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Aromatic δ-Peptides

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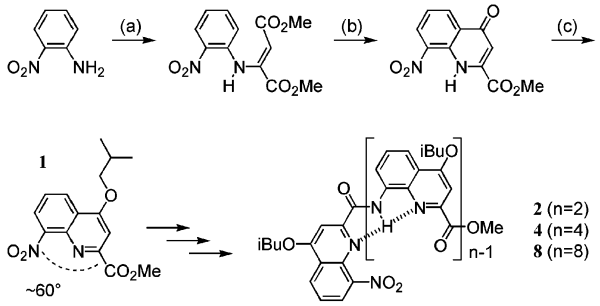
Aliphatic β-, γ-, and δ-homologues of α-peptides adopt helical or linear conformations mimicking the structures and potentially the functions of their natural counterparts.[1,2] Oligoamides of aromatic amines and acids can also fold into well-defined structures that may prove useful in the field of peptidomimetics.[1,3−5] Yet, these compounds have been less studied despite the fact that their conformations are often more predictable than those of their aliphatic analogues. The predictability of the folding of an oligomeric molecule is largely increased when stabilizing intramolecular interactions (e.g., hydrogen bonds) take place between consecutive units, because it allows the extrapolation of the conformation of short strands to longer ones. Following this principle, we have designed and now report on the helix formed by oligomers of a new quinoline-derived δ-amino acid.

Oligoamides of some *meta*-substituted pyridine- and benzene-derived amines and acids have been shown to fold into crescent and helical structures.[3,4] In principle, a *meta* substitution defines an orientation of 120° between substituents and should lead to 6 units per turn in these bent conformations. In practice, intramolecular hydrogen bonding has an effect on the bending of the strands, and helices of *meta*-substituted aromatic oligoamides comprise from 4.5 to 8 units per turn, which remains larger than the 2−4 units per turn encountered in helices of aliphatic α, β, and γ peptides. We speculated that aromatic oligoamides with substituents oriented at 60° (for example, *ortho* substituents) may be more bent and give rise to helices with approximately 3 units per turn. Quinoline monomer **1** was designed for this purpose. Its nitro and ester groups can respectively be reduced to an amine and saponified to an acid, oriented at ∼60° (Scheme 1). In oligomers of **1**, intramolecular hydrogen bonding between the amide hydrogen and both adjacent quinoline nitrogens is expected to stabilize a bent shape, eventually giving rise to a helix for strands as short as a trimer.

Quinoline **1** was prepared in only three steps: addition of 2-nitroaniline to dimethyl acetylenedicarboxylate, thermal closure of the pyridine ring, and formation of the alkyl−aryl ether using isobutanol under Mitsunobu conditions (Scheme 1).[6] This latter step should allow the facile introduction of numerous groups other than isobutyl in position 4 of the quinoline. Such groups, which mimic peptide side chains, are expected to diverge from the helix and control its physical properties (solubility, amphiphilicity, recognition motifs). A segment doubling strategy[7] involving selective deprotections and couplings via acid chlorides was then adopted to yield dimer **2**, tetramer **4**, and octamer **8** in a convergent manner.

The ^{1}H NMR spectra of **2**−**8** in $CDCl_3$ are sharp (Figure 1) and show no indication of hybridization into double helices or other types of aggregates, as was observed for pyridine-derived oligoamides.[8] The signals are spread over a large range of chemical shifts despite the repetive nature of the sequences, suggesting different

Scheme 1. Synthesis of Quinoline Monomer **1** and Structure of Oligomers **2**−**8**[a]



[a] (a) Dimethylacetylene dicarboxylate, MeOH, room temperature; (b) diphenyl ether, reflux; (c) ^{i}BuOH, DEAD, PPh_3, THF, room temperature.

environments of each units. Amide protons are deshielded at 10−12.5 ppm, as is expected for a hydrogen-bonded structure. Increasing strand length results in a strong shielding of aromatic, amide, and ester protons that can be attributed to tight contacts between aromatic rings. For example, the signal of the ester CH_3 shifts from 4.23 ppm in **2** to 2.99 ppm in **8** (Figure 1), and the singlets assigned to the protons in position 3 of the quinoline are found between 7.63 and 8.01 ppm in **2**, and between 6.12 and 7.04 ppm in **8**.

Upon adding chiral shift reagent Eu(hfc)$_3$ to a $CDCl_3$ solution of **8**, amide, aromatic, and ester ^{1}H NMR signals split into two signals of equal intensities, suggesting that this compound exists as a mixture of enantiomers and that stereoselective interactions with Eu(hfc)$_3$ do not induce an enantiomeric excess. This is also supported by the pattern of the signals of the OCH_2 groups at 3.4−4.4 ppm. In the absence of Eu(hfc)$_3$, these signals appear as sharp doublets in **2** and as diastereotopic motifs in **8**. For tetramer **4**, three OCH_2 doublets are seen along with a broad signal, and diastereotopic splitting is observed only at low temperature (−20°). This compound adopts a chiral conformation as well, but its inversion is faster. For comparison, inversion of **8** is slow even at high temperatures in polar solvents. For example, no coalescence is observed at 120° in d_6-DMSO (!), suggesting an exceptionally stable chiral conformation.

All of these data are consistent with helical structures of **4** and **8** inverting slowly on the NMR time scale. ROESY experiments on **8** show correlations between protons in position 3 of the quinolines and protons in positions 5 and 7. We expect that these correlations will give direct evidence of a helical structure in solution, but we have failed in assigning these signals unambiguously to the corresponding quinoline rings in the sequence. Meanwhile, we were able to characterize the structure of **8** in the solid state through single-crystal X-ray diffraction (Figure 2).[9] It shows a helix extending to more than three turns very similar to the helix predicted by molecular modeling (MM3 in MacroModel). The pitch of **8** is identical to the pitch of other helical aromatic oligoamides and corresponds to the thickness of one aromatic ring

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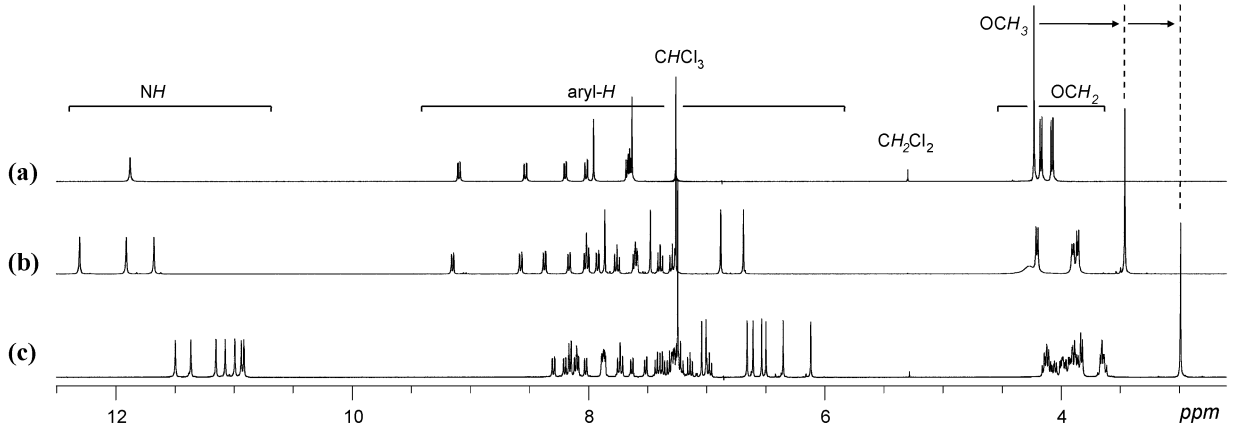

Figure 1. Part of the ^{1}H 400 MHz NMR spectra of (a) **2**, (b) **4**, and (c) **8** in $CDCl_3$.

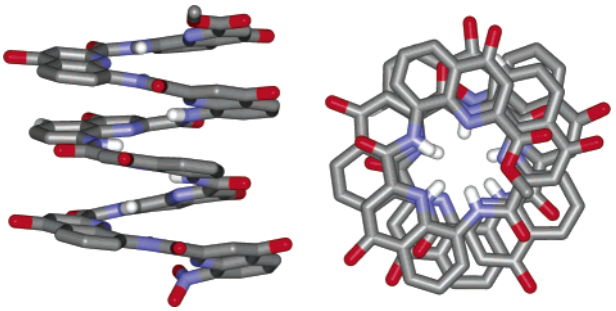

Figure 2. Side view and top view of the structure of **8** in the crystal. Included solvent molecules, hydrogens, and isobutyl chains have been omitted for clarity.

(3.4 Å).[3−5] The inner rim of the helix accomplishes approximately one turn every 15 main chain atoms and adopts a conformation similar to that of a pentaaza-15-crown-5 macrocycle, with alternating amido and pyrido nitrogens. Thus, almost exactly 5 units are required for two helical turns (equivalent to 30 atoms of the inner rim), which corresponds to the highest curvature reached by helical aromatic oligoamides until now. Consequently, helices of quinoline-derived **4**−**8** also have the largest length per number of units: the helix of octamer **8** is about 13 Å long, as compared to 6.8 Å for octamers of pyridine oligoamides.[3] The amido protons fill the helix hollow and completely prevent penetration of solvent molecules. As expected, they are all involved in two hydrogen bonds with the adjacent quinoline nitrogens that set the orientation of the amido and quinoline moieties (Scheme 1). The relative inclination of consecutive units can be estimated from the torsion angles between the N(1)−C(2) bond of a quinoline and the C(8)−C(9) of the next quinoline which range from 159.2 to 169.5°. The isobutyl chains adopt various conformations. On the contrary, the core of the helix has a very regular structure, illustrated by almost constant distances between the oxygens in position 4 of the quinolines (from 11.87 to 11.93 Å). Bending is even along the strand and does not depend on the central or terminal position of the units, or the conformation of the side chain or interactions associated with crystal packing.

In summary, we have presented a new class of aromatic foldamers based on an easily accessible and functionalizable quinoline amino acid, which adopt remarkably stable helical conformations. Future developments include the preparation of longer oligomers with water-soluble and amphiphilic properties.

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Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Crystal data for **8**: crystallization solvent/precipitant chlorobenzene/hexane, monoclinic, space group *C*2/*c*, color yellow, $a = 46.711(2)$, $b = 18.829(2)$, $c = 30.085(2)$ Å, $\beta = 96.79(2)°$, $T = 296(2)$ K, $Z = 8$, GOF = 0.997. The final *R* indices were R_1 ($I > 2\sigma(I)$) = 0.1373, wR_2 (all data) = 0.5130. The poor quality of this structure is due to weak diffraction intensity and strong disorganization of isobutyl side chains and included solvent molecules. However, all atoms belonging to the backbone of the helix were accurately located (equivalent isotropic displacement parameters of 0.11 Å^2 or less).

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