Diversity of interstrand π—π stacking motifs in the double helices of pyridinedicarboxamide oligomers*

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Winding of oligoamide strands of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid into molecular duplexes is illustrated by two new crystal structures of double helical dimers. The relative positions of the two strands within the double helices in these two structures are different; they also differ from the structures reported previously. Unlike the single helical structure of the monomeric strands, the double helical motif is not highly stable in the solid state. This implies that the interactions that lead to duplex formation are not directional. It suggests that the two strands have a significant motional freedom in the duplex.

Key words: conformational analysis, helical structures, hydrogen bonds, stacking of aromatic fragments, supramolecular chemistry.

In recent years, much effort has been devoted to the design and characterization of artificial molecular strands capable of pairing into duplexes through multiple cooperative and selective interactions. These structures are useful tools for the control of self-assembly and self-organization at a nanometer level. They also give new insights into the relation between specific intermolecular interactions and information storage and duplication.

Artificial molecular duplexes may be stabilized by (self)-complementary H-bond arrays. These can directly mimic natural hybridization motifs, for example, pairing of nucleobases[1,2] or the double stranded β-barrel of the bacterial peptide Gramicidin D.[3] Several unnatural hydrogen bond arrays have also been designed.[4—11] Another common way for directing the assembly of a molecular duplex is the use of metal ions[12] or anions[13] as templates around which the two strands wind upon establishing selective interactions. Artificial duplexes based on interstrand aromatic—aromatic interactions are less common.[14] We have reported that oligoamide strands derived from 2,6-diaminopyridine and pyridine-2,6-dicarboxylic acid (AOA) are self-organized into single helical conformers[15] that reversibly assemble giving rise to double helical dimers (Fig. 1).[16] These artificial molecular duplexes represent an original example of double helices stabilized by direct interactions between the strands following an unnatural hybridization motif. Unlike natural double helices and their synthetic analogs,[1—3] the double helices of AOA undergo extensive aromatic—aromatic interstrand interactions[16] and, in contrast with helicates,[12,13] they do not require a template for double helical winding.

We have shown previously[15,17] that folding of monomeric strands of AOA into single helices is directed by local conformational preferences at each arylamide bond, which are imposed by repulsive and attractive interactions (*e.g.*, hydrogen bonds) between each amide group and the adjacent pyridine units. Crystallographic studies have shown that the single helical structure is highly conserved in the solid state, regardless of the length of the oligomer, the nature of the side chains or the end-capping groups, or the nature of the solvent used for crystallization or the presence of included solvent molecules. About 4.5 pyridine units are necessary to span one helical turn and the pitch is equal to the thickness of one aromatic ring (3.45 Å). The double helices of AOA have been characterized by two crystal structures showing significant differences in the relative positions of the two strands within the duplex.[16] In order to gain better understanding of the

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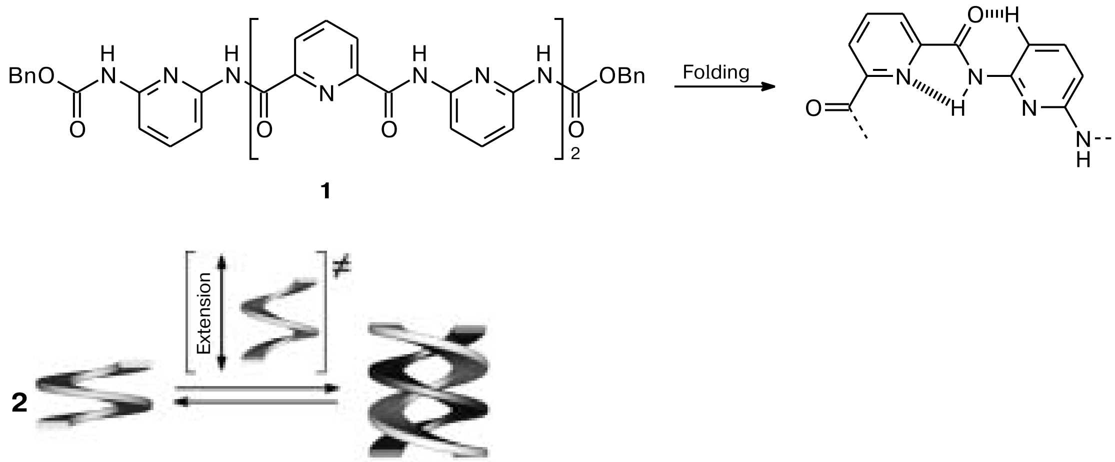

Fig. 1. Structure of an AOA and some of the interactions that stabilize its helical structure. Schematic representation of the single helix—double helix equilibrium.

driving force of AOA hybridization into double helices, we have pursued crystallographic studies and now report two new crystal structures of double helices that show further structural differences from the structures reported earlier. This result demonstrates that interstrand interactions within AOA duplexes are not strongly directional and that a substantial motional freedom exists in the double helices.

Results and Discussion

The pentameric strand **1** consists of two pyridine-2,6-dicarbonyl units alternating with three 2,6-diaminopyridine units capped by two benzyl carbamate end groups (see Fig. 1). The crystals of **1** were obtained either from a hot solution in DMSO or by diffusion of Et_2O into a solution in DMF. Both sorts of crystals proved to be suitable for X-ray diffraction analysis, which revealed structures **A** and **B**, respectively (Fig. 2). Both structures represent double helices consisting of two crystallographically independent strands involved in extensive intermolecular π—π contacts. Two water molecules are included in the helix channel. In the case of structure **B**, positions of the water hydrogen atoms were accurately located. The crystallographic parameters indicate that the two structures are strongly related (Table 1). They belong to the same space group and the unit cell parameters are only slightly different. The double helices of structures **A** and **B** (see Fig. 2) are closely similar and even the positions of water molecules differ little. As in the double helices we characterized previously,[16] the double helical pitch is twice the thickness of the aromatic ring (~6.9 Å). The curvature is slightly greater than that in single helices and only four pyridine units are necessary to span one helical turn. In each structure, three of the four benzyl groups are apparently not involved in intermolecular interactions. The fourth benzyl group is involved in π—π stacking at the bottom of the helix (see Fig. 2) but the distance between

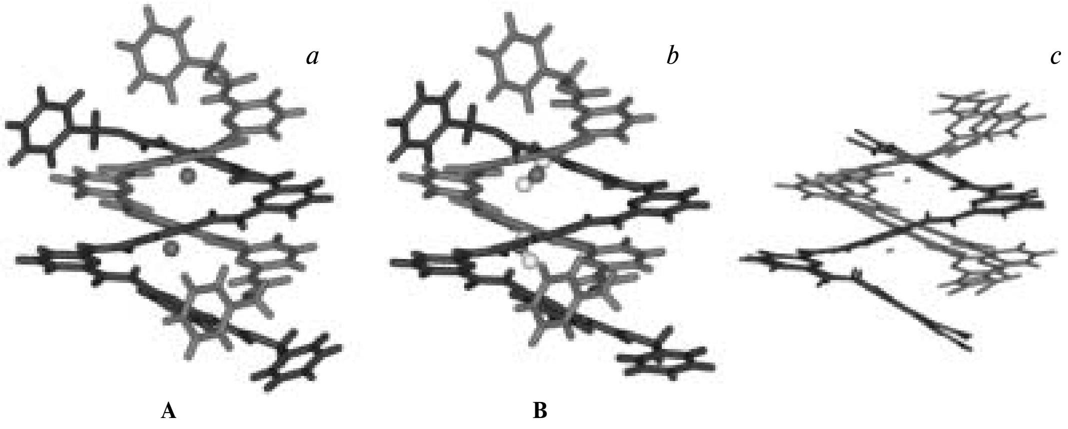

Fig. 2. Crystal structures of pentameric strand **1**. (*a*) structure of crystals **A** grown from DMSO; (*b*) structure of crystals **B** grown from DMF—Et_2O; (*c*) superposition of structures **A** and **B**. In the two structures, the included solvent molecules other than water molecules are omitted for clarity. The π—π stacking interactions with the base of the AOA helix involve only one benzyl group.

Table 1. Crystallographic parameters for the structures determined by X-ray diffraction analysis

Parameter	Structure **A**	Structure **B**
Formula	$C_{94}H_{86}N_{22}O_{20}S_2$	$C_{96}H_{88}N_{24}O_{20}$
Composition	$(\mathbf{1})_2(DMSO)_2(H_2O)_2$	$(\mathbf{1})_2(DMF)_2(H_2O)_2$
Solvent for crystallization	DMSO	DMF—Et_2O
Molecular weight/g mol^{-1}	1907.96	1897.88
Crystal dimensions/mm	0.25×0.10×0.05	0.10×0.05×0.05
Color	Colorless	Colorless
Radiation	Cu-Kα	Mo-Kα
Temperature/K	296(2)	150(2)
Unit cell	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a/Å	14.460(2)	14.446(2)
b/Å	26.103(5)	24.770(5)
c/Å	24.606(5)	25.369(5)
β/Å	94.82(2)	96.18(2)
V/Å^3	9255(3)	9025(3)
Z	4	4
d_{calc}/g cm^{-3}	1.370	1.397
Scanning range for θ	$2.47 \le \theta \le 44.94$	$2.92 \le \theta \le 22.76$
Measured independent reflections	7453/1244	12085/1278
GOF	1.042	0.979
R_1 (%)	7.32	7.13

the aromatic fragments (4.26 Å) is longer than that usually observed for strong aromatic—aromatic interactions.

However, the superposition of structures **A** and **B** reveals a relative offset of the strands of more than 1.5 Å in a plane perpendicular to the helix axis (Fig. 2, *c*). This significant difference implies that no interactions strongly dependent on the distance between the strands (*e.g.*, hydrogen bonds) are involved. The two water molecules occupy well-defined positions relative to one strand of the duplex but not to the other strand. As we have demonstrated previously,[16] the water molecules are simply bound in the polar helix channel and do not stabilize the duplex through the formation of bridging hydrogen bonds.

The difference between the double helices **A** and **B** prompted us to compare in detail these two structures with the structures of the two double helices that we have described previously.[16] Three of these four structures consist of pentameric strands, and one consists of heptameric strands. The end groups vary from one structure to another; these can be benzyl carbamates, *tert*-butyl carbamates, or free amines. The included solvent molecules are water and an organic solvent (DMSO, DMF, or nitrobenzene). Of the four double helices, only one has two crystallographically related strands (C_2 symmetry). Thus, a total of seven independent strands are available for comparison (six strands from three structure and one strand from the fourth structure). The superposition of these seven strands is shown in Fig. 3. The match is excellent, except for the terminal units, whose positions are slightly different. These differences probably arise from involvement of the terminal units in the intermolecular interactions with other helical strands or with included solvent molecules. A comparison of the seven strands shows that the double helical pitch and the number of units per turn are overall well conserved in the structures of double helical dimers, just as they are conserved in the structures of single helical monomers. It also shows that the two strands within each duplex have similar structures.

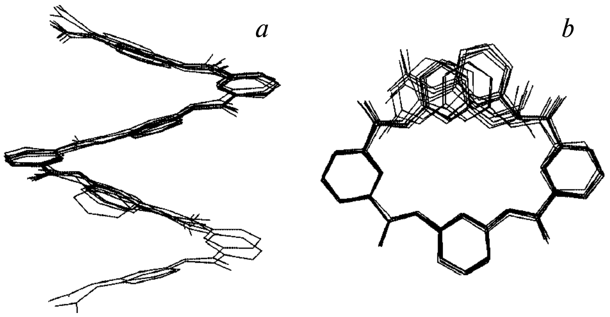

Fig. 3. Superposition of seven strands from four crystal structures of the AOA double helices. The end groups are omitted for clarity: (*a*) side view (all pyridine rings are presented); (*b*) top view (only five pyridine rings per strand are shown).

However, it proved to be much more difficult to find a good match between the four double helical dimers than between the seven strands taken separately. If one superposes one strand of each of the four double helices, the four other strands are found to occupy very different positions (Fig. 4). This is especially true in the projection onto the plane perpendicular to the helix axis where the offsets can be as large as 8.5 Å (see Fig. 4, *d*). Along the direction parallel to the helix axis, all the strands are found at similar positions, which are defined by the grooves of the first strand (see Fig. 4, *c*). Thus, the variability of positions arises essentially from helical screw motions of one strand of a duplex with respect to the other strand.[18] This result brings further support to our interpretation of the dynamics observed within the double helices in solution as helical screw motions.[16]

The winding of the two strands to form a molecular duplex requires a slight increase in the dihedral angles at each arylamide bond so as to double the helical pitch of the single helix to accommodate another strand in the groove. Such an increase in the dihedral angles is energetically unfavorable, as it results in slightly longer NH...N hydrogen bonds and favorable CO...H contacts within each strand of the duplex. The energy expenditure is counterbalanced by extensive interstrand π–π contacts in the double helices, involving a larger surface area than

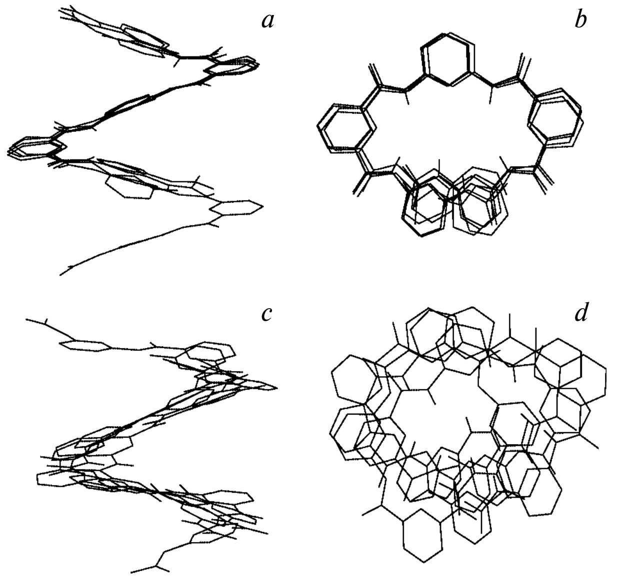

Fig. 4. Side view (*a*) and top view (*b*) of the superposition of four strands of four double helices of the AOA crystal structures. Side view (*c*) and top view (*d*) of the relative orientation of the other strands.

the intramolecular π–π contacts in the single helical monomers.

The interactions of aromatic fragments result from the interplay of electrostatic and van der Waals interactions as well as solvent driven forces.[18] In aprotic solvents such as chlorinated or aromatic solvents in which the AOA double helices are observed, the solvophobic effects are weak and π–π interactions are mainly determined by the electrostatic components. As a rule, these depend appreciably on the orientation and on charge distribution in the aromatic rings.[19] In order to find out whether the different double helices of AOA observed in the solid state correspond to maxima of electrostatic interactions, we examined more closely the patterns of interstrand π–π stacking within the four crystal structures. The patterns shown in Fig. 5 clearly illustrate the variability of the relative positions of the two strands. However, analysis of these positions based on charge distribution[19a] does not allow one to conclude that they are associated with particularly favorable interactions. In all four cases, local repulsions between two like partial charges are encountered as frequently as local attractions between opposite partial charges.

Thus, a comparison of the two new crystal structures of the AOA double helices with the structures described previously provides additional evidence for the fact that the relative positions of the two strands in the duplexes are highly variable. This suggests that the interactions between the two strands are not strictly directional. No interstrand hydrogen bonds are observed, and apparently the π–π interactions are not strongly affected by charge distribution in the aromatic groups. These results suggest that the two strands have a significant motional freedom in the duplex and are consistent with the assumption of screw motions that we have made previously to explain the dynamics observed within the duplexes in solution.[16]

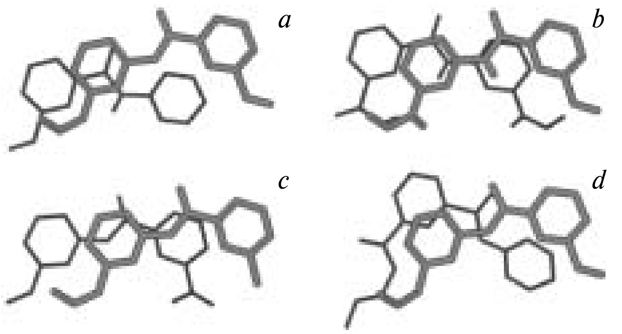

Fig. 5. Patterns of π—π stacking between one strand (thick lines) and the other strand (thin lines) for four AOA crystal structures. The views are perpendicular to the planes of aromatic fragments and are not exactly parallel to the helix axis: (*a*) structure of 1B4, (*b*) structure 1A, (*c*) a heptameric strand with *tert*-butyl carbamate end groups,[16] (*d*) a pentameric strand with end amino groups.[16]

Experimental

The structure of **1** was determined by single-crystal X-ray diffraction. For the crystals grown from DMSO, the data were collected on a CAD4 Enraf-Nonius diffractometer (graphite monochromator, Cu-Kα radiation). The cell parameters were determined by least squares calculations from the setting angles for 25 reflections. An empirical absorption correction was applied (absorption coefficient 2.445 mm^{-1}). The data were also corrected for Lorentz and polarization effects. For the crystals grown from a DMF—Et$_2$O system, a Bruker-Nonius κ-CCD diffractometer (graphite monochromator, Mo-Kα radiation, λ 0.71073 Å) was used for the single crystal experiment. The data collection was based on ϕ-scans completed by ω-scans. The final unit cell parameters were determined using all of the collected frames. The data were processed using the COLLECT software (Nonius, 1998). The positions of nonhydrogen atoms were determined by the SHELXS 87 program and the positions of the H atoms were deduced from the coordinates of nonhydrogen atoms and confirmed by Fourier synthesis. The H atoms were included in the structure factor calculations but not refined.

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