in compound **2**.[11] The largest upfield shift for H4 and its equivalent H8 ($\Delta\delta$ = 2.27 ppm) is consistent with its position directly exposed to the ring current of a quinoline ring as observed in the solid-state structure of **2**. The signals of the amide protons are shifted downfield—as high as 14.3 ppm for the amides directly connected to the anthraquinone—consistent with their involvement in intramolecular hydrogen bonds. The CH_2 groups of the isobutoxy chains of **2** and **3** give rise to diastereotopic signals, showing that the P and M helical conformers are inverting slowly on the NMR time scale. This latter fact is particularly important because two sets of NMR signals would be expected for P−M diastereomers on one hand, and for P−P and M−M enantiomers on the other hand.[12] However, only one set of signals is observed, implying that only one species prevails in solution[13] and giving strong evidence that the solution conformations of **2** and **3** are the same as in the solid state.

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(11) In the spectrum of **2**, the signals of H4 and H2, at 6.92 and 8.58 ppm, respectively, overlap with other signals belonging to the quinoline protons. However, they can be unambiguously assigned from 2D NMR experiments.

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(13) As suggested by a reviewer, one set of signals with diastereotopic patterns could, in principle, be observed when the P−M helix inverts slowly on the NMR time scale, and when a small fraction of P−P and M−M helices are in fast exchange with the P−M helix. The signals of the P−P and M−M enantiomers should then appear at low temperature when inversion of all helices becomes slow. However, low-temperature studies on **2** and **3** showed that this is not the case. For both compounds, only one species prevails in solution.

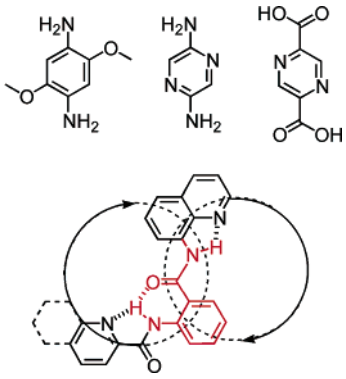

Figure 4. Examples of spacers expected to lead to an inversion of handedness within an aromatic amide helical oligomer.

The centrosymmetric structure of **2** and **3** implies that the inversions of the two helical segments are coupled: for one inversion to occur, the other segment must be at least partially unfolded, and after inversion of one segment has occurred, the other segment cannot rewind to its initial helicity and must invert as well. This explains that the inversion of the tetrameric segments in **2** and **3** is slower than in isolated tetramers for which inversion is fast on the NMR time scale at room temperature.[7]

The AOA oligomers on either side of the anthraquinone and the dimethoxyterephthaloyl spacers have a well-defined relative position that results from mutual steric exclusion. There is no contact between them. This is in sharp contrast with the general modes of folding of natural or artificial tertiary structures, which imply numerous direct interactions between the secondary elements as, for example, the collapse of hydrophobic residues. Many linkers can be designed to induce an inversion of helix handedness within an aromatic amide helical oligomer (Figure 4). When the spacer is a diamine or diacid, it also produces an inversion of C to N polarity of the strand. When the spacer is an amino acid, an inversion of handedness is expected without an inversion of C to N polarity. This is the case, for example, for a simple 2-aminobenzoic acid unit (Figure 4).

Conclusion

We have presented a simple strategy to control the relative orientation of two folded helical oligomers in such a way that they diverge from an aromatic linker and have opposite helical handedness. This strategy has allowed the preparation of the first designed *meso*-helices. Future development of this work includes the study of molecular strands with multiple centers of inversion. For instance, molecular strands built solely from spacer units as those shown in Figure 4 can adopt linear conformations.[14] Other developments include switchable inversion centers and the combination of helix inversion centers with chiral residues that promote absolute helical handedness.[12]

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Supporting Information Available: Crystallographic data in CIF format, and synthetic procedures for the preparation of the *meso*-helices and methods for the crystallographic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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