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The Herringbone Helix: A Noncanonical Folding in Aromatic−Aliphatic Peptides

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Synthetic oligomers and polymers having folded conformations in solution—foldamers—constitute a chemically very diverse ensemble.[1] In contrast, the folding patterns themselves show less diversity: most belong to the canonical folds found in biopolymers—helices, turns, linear strands—and other folding modes as knots,[2] "tail biters",[3] or pillars[4] are rare. A reason for this may be that canonical folds predominate in sequences based on the repeat of a single folding codon and in sequences based on closely related codons, as in $\alpha/\beta/\gamma$-peptide hybrids[5] or in aromatic peptide hybrids.[6] Indeed, a majority of the reports of unconventional folds to date concern the less explored oligomers that include folding codons of different nature as, in particular, combinations of aliphatic and aromatic backbone moieties.[2−4,7] Consistent with this trend, we herein describe the unprecedented folding mode of aromatic−aliphatic δ-peptides.

Oligoamides of 8-amino-2-quinoline carboxylic acid (Q in Figure 1) adopt exceptionally robust helically folded conformations in solution[8] and represent versatile building blocks to elaborate large folded architectures.[9] Robustness, however, is not always a desirable feature for biological applications and often causes synthetic difficulties due to the resulting steric hindrance.[10] We thus sought for solutions to introduce flexibility within Q_n oligomers, taking a path opposite to that followed by many peptide chemists who introduce rigidity into otherwise flexible backbones.[11] Monomer P (Figure 1) was designed as a structural analogue of Q that may impart flexibility because of its reduced surface for intramolecular $\pi-\pi$ stacking and because its aliphatic methylene unit interrupts π-conjugation and introduces an additional rotatable bond.

Molecular modeling studies were carried out to assess the compatibility of P with folded helices of Q oligomers. As shown in Figure 1b,c, energy minima are found for helical conformations of P_{16} and $(PQ)_8$ resembling Q_{16} helices.[8,9] The two methylenic protons which protrude on either side of the pyridine planes apparently do not perturb intramolecular π-stacking, giving rise to a helical pitch of 3.5 Å in all cases. The reduced bending angle at the sp^3 carbon negligibly alters curvature (2.5 units/turn).

Encouraged by these findings, we prepared monomer P from dimethyl 2,6-pyridinedicarboxylate (Figure 1) and undertook the synthesis and conformational studies of P_{2n} and $(PQ)_n$ oligomers with $n = 1, 2, 4$ (see Supporting Information). The ^{1}H NMR spectra of P_{2n} oligomers in $CDCl_3$, toluene-d_8, or DMSO-d_6 much contrast with those of Q_{2n} and readily suggest that no folding occurs for this series in nonprotic solvents, even at low temperature. Specifically, protons at equivalent positions of each unit give signals at comparable chemical shifts regardless of the unit position in the sequence and regardless of chain length (Table 1).[12] Upon drying, P_{2n} oligomers form waxy solids, precluding crystallographic analysis of their conformation. This behavior reveals that P does impart considerable conformational flexibility, and that the energy minimum found in modeling studies (Figure 1b) is probably a shallow minimum.

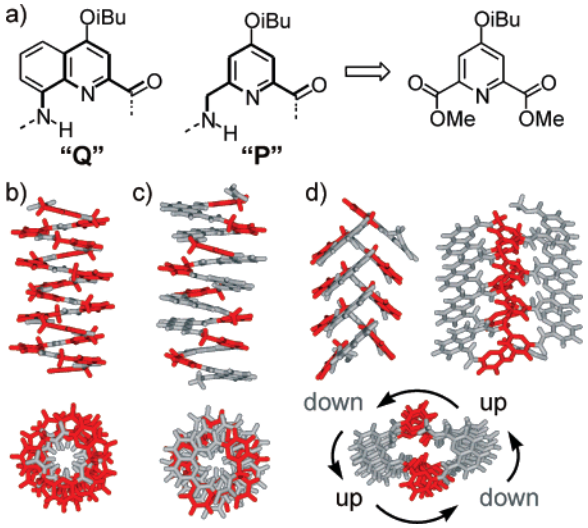

Figure 1. Top: structures of monomers P and Q; (a) the backbone common to the two structures is emphasized by bold lines. Bottom: side view and top view of energy minimized conformations (MacroModel v8.6; force field MM3) of P_{16} (b) and $(PQ)_8$ (c) as canonical helices and $(PQ)_8$ (d) as a noncanonical "herringbone" helix. Amide and quinoline moieties are shown in gray; 6-aminomethyl units are shown in red. Isobutyl side chains have been omitted for clarity.

Table 1. Chemical Shift Values[a] of Terminal Methylenic Ester Protons

n	1	2	4
$O_2N-Q_{2n}-OCH_3$[b]	4.23	3.46	3.01
$Boc-P_{2n}-OCH_3$	4.01	3.94	3.91
$Boc-(PQ)_n-OCH_3$	4.11	3.62	3.57

[a] In $CDCl_3$ at 25 °C. [b] The nitro group replaces the terminal NH unit.

We expected that alternating Q with P monomers would restore some rigidity and promote folding. Indeed, NMR spectra of $(PQ)_n$ oligomers show sequence and chain length dependence of chemical shifts (Table 1). A solid-state structure of $(PQ)_4$ revealed a folded architecture, but not the canonical helix (Figure 1c) expected by analogy between P and Q. Instead, an unprecedented[13] conformer was observed in which PQ pairs form planes orthogonal to the contiguous PQ pairs in the sequence. The 90° kink occurs where the π-conjugated backbone is interrupted by the aliphatic methylenic unit; it reflects the poor tendency of the 6-amidomethylpyridine to form an intramolecularly hydrogen-bonded ring (Figure 2b). A surprising feature is that this arrangement allows for a large overlap and thus extensive $\pi-\pi$ interactions between PQ pairs in position

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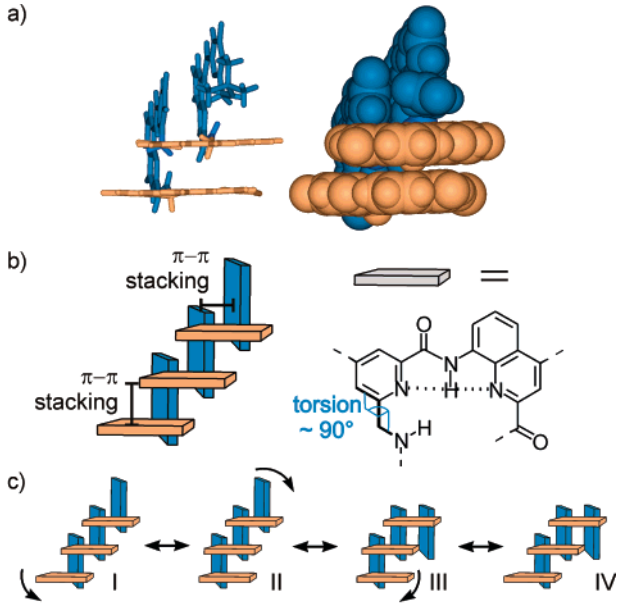

Figure 2. (a) Stick and CPK representations of the crystal structure of Boc(PQ)$_4$OMe. Isobutyl chains and included solvent molecules have been omitted for clarity. (b) Simplified schematic representation of a right-handed herringbone helix showing two color-coded stacks of π-conjugated groups; each group consists of a PQ dyad orthogonal to the previous and following dyads in the sequence. Changes in the tilt angle of the strand with respect to the axis are not depicted in this scheme (see Figure 1d). (c) Alternate conformers resulting from 180° flips of the terminal PQ dyads. The structure in (a) corresponds to form II.

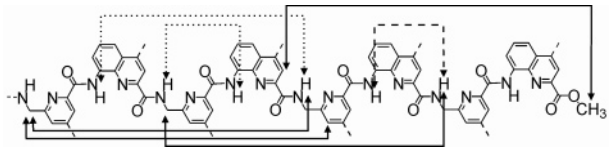

Figure 3. NOE correlations compatible with a herringbone helix (solid lines), with a canonical helix (dotted lines), and with both (dashed line).

i and *i*+2. The resulting structure is helical in that it possesses a twist sense but does not fit the canonical definition of a helix: the tilt angle with respect to the helix axis is not constant but changes sign four times per turn at each pyridine methylene and carbonyl group (Figure 1d). Thus, the overall aspect of the fold is that of two stacks of aromatic rings perpendicular to each other, resembling a herringbone motif. Modeling studies confirm that (i) such a pattern can be propagated over long sequences (Figure 1d); (ii) terminal PQ pairs can be flipped by 180° without disrupting the rest of the structure (Figure 2c); and (iii) this 180° rotation cannot be accommodated at PQ pairs within the sequence without perturbing $\pi-\pi$ stacking due to internal sterics.

NMR structure studies were carried out to assess whether the structure found in the solid state also prevails in solution. Spectra are slightly broad at 25 °C, broaden further upon cooling, and sharpen upon heating. A full assignment of the spectra was possible in toluene-d_8 at 75 °C based on HMBC and HSQC experiments as described previously.[8c] NOESY experiments allowed us to identify seven strong NOE correlations between protons remote in the sequence (Figure 3). Four of them are indeed compatible with the herringbone fold observed in the solid state, or to alternate herringbone helices where terminal PQ units may be flipped by 180°, but other correlations are incompatible and, on the contrary, match with a canonical helical fold (Figure 1c). These results together with the slight broadening of the spectra at lower temperature suggest that the two types of folds coexist in solution. Other folding modes cannot be strictly excluded. Fast equilibrium on the NMR time scale is confirmed by the absence of diastereotopic motifs in main chain and side chain methylenic signals despite the chiral nature of the conformers. It might be speculated that a subtle balance of P and Q monomers would favor one or the other fold, or even allow for alternate patterns.

These results support the view that aliphatic−aromatic hybrid oligomers often adopt unconventional conformations. Though aliphatic moieties are reduced to methylene bridges in P_{2n} and $(PQ)_n$, their effect on folding is dramatic. Such hybrids are likely to be the object of increased scrutiny in the coming years.

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Supporting Information Available: Synthetic procedures, characterization of new compounds, spectroscopic data, and complete ref 6a. This material is available free of charge via the Internet at http://pubs.acs.org.

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