Helical Structures

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Quadruple and Double Helices of 8-Fluoroquinoline Oligoamides**

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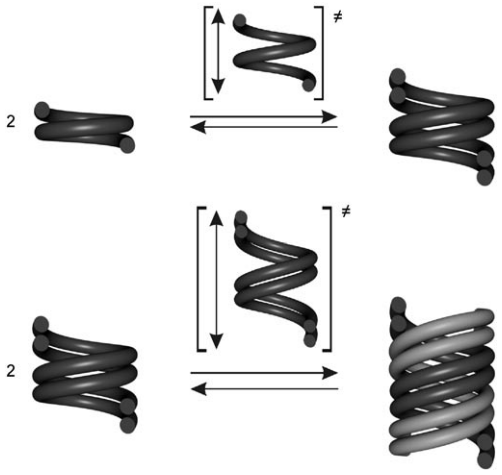
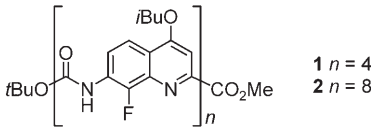
Dedicated to Professor Huijun Xu

The assembly of molecular strands into multiple helical hybrids represents a major strategy that nature uses to control elongated supramolecular architectures such as nucleic acids, collagen, or other coiled strands. Multiple-helix formation from non-natural oligomers has thus emerged as an important subject.[1] Nucleic acids[2] and some artificial oligomers[3] adopt a single-stranded helical conformation in the monomeric state and can wind around one another without significantly changing their helical pitch. In other hybrids, for example, pyridine carboxamide oligomers[4,5] and gramicidin D,[6] compact single-helical conformers must increase their helical pitch and undergo a springlike extension to accommodate a complementary strand and wind into a double helix (Scheme 1, top). For those latter hybrids, double-helix formation thus critically depends on the ease of increasing the helical pitch.

We recently found that the hybridization of pyridine carboxamide oligomers is dramatically enhanced when one unit that is designed to enlarge the helix diameter—that is, consisting of three fused aromatic rings—is introduced in the sequence, precisely because this unit lowers the enthalpic cost of springlike extension.[5] Aggregation and, possibly, hybridization are also promoted in helical pyridine–pyridazine oligomers because of their large diameter.[7] Intrigued by the possible outcomes of using exclusively units that give rise to a large helix diameter, we designed tetrameric and octameric amides of 7-amino-8-fluoro-2-quinolinecarboxylic acid, compounds **1** and **2**. Herein, we present their remarkable aggregation behavior; we notably show that **1** is able to adopt a helical conformation with a large pitch, which allows the formation of an unprecedented quadruple helix and that **2** dimerizes as an antiparallel double helix.



Scheme 1. Schematic representation of the hybridization of a single helix to a double helix (top), and of a double helix to a quadruple helix (bottom), both through springlike extension.



Several families of aromatic oligoamides have been shown to adopt helical conformations when an aromatic endocyclic nitrogen atom[4,5,8] or exocyclic fluorine atom[9] is placed adjacent to each amide group.[10] In aromatic oligomers, the helix diameter can be tuned upon incorporating larger aromatic subunits with multiple fused rings[5,10,11] and upon manipulating the orientations of the linkages on the aromatic rings.[7,10,12] The motivation to develop helices with a large diameter is generally the potential use of their hollow spaces in molecular recognition.[13,14] Nevertheless, large diameters

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may be associated with characteristic aggregation behaviors, including, as shown below, the formation of a quadruple helix.

Monomer design, monomer preparation, and oligomer assembly for the synthesis of **1** and **2** were inspired from the design and synthesis of oligomers of 8-amino-2-quinolinecarboxylic acid[8] and are described in the Supporting Information. To ensure the preference for helical conformations, an exocyclic fluorine atom (a hydrogen-bonding acceptor)[9] was introduced in the 8-position of each quinoline ring (Scheme S1 in the Supporting Information). Fluorine was preferred to an endocyclic nitrogen atom because of the synthetic hurdles, low solubility, and poor amide stability of 1,8-naphthyridine derivatives.[15] The orientation of the amine and acid functions in **1** and **2** are similar to those in 2,6-disubstituted pyridine oligomers.[4,5] The two families of helices are thus expected to possess the same numbers of units per turn (about four), the quinoline helices being wider owing to the larger size of the monomers. These predictions were verified in the structure of the single-helical conformer of **1** observed in crystals grown from chlorobenzene/hexane (Figure 1a). In the solid state, this tetramer spans just about one turn and, because of steric hindrance, its two ends deviate from planarity and overlap into a single helix with a pitch of approximately 3.5 Å. Consistent with the spectral features of other helical aromatic oligoamides,[12,16] the low-concentration ^{1}H NMR spectrum of **1** is sharp and shows three amide signals at low field ($\delta > 11$ ppm), which is in agreement with the involvement of these protons in intramolecular hydrogen bonds.

Crystals of **1** obtained from a different solvent mixture (toluene/dichloroethane/hexane) were also analyzed by X-ray diffraction and revealed an unprecedented quadruple helix (Figure 1c) in which two molecules of **1** stack in a head-to-tail dimer, and two such dimers are further entwined with offset helical axes so that the four bulky *tert*-butoxycarbonyl (Boc) groups stick out of the quaduplex while the methyl ester groups remain buried in the helix. The structure thus shows two pairs of grooves within and between the head-to-tail dimers, respectively (Scheme 1). Owing to the large diameter of the helix, the vertical rise per turn is accommodated with a tilt angle of the strands with respect to the helix axis comparable to that seen in double helices of pyridine carboxamide oligomers (Figure 1b) and does not require large twist angles at the aryl–amide linkages. In fact, the vertical rise originates from a single twist between the two central quinoline units (31°), while the terminal quinoline rings are essentially coplanar. This particular quadruplex structure arises from two duplexes clipped into one another. It appears to be made possible by the fact that tetramer **1** spans only one helix turn.

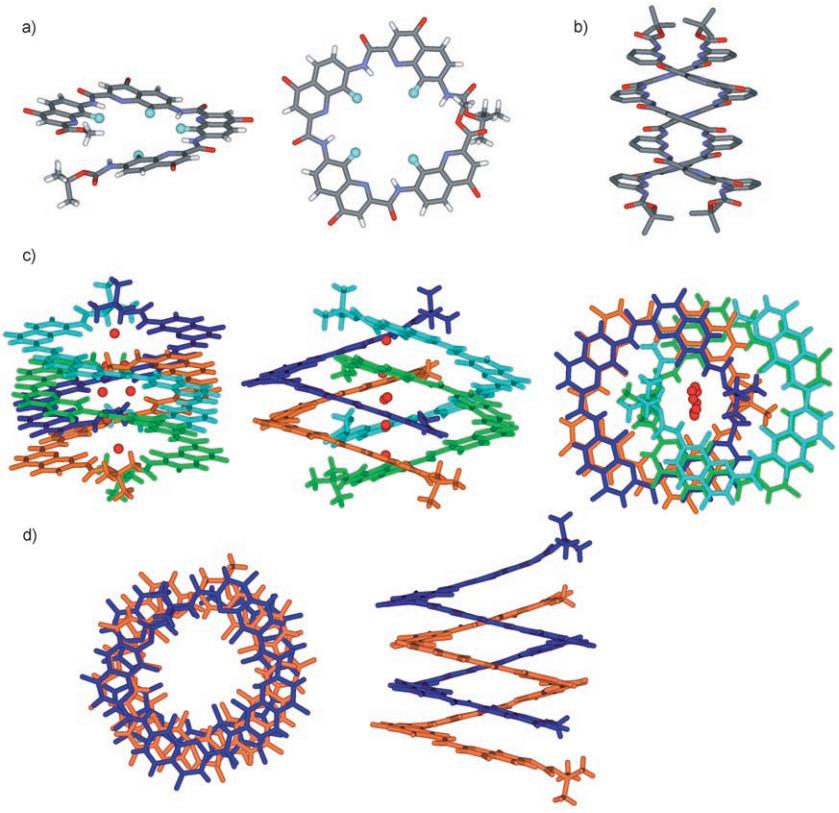

Figure 1. Side views and top views of the crystal structures at the same scale of: a) compound **1** as a single helix; the fluorine atoms converging towards the helix hollow space are shown as spheres; b) a narrow double helix composed of pyridine rings only (shown for comparison);[4a] c) compound **1** as a quadruple helix; a string of sites partially occupied by water molecules is shown as spheres; d) compound **2** as a double helix; alkoxy residues and solvent molecules are omitted for clarity. The similarity between the head-to-tail duplex of **2** and the head-to-tail duplexes that constitute the quadruplex of **1** appears clearly when focusing on the orange and dark blue strands in (c) and (d).

We studied the aggregation of **1** in $CDCl_3$ solutions by ^{1}H and ^{19}F NMR. Upon increasing the concentration (0.5–40 mM), the BocN*H*, ester CH_3, and aromatic signals are shifted upfield ($\Delta\delta$ up to −0.39, −0.41, and −0.31 ppm, respectively). Similar shifts of even larger amplitudes and broadening were observed upon cooling the samples at various concentrations (2–40 mM) from 298 to 223 K (at 2 mM, $\Delta\delta$ up to −1.07, −1.09, and −0.60 ppm, respectively; Table S1 in the Supporting Information). The ^{19}F NMR signals are shifted as well upon cooling ($\Delta\delta > 1$ ppm; Figure S5 in the Supporting Information). Such chemical-shift variations are a typical signature of ring-current effects arising from intermolecular π–π stacking within aggregates of **1** that are in fast exchange with monomeric species on the NMR timescale. Diffusion coefficients were calculated from ^{1}H DOSY measurements recorded at 296 K using 2 mM and 40 mM samples (Figure S6 in the Supporting Information), a concentration range that spans most of the variation in chemical shift. The diffusion coefficients are 5.6×10^{-10} and 3.8×10^{-10} m^2s^{-1} at 2 and 40 mM, respectively. According to the Stokes–Einstein equation, the ratio between these values is consistent with a

volume ratio of 3 in the approximation that the average entities at 2 and 40 mM are assimilated into spheres. Though the approximation of molecular shape to spheres prevents a refined analysis of such data, this ratio is within the range expected for single helix–duplex and duplex–quadruplex equilibria (Scheme 1). The concentration-dependant chemical-shift values at 298 K are well fitted by a simple dimerization isotherm yielding $K_{dim} = 66\ L\,mol^{-1}$.[17] Additionally, NOESY experiments reveal correlations between the quinoline protons at C3 (the only aromatic singlets) and the quinoline protons at C5 and C6 (the aromatic multiplets). Given the distance between these protons on the same quinoline ring, these correlations are unlikely to be intramolecular and are not observed in the NOESY spectra of a precursor of **1** consisting of only two quinoline rings (Figure S7 in the Supporting Information). They may emerge from a stacked head-to-tail dimeric arrangement, as seen in each of the duplexes that constitute the quadruplex crystal structure. Altogether, these data suggest that aggregation does occur in solution in a way that is consistent with the structure observed in the solid state. These aggregates, possibly duplexes or quadruplexes, are labile and remain in fast exchange with monomeric helical species at room temperature.

At low temperature, the spectra of a concentrated sample of **1** (40 mM) reveal the emergence of a second set of signals (Figure 2). The proportion of these signals increases upon decreasing the temperature (up to 35% at 233 K), thus showing that a higher aggregate exists that is in slow exchange on the NMR timescale with the monomeric and aggregated species observed at room temperature. The signals of this aggregate are found at even higher field, suggesting that it involves additional intermolecular π–π stacking. Attempts to assess the size of this aggregate through DOSY experiments were hampered by its precipitation at 233 K over long acquisition times. This problem persisted at slightly higher temperatures (243 K), and at even higher temperatures (273 K) the signals of the aggregate were not intense enough. However, the slow exchange and the sharp NMR lines point to a well-defined species. Since the solid-state quadruplex structure consists of two head-to-tail duplexes and given the size estimate of the aggregates observed at room temperature, the new species observed at low temperature by NMR could well be the quadruplex itself. Yet other aggregation modes cannot be ruled out.

The structure and aggregation behavior of octamer **2** was investigated as well. In the solid state, it forms an antiparallel double helix (Figure 1 d) wherein the relative arrangement of the two strands is very similar to the head-to-tail stacks of two molecules of **1** found in the quadruplex. The first quinoline ring of each strand largely overlaps—with a small offset—with the last quinoline ring of the other strand, thus bringing the terminal ester and *tert*-butyl groups of opposite strands in close proximity. Within each strand, the position and orientation of the fluoroquinoline and amide units are consistent with the initial design and with the two structures of the tetramer. In particular, all fluorine atoms are found within the hollow space of the helix. The strands of $(\mathbf{2})_2$ span about two helical turns.

The ^{1}H NMR spectra of **2** in solution ($CDCl_3$) show a single set of slightly broad signals, which are all found considerably upfield from the corresponding signals of tetramer **1**. Upon increasing the concentration (from 1 to 20 mM) or upon cooling (from 298 K to 223 K), only minor variations in chemical shift are observed, the largest variations being for the signals of the BocN*H* and ester CH_3 groups ($\Delta\delta < 0.22$ ppm). In contrast to the corresponding shifts observed for tetramer **1**, these are downfield and not upfield shifts. In pyridine, a solvent in which double helices of aromatic oligoamides tend to dissociate,[5] no significant change occurs. However, whether in chloroform or pyridine, heating or high dilution results in the onset of a second set of

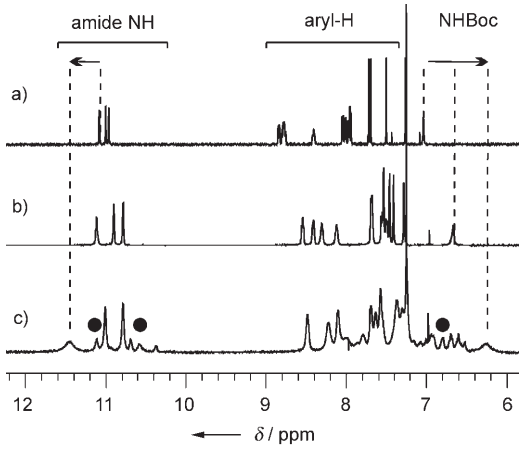

Figure 2. Excerpts of the ^{1}H NMR spectra of **1** in $CDCl_3$. a) 2 mM at 298 K; b) 40 mM at 298 K; c) 40 mM at 243 K. Increasing the concentration at room temperature causes chemical-shift variations indicative of aggregate formation. Cooling at high concentration leads to the onset of a second species (black circles) corresponding to a higher aggregate. This species is not observed upon cooling a 2 mM solution (spectrum not shown).

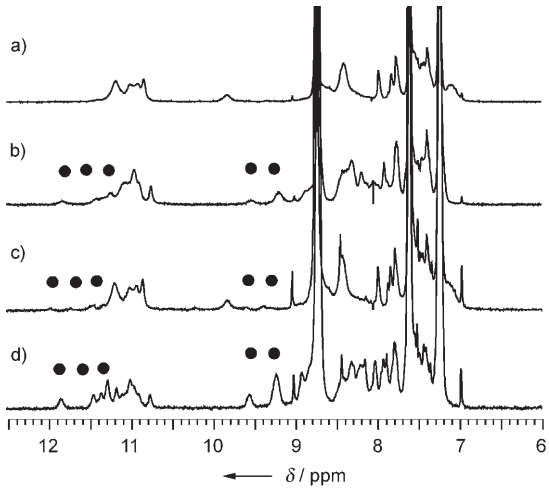

Figure 3. Excerpts of the ^{1}H NMR spectra of **2** in [D_5]pyridine. a) 6 mM at 298 K; b) 6 mM at 360 K; c) 1 mM at 298 K; d) 1 mM at 360 K. Both decreasing the concentration and increasing the temperature lead to the onset of a new species in slow exchange on the NMR timescale (black circles).

signals at lower field in the ^{1}H NMR (Figure 3) and ^{19}F NMR spectra. In light of the multiple experiments performed with pyridine-based oligomers[4,5] and in view of the solid-state structure of **2**, this behavior suggests that **2** forms a very stable double helix in solution that prevails even at low concentration and that dissociates into two single helices at high temperature, giving rise to the new set of signals. The multiplicity of the signals of $(\mathbf{2})_2$ indicates that only one of the two possible duplexes is formed, presumably head-to-tail, as observed in the solid state, and not head-to-head. Integrations of the small aggregate signals observed in dilute solutions of **2** allowed us to estimate the dimerization constant at 25 °C: $K_{dim} = 3.6 \times 10^5\ L\,mol^{-1}$ in [D$_5$]pyridine and $8.5 \times 10^5\ L\,mol^{-1}$ in $CDCl_3$. The enthalpy and entropy of hybridization in pyridine were extracted from a van't Hoff plot to be $-73.2\ kJ\,mol^{-1}$ and $-136.3\ J\,K^{-1}$, respectively. The large value of ΔS is illustrated by the strong temperature dependence of the molar ratio between **2** and $(\mathbf{2})_2$. Attempts to form higher aggregates of **2**, as the quadruple helix of **1**, at high concentration and low temperature proved unsuccessful. As mentioned above, the quadruplex structure appears to be made possible by the fact that **1** spans only one helical turn; such a structure might not be accommodated by **2**.

In conclusion, we have found that the ability of helical aromatic amides to hybridize into double helices is not restricted to the pyridine-based oligomers studied previously but also applies to fluoroquinoline carboxamide oligomers, the structures of which are quite remote from the former. One may speculate that this behavior bears some generality, especially for helices with a large diameter. Our study also revealed that hybridization of aromatic oligoamides may not only lead to a duplex, but also to higher organizations such as a quadruplex, at least for a short oligomer. We are currently focusing on the molecular-recognition properties of the hollow spaces of these large multiple helices.

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