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# Multivalent Interactions between an Aromatic Helical Foldamer and a DNA G-Quadruplex in the Solid State

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Quinoline-based oligoamide foldamers have been identified as a potent class of ligands for G-quadruplex DNA. Their helical structure is thought to target G-quadruplex loops or grooves and not G-tetrads. We report a co-crystal structure of the antiparallel hairpin dimeric DNA G-quadruplex $(G_4T_4G_4)_2$ with tetramer **1**—a helically folded oligo-quinolinecarboxamide bearing cationic side chains—that is consistent with this hypothesis. Multivalent foldamer–DNA interactions that modify the packing of $(G_4T_4G_4)_2$ in the solid state are observed.

Aromatic oligoamide foldamers[1] may adopt stable folded conformations with predictable shapes such as helices,[2] flat macrocycles,[3] sheets,[4] or linear and zig-zag rods,[5] the surfaces of which can be functionalized with proteinogenic side chains organized at precise positions in space. These decorated scaffolds are typically in the 1–5 kDa range and constitute potent medium-sized candidates—larger than small molecules and smaller than proteins—to recognize surfaces of proteins or nucleic acids. For example, rod-like α-helix mimetics have been developed as protein–protein interaction inhibitors,[6] anionic oligomers were shown to bind to and to interfere with folding and aggregation of the islet amyloid polypeptide,[7] pyrrole-imidazole oligomers are strong B-DNA minor groove binders,[8] and some helical aromatic oligoamides have been shown to interact with the surface of human carbonic anhydrase II.[9] In the context of these studies, accurate structural information is important but has proved to be difficult to obtain.[8,9] The results presented below thus constitute a rare example of structure elucidation of an aromatic foldamer–biopolymer assembly.

We have found that helical oligoamides based on 8-amino-quinoline-2-carboxylic acid and bearing cationic side chains, such as tetramer **1** (Figure 1), bind to DNA G-quadruplexes in solution, including the human telomeric G-quadruplex (H-telo) and quadruplex sequences of several gene promoters (e.g., *c-kit*1,[10] *c-kit*2,[11] *c-myc*,[12] *k-ras*,[13] and *bcl*2[14]).[15] In contrast, FRET melting assays showed that binding to duplex DNA is weaker. These findings were corroborated by the fact that directed DNA evolution studies against a related foldamer sequence twice as long as **1** yielded aptamers that were all G-quadruplex folds.[16]

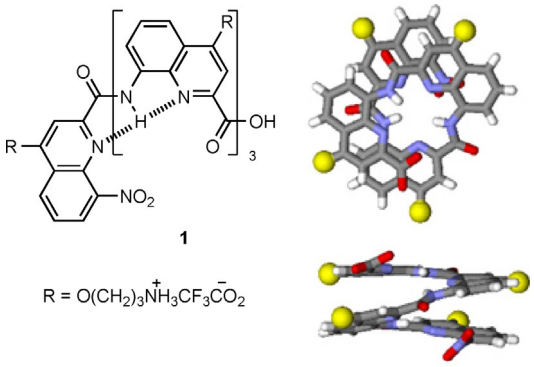


**Figure 1.** Formula and solid-state folded structure of cationic tetramer **1**.

Oligomers such as **1** adopt a very stable helical conformation in water, due to the contribution of hydrophobic effects in intramolecular π–π interactions.[17] Because **1** possesses no stereogenic centre, it exists as an equimolar mixture of right-handed and left-handed helices spanning over 1.5 turns. Foldamer–quadruplex interactions have been shown to be handedness-selective in the cases of H-telo[15a] and of a DNA-aptamer.[16] The non-flat shape of the helices hints at a foldamer binding mode to G-quadruplexes distinct from the classical stacking of flat cationic aromatic ligands on top of G-tetrads.[18] Indeed, other ligands have been shown to bind to groove[19] or loop[20] regions of G-quadruplexes. Helical and $C_3$-symmetrical aromatic objects have also been found to bind in the cavity of a three-way junction.[21] In order to gain insights into the inter-

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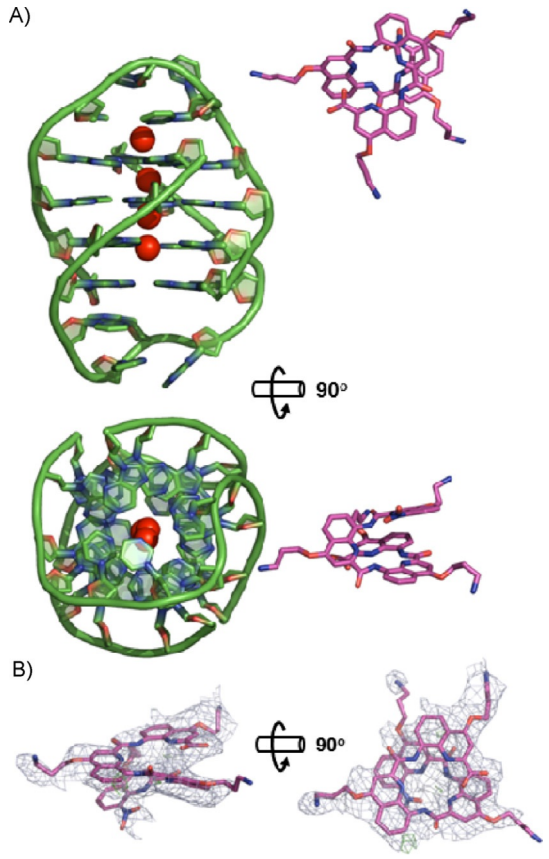


**Figure 2.** A) Asymmetric unit consisting of d(GGGGTTTTGGGG)$_2$ (green) and **1** (magenta). $K^+$ ions shown as red spheres. B) Sigma-weighted $2F_o-F_c$ (grey mesh, contoured at the $1\sigma$ level) and $F_o-F_c$ (green mesh, contoured at the $3\sigma$ level) electron density map superimposed onto **1**.

actions between **1** and G-quadruplexes, we have sought for structural information and now report the co-crystal structure of **1** with the *Oxytricha* dimeric intermolecular G-quadruplex formed from two strands of d(GGGGTTTTGGGG)[22] at a resolution of 2.48 Å. The structure (Figure 2A) shows multivalent foldamer–quadruplex interactions, suggesting a complex binding stoichiometry rather than a well-defined 1:1 complex. These interactions induce a different packing mode of the quadruplex and are consistent with our hypothesized absence of stacking onto G-tetrads.

Initial attempts focused on the crystallization of various cationic foldamers and macrocycles together with the H-telo sequence for which interactions had been detected in solution.[15c] Crystallization by the standard hanging-drop vapour diffusion method from aqueous solutions only led to the formation of precipitates immediately after mixing of the foldamers and DNA. No crystal grew from these samples. This precipitation was attributed to potential multivalent electrostatic interactions between the multianionic DNA and the multicationic foldamers, which are both independently readily soluble. Lowering the concentration or adding monovalent or divalent metal ions did not prevent precipitation and did not help to provide X-ray-quality crystals.

The native *Oxytricha* sequence is well established to fold into a symmetric, bimolecular quadruplex both in crystalline and in solution forms.[22,23] We attempted co-crystallization of **1** with this sequence because it was known to crystallize more easily than the H-telo quadruplex. [It should be pointed out that these crystallization attempts were made prior to our recent development of a racemic DNA crystallographic approach in which both D- and L-DNA are mixed in equimolar amounts.[24] Hence, only the D enantiomer—that is, D-d(GGGGTTTTGGGG)—was used.] As with H-telo, the general outcome of mixing the foldamer and DNA was the immediate formation of a precipitate. However, in the case of **1**, crystals eventually grew. Data collection and resolution led to the structure described below. Crystal data and refinement parameters (Table S1 in the Supporting Information) and experimental details are presented in the Supporting Information.

The tetragonal unit cell dimensions observed for this crystal—that is, $a=b=31.70$ Å and $c=97.37$ Å in space group $P4_1$—are unique among the various structures of the *Oxytricha* sequence (see Table S2 for comparisons). Other structures reported in the PDB[25] belong to the orthorhombic space group $P2_12_12_1$ and the trigonal space group $P3_221$ for native, ligand-free, forms[22] and the orthorhombic space groups $P2_12_12_1$ and $P2_12_12$ for ligand-bound forms.[26] The crystallographic asymmetric unit contains two DNA molecules assembled in a hairpin dimer G-quadruplex and one molecule of **1** (Figure 2A). The G-quadruplex comprises two strands of d(GGGGTTTTGGGG) with a diagonal fold topology, in which the thymine loops d(TTTT) are lying diagonally across the top and bottom of the stack of guanine quartets, and the strands of each sequence are antiparallel to each other (Figure 2A). This G-quadruplex fold is identical to that found in crystal structures of the *Oxytricha* native G-quadruplex[22] and by NMR studies in $Na^+$ and $K^+$ environments.[23] The electron density of **1** is well resolved and allows the assignment of the N-terminal and C-terminal orientation of the helix, the positions of the side chains, and a left-handed helix sense (Figure 2B). In solution, negative circular dichroism bands were observed near 400 nm in the absorption region of the quinoline chromophores of **1** upon addition of the *Oxytricha* sequence (Figures S1 and S2). On the basis of previous unambiguous assignments,[27] this indicates that a left-handed helix also prevails in solution.

The solid-state structure is not that of a discrete complex but that of a co-crystal in which each foldamer interacts with several quadruplexes, and each quadruplex interacts with several foldamers, thus establishing an infinite network of molecules linked through multivalent interactions (Figure 3A). Figure 3B–D compares *Oxytricha* DNA quadruplex packing in the absence and in the presence of ligands. Square-like arrangements of quadruplexes have been reported before[26a] but do not leave enough interstitial space to accommodate a foldamer. In contrast, multivalent DNA–foldamer interactions here promote increased quadruplex–quadruplex distances, thus suggesting that they have guided crystal growth and packing. Cationic foldamer side chains were found to protrude towards DNA backbone loops and guanine grooves of adjacent G-quadruplexes. The limited resolution of our X-ray data prevent-

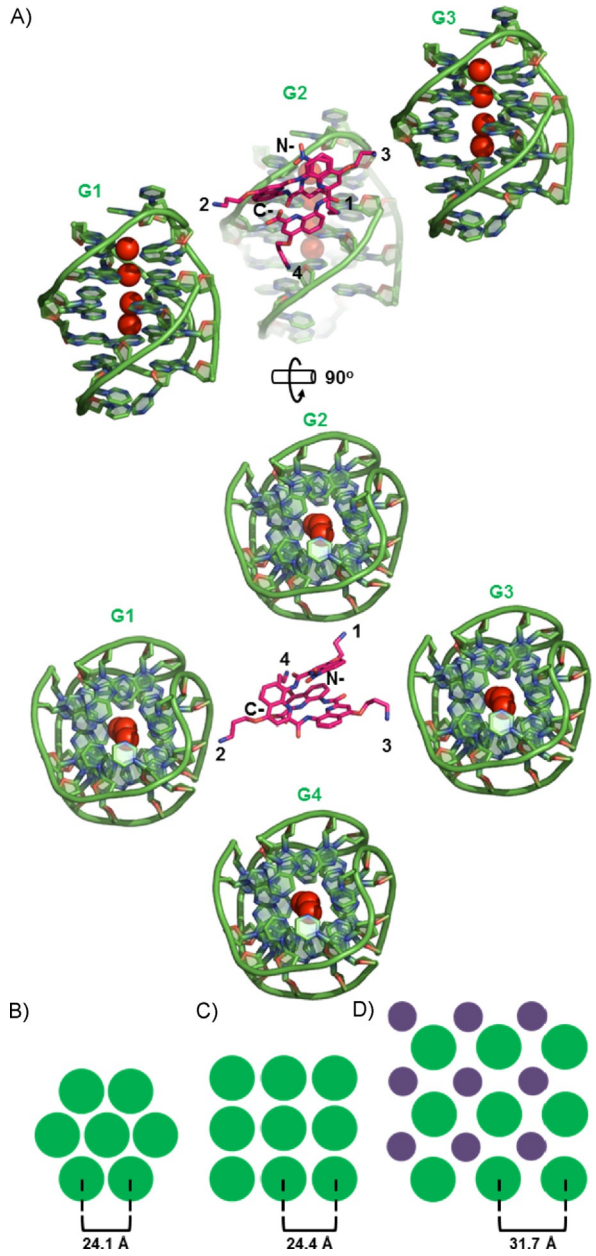


**Figure 3.** A) Packing arrangement of **1** (magenta) surrounded by symmetry-related d(GGGGTTTTGGGG)$_2$ G-quadruplexes (green, numbered G1–G4). The cationic side chains are numbered 1–4. B)–D) Packing arrangement of d(GGGGTTTTGGGG)$_2$ (green circles, viewed down the quadruplex axis) in: B) native, ligand-free form,[22c] C) flat aromatic ligand-bound form,[26a] and D) with bound **1** (dark blue). Quadruplex–quadruplex distances were calculated by using vertical alignments of consecutive $K^+$ ions in the central cores of these G-quadruplexes.

ed an accurate description of foldamer–DNA contact points, but these are presumably guided by ammonium–phosphate electrostatic interactions. These interactions occur at locations distinct from the phosphate–ammonium interactions observed between a spermine molecule and the native *Oxytricha* quadruplex sequence in the solid state (PDB ID: 3UEI).[26b] In that case, two salt bridges [phosphate–ammonium (i.e., oxygen–nitrogen) distance $<3.3$ Å] are observed between spermine ammonium groups and the last two (3′-end) dG phosphate groups of a d(GGGGTTTTGGGG) strand. In the foldamer·quadruplex co-crystal, probable ammonium–phosphate interactions involve the dT in the loops (side chain 2 in Figure 3 A). It is noteworthy that spermine is present in the crystallization medium but absent from the electron density map of the foldamer·quadruplex co-crystal.

The contacts between the foldamer and the quadruplex groove and loops are consistent with our assumption that an aromatic helix is ill-suited to stack on top of G-tetrads as many flat ligands do. The role of "molecular glue" that **1** plays in G-quadruplex packing is reminiscent of a recently described protein assembly driven by calixarene molecules.[28]

In conclusion, we have provided the first piece of structural information about interactions between aromatic amide foldamers and G-quadruplex DNA. The structure shows multivalent foldamer–DNA electrostatic interactions that guide DNA packing, and reveals a preferred left-handed screw sense of the foldamer helix upon interacting with the *Oxytricha* sequence. The structure validates our previous hypothesis of an absence of stacking of the foldamer onto G-tetrads. A well-defined DNA·foldamer complex, if it exists, is not stable enough to overcome the observed interactions. We anticipate that more selective interactions that would serve structure-based rational foldamer design might exist between G-quadruplex DNA aptamers and the cationic foldamer that they have been selected to bind.[16] Efforts to grow crystals of this complex are currently under way.

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