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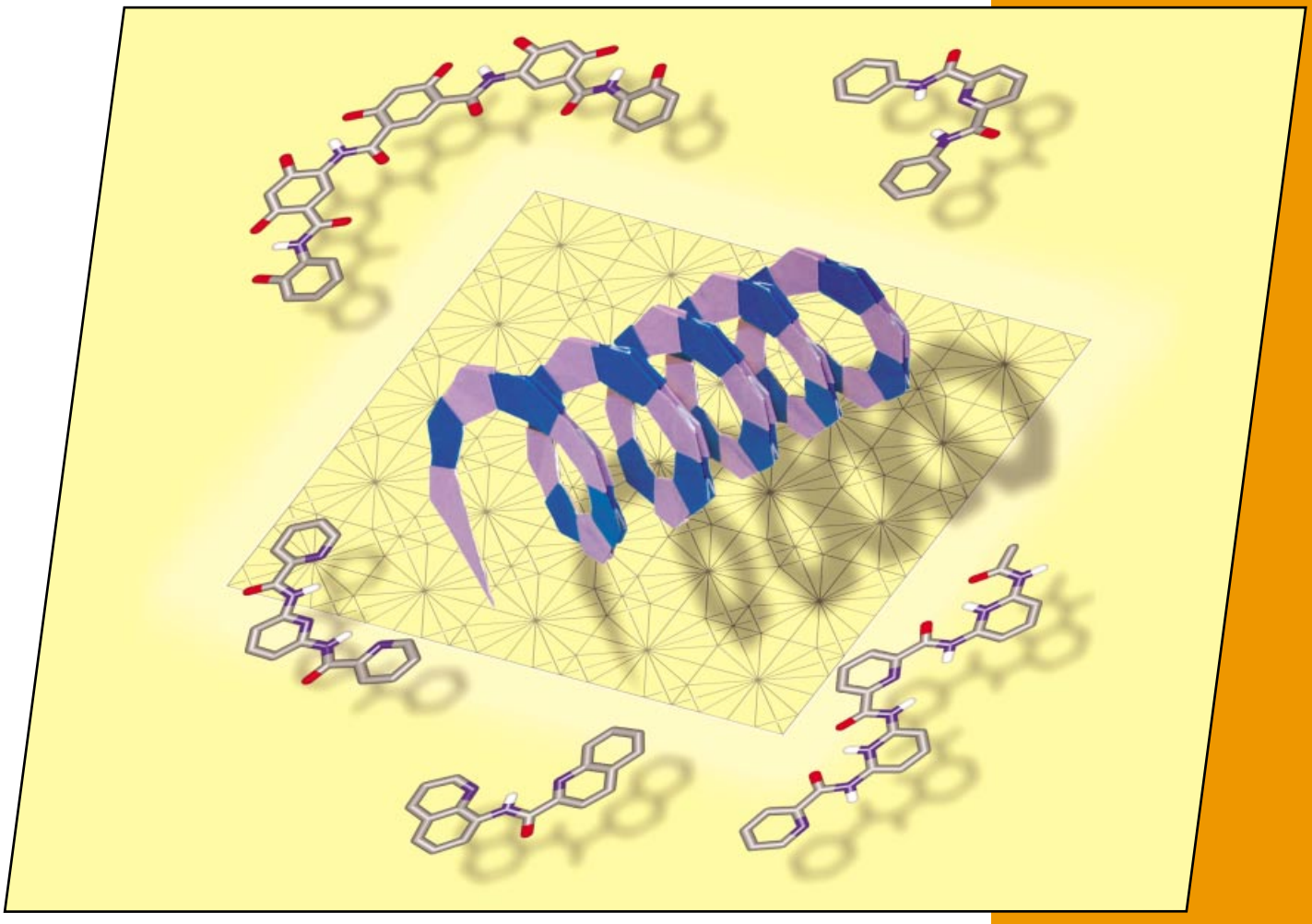

Microreview

Ivan Huc

Aromatic Oligoamide Foldamers

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Aromatic Oligoamide Foldamers

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Aromatic oligoamide foldamers possess a high potential for mimicking the secondary structures of biopolymers. These oligomers are efficiently designed, easy to synthesize, and allow one to reach a wide range of stable folded states. The aryl–amide bond rotation can be restricted through specific attractive and repulsive interactions between the amide and the other functional groups at the *ortho* position on the aryl moiety. The overall conformation of an oligomer results from the simple linear combination of the local conformational preferences at each amide bond. Thus, the curvature of the oligomeric strand may be tuned from strictly linear to highly bent, giving rise to helices of controllable diameter and extended linear conformations. Conformational rearrangements such as helical–linear strand transitions may be induced upon changing the local conformational preference of aryl–amide bonds. These oligomers also aggregate in various ways, such as stacks of discs, face-to-face hydrogen-bonded linear dimers, or entwined double helices.

1. Introduction

The amazing variety of structures and different functions displayed by proteins is attainable with a set of only 20 amino acid constituents arranged in a linear sequence. One can only wonder what structures and what functions are attainable by appropriately combining the innumerable nonnatural monomers available to chemists. To answer this question, synthetic foldamers, or oligomers that fold into well-defined conformations in solution, have been the object of great attention and very active research over the past ten years.[1] It has been shown that the secondary structural motifs of proteins are not restricted to the α-peptide backbone but belong to many classes of oligomers as, for example, the numerous molecular strands reported to wind into helices.[1–3] Among the most studied families of nonnatural oligomers are aliphatic β-, γ-, and δ-peptides, which bear particular significance because of their similarity to α-peptides.[1,4]

The potential usefulness of a particular class of foldamer in the design of secondary and tertiary structural motifs, and ultimately in the endowment of these structures with functions, depends much on the *predictability* of their folding. Of course, predictability is for a large part empirical and increases with the time spent studying such structures. For example, the prediction of the folding of an α-peptide from its sequence is a very difficult task, yet our understanding of protein folding is now sufficient to design remarkably large and complex folded peptides.[5] But predictability may also be associated with the structure itself,

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Ivan Huc was born in Besançon, France, in 1969. He studied chemistry at the Ecole Normale Supérieure in Paris, and received his PhD in 1994 from the Université Pierre et Marie Curie (Paris) under the joint guidance of Dr. C. Rolando (Ecole Normale Supérieure) and Prof. J. Rebek, Jr. (Massachusetts Institute of Technology), working on synthetic enzyme mimics. After a one-year postdoctoral period studying DNA recognition with Dr. J.-P. Behr in Strasbourg-Illkirch, he received a CNRS Chargé de Recherche position in the laboratory of Prof. J.-M. Lehn in Strasbourg, where he stayed from 1995 until 1998 working on dynamic combinatorial chemistry. Since 1998, he has been appointed as a group leader at the Institut Européen de Chimie et Biologie in Bordeaux. His current research interests include biomimetic chemistry of peptide and nucleotide structures, chiral model membrane systems, and the use of biomolecules as templates to generate complementary ligands.

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which can be designed to have no choice but to fold in a desired conformation.

Another essential feature of a foldamer is the *ease of synthesis*. Many synthetic strategies can be envisaged to prepare small molecules, but a limited set of very effective reactions are acceptable to prepare high molecular weight compounds. In this respect, amide functions are the object of a wide consensus, and have become the choice of numerous research groups.[1,4]

A third desirable aspect of a foldamer is the *stability* of its folded secondary structures. Though conformational lability may give rise to interesting dynamics, it may also seriously complicate the prediction of the folded states. Tertiary structures are hard to build using unstable secondary building blocks.

Finally, one would prefer a foldamer to be *tunable*, to reach a wide variety of structures using the same design principles.

This manuscript will focus on the promising family of aromatic oligoamide foldamers which, as we will show, feature a remarkable combination of structural predictability, stability, tunability and ease of synthesis. Research in this area is still largely devoted to structural studies, and so is the focus of this manuscript. No section is dedicated to functions, and possible applications are simply evoked in the text.

2. Restricted Rotations about Aryl−Amide Bonds

Rotations about NHCO−aryl and CONH−aryl bonds are not as free as rotations about NHCO−alkyl and CONH−alkyl bonds, because of the conjugation between the amide and aromatic groups. Energy minima are found in both the *syn* and *anti* conformations where aryl and amide groups are coplanar or close to coplanar.[6] These conformations can be further stabilized and, more importantly, the *syn* and *anti* conformations can be discriminated using specific attractive and repulsive interactions between the amide and other functional groups on the aryl moieties. Representative examples of these rotational restrictions are presented in the following.

Rotation about the NHCO−aryl bond may be restricted by a hydrogen bond between the amide proton and a hydrogen-bond acceptor at the *ortho* position on the aryl group (Figure 1, a−d). When the hydrogen-bond acceptor is exocyclic, an *anti* conformation is stabilized through a favorable six-membered hydrogen-bonded ring (Figure 1, a−c). The hydrogen-bond acceptor may be an ether oxygen atom,[7−11] an *N*-oxide group,[12] or the nitrogen atom of a fused aromatic ring.[13] The extent of stabilization depends on the hydrogen-bonding ability of the acceptor (e.g., an *N*-oxide group is a better acceptor than an ether oxygen atom).[14] It also depends on the repulsive interactions between the acceptor and the amide carbonyl group in the *syn* conformation. When the hydrogen-bond acceptor is endocyclic, as for example a pyridine nitrogen atom (Figure 1, d), the hydrogen bond forms a five-membered ring. This hydrogen bond is longer and has a less favorable orientation than for an exocyclic acceptor. However, the *anti* conformation is still largely preferred, presumably because of the strong repulsion between the pyridine nitrogen atom and the amide carbonyl group, and this building block is one of the most widely used.[15−27]

Restriction of the NHCO−aryl rotation may also arise from a hydrogen-bond donor on the aryl moiety as, for example, OH,[28] NH,[12,23,24,29] or N^+H[30] groups (Figure 1, e−g). These groups form hydrogen bonds to the amide carbonyl group, which stabilize the *syn* conformation. In the case of exocyclic donors (OH or NH), the *anti* conformation is stabilized by a hydrogen bond as well, but this hydrogen bond is weaker than in the *syn* conformation because of either the poorer donors and acceptors involved[28,31] (Figure 1, e) or a less favorable orientation (Figure 1, f). When the hydrogen-bond donor is N^+H (Figure 1, g), an NH/N^+H repulsion in the *anti* conformation is expected. The *syn* conformation is thus preferred, but it easily deprotonates to give the *anti* conformation of the corresponding base (Figure 1, d).[30]

In a similar way, the *anti* conformation of the CONH−aryl bond can be stabilized by a hydrogen bond between the amide NH group and acceptors in the *ortho* position on the aryl ring (Figure 2). The hydrogen-bonded cycle may be a six-membered ring with carbonyl[12,29] or 2-pyridyl[32] acceptors (Figure 2, a−b), a five-membered ring

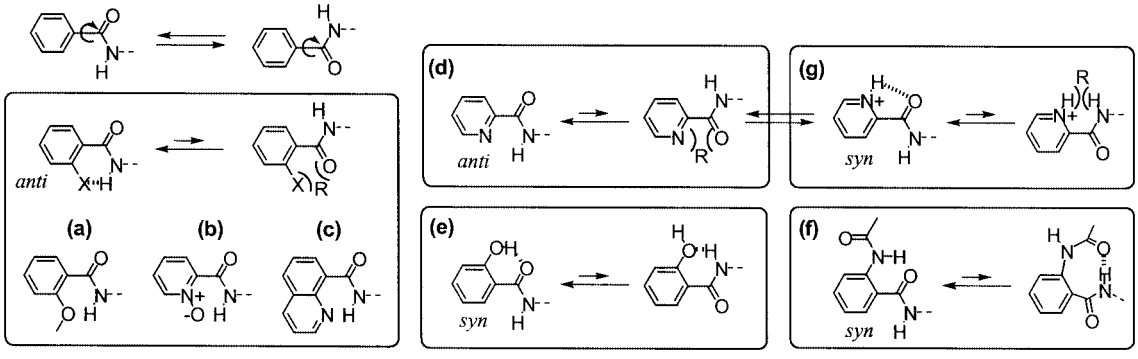

Figure 1. Conformational preferences of various NHCO−aryl linkages; "R" denotes electrostatic repulsions

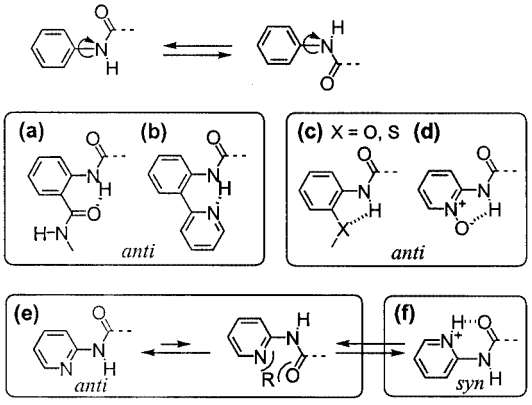

Figure 2. Conformational preferences of various CONH−aryl linkages; "R" denotes electrostatic repulsions

with alkoxy,[9−11,27] thioalkoxy[33,34] or *N*-oxide substituents[35] (Figure 2, c−d), or even a four-membered ring with an endocyclic pyridine nitrogen atom as acceptor (Figure 2, e).[15,19−22,36] Again, repulsive interactions between the acceptor and the amide carbonyl group probably contribute significantly to the stabilization of the *anti* conformation. The *syn* conformation may be stabilized by a N^+H hydrogen-bond donor (Figure 2, f).[30,37,38]

Hydrogen bonding represents the most versatile means with which to discriminate between the *syn* and *anti* conformations of CONH−aryl and NHCO−aryl bonds. A related method consists in deprotonating the amide group and replacing the proton by a transition metal atom such as Cu^{II} or Ni^{II}, which may then coordinate to electron donors at the *ortho* position on the aryl group. This approach has been shown to be very effective for 2-pyridylcarboxamide linkages and anthranilamide linkages.[39,40,41] Metal coordination also restricts the conformation of 2-(carbonylamino)pyridine moiety in a similar way to protonation (Figure 2, f).[42] Restriction of the aryl−amide bond rotations can also be imposed by steric hindrance, using bulky substituents at both positions *ortho* to the amide group. The amide plane is then forced to lie more or less perpendicularly to the aryl moiety. However, these restrictions do not discriminate between the two possible conformers.[25,26,43]

All of these preferred conformations have been characterized, sometimes extensively, by experimental studies of aryl−amide monomers and oligomers in solution and/or in the solid state. However, little information is available in the literature on the actual energy differences between the favored and disfavored conformations. A few theoretical studies using ab initio calculations have been reported to quantify the conformational preference of NHCO−(*o*-methoxyaryl), and CONH−(*o*-methoxyaryl),[10,11] CONH−(*o*-thiomethoxyaryl),[34] and 2-pyridinecarboxamide[6,18] linkages. A more thorough and systematic theoretical investigation is much needed, since it would allow one to directly evaluate and compare the numerous conformations described above. Two particular issues that theoretical approaches may address are firstly, the relative contributions of attractive and repulsive interactions in the stabilization of a conformer, and secondly, the cooperativity involved when several interactions take place at the same position of an oligomer. Are hydrogen bonds strengthened or weakened when a donor's hydrogen atom bonds to two acceptors, and/or when an acceptor hydrogen atom bonds to two donors? In the case of (*o*-methoxyaryl)−CONH−(*o*-methoxyaryl), the hydrogen bonds between the amide proton and the ether oxygen atoms have been shown to operate cooperatively: they are strengthened by one another (Figure 3).[10,11]

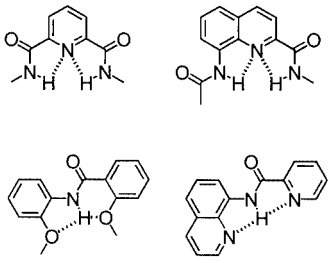

Figure 3. Examples of hydrogen bonds involving two protons and one acceptor (top) or one proton and two acceptors (bottom)

3. Combining Elementary Motifs in Oligomers: From Design Principles to Secondary Structures

3.1 Design Principles

The rotational restrictions described in Section 2 are generally strong enough to allow an accurate design of aromatic oligoamides having well-defined and predictable conformations. We could find only two cases where "wrong" rotamers were characterized in which the expected intramolecular hydrogen bonding does not take place, and they both involve amides of anthranilic acid.[24,29] Thus, at each amide−aryl bond of the oligomer, a *syn*- or *anti*-conformational preference can be induced by the appropriate functional groups on the aryl moiety. The main consequence of this strategy is that all conformational preferences involve structural elements that are adjacent in the sequence and, in a first approximation, do not operate cooperatively. This greatly facilitates the prediction of the overall conformation of the oligomer, which may be considered as being the linear combination of all local conformational preferences. Of course, interactions between units remote from each other in the sequence will contribute to the stability of the structure. But in most cases, it may be assumed that these interactions will not significantly alter the motif determined by the interactions taking place locally at each amide bond. In principle, additional units may simply be adjoined to the oligomer without perturbing the rest of the structure.

When the same structural motif is repeated in the sequence, the computational and/or experimental studies of a simple dimer or trimer provides accurate data on relative positioning of consecutive units that may be extrapolated to longer oligomers. In contrast, the conformational study of a dimeric, trimeric, or tetrameric α-peptide gives little indication that longer sequences may fold into an α-helix, a

3_{10}-helix or a π-helix, because the interactions that stabilize these structures occur between units that are not consecutive in the sequence. The same can be said about aliphatic β-peptides for which a very rich variety of stable conformations have been characterized[4,43] that would have been, a priori, hard to predict in the first place.

3.2 Mixed Aromatic−Aliphatic Sequences

One of the simplest applications of aromatic amides consists of the incorporation of isolated rigid elements within aliphatic peptide sequences, so as to induce or to template an extended structure of the strand. For this purpose, the research groups of J. S. Nowick and B. Gong have extensively used the 2-alkoxy-5-aminobenzenecarboxylic acid hydrazide and amide units. Aromatic oligomers may serve as intramolecular or intermolecular templates for the formation of β-strands and β-sheets in α-peptides (Figure 4, a).[7] Using complementary hydrogen-bonding patterns, oligomers have been designed to assemble in linear dimers (Figure 4, b), which may in turn promote the formation of antiparallel β-sheets.[8]

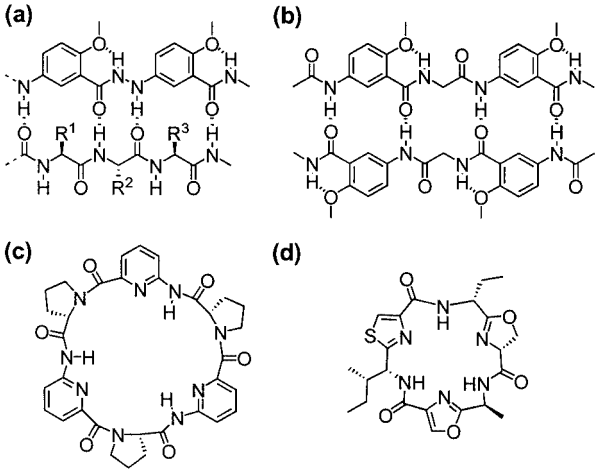

Figure 4. Mixed aliphatic−aromatic oligoamide foldamers

Aromatic amide units which have strong conformational preferences have also been incorporated within hexameric cyclic peptides comprising several proline units (Figure 4, c). The rotational restrictions induced by the aromatic amide unit determine the conformation of the macrocycle and allow one to tune its ionophoric properties.[45] Such synthetic macrocycles are strongly related to natural cyclopeptidic ionophores (Figure 4, d) in which thiazole and oxazoline units induce rotational restrictions through intramolecular hydrogen bonds.[46]

Last but not least, a spectacular example of a conformationally well-defined cyclic oligoamide is the knot reported by Vögtle et al.[26]

3.3 Branched Oligomers

As will be presented in the following sections, most conformationally well-defined aromatic oligoamides are not branched, although a few examples of branched structures have been presented. Oligomers consisting of three 3,3′-bis-(carbonylamino)-2,2′-bipyridine branches attached to a 1,3,5-phenylene core (Figure 5, b) have been shown to assemble into stacks of flat extended conformations.[32] Dendroamides of 4-amino-2,6-pyridinedicarboxylic acid bearing anthranilamide peripheral groups have been prepared up to the third generation (Figure 5, a).[23,24,41]

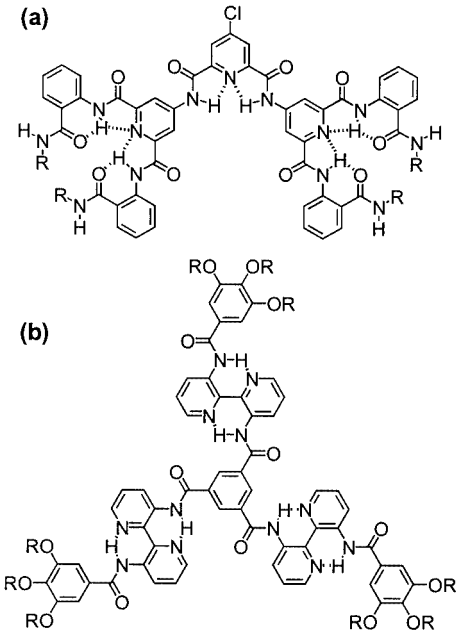

Figure 5. Examples of branched aromatic oligoamide foldamers; a crystal structure of the dendrimer shown in (a) is represented in Figure 16

These structures are significant because they are the first conformationally well-defined dendrimers. Dendrimers have often been compared to proteins because of their size, their globular shape, and the possibility to specifically functionalize their surface and interior grooves.[47] However, their conformation is ill-defined unlike that of proteins. Structurally well-defined dendrimers are thus very interesting objects to investigate. They may be crystallized[24] to provide new insights into the folding of large structures. They may also serve as a framework to implement protein-like functions in synthetic molecules.

3.4 Linear Oligomers

The simplest structural motif of nonbranched oligoamides is the linear conformation. In a linear strand, no contact between units remote from each other in the sequence is expected and the design principle described in Section 3.1 fully applies. Several buildings blocks allow the construction of linear structures (Figure 6) and they may, a priori, be combined at will.

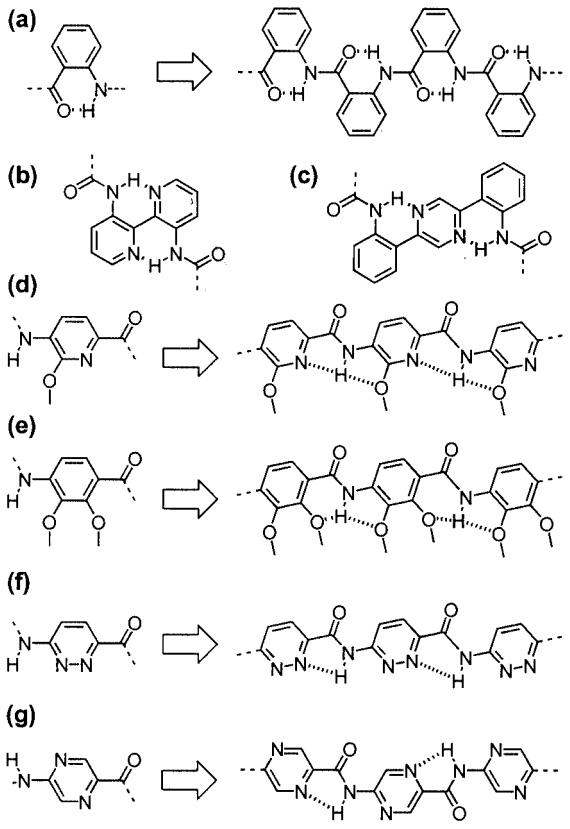

Figure 6. Aromatic oligoamides adopting linear conformations

Oligoamides of anthranilic acid have been prepared by Hamilton et al (Figure 6, a).[12] Amides of 3,3′-diamino-2,2′-bipyridine and 2,5-bis(2-aminophenylene)pyrazine also form linear motifs (Figure 6, b and c).[32] Oligoamides of 6-alkoxy-5-aminopicolinic acid form linear oligomers in which the amide proton hydrogen-bonds to both the ether oxygen atom and the endocyclic pyridine nitrogen atom (Figure 6, d).[27] These oligomers can mimic the molecular recognition properties of α-helical peptides, because the distance between the alkoxy residues in the oligomer matches the distance between the side chains along one face of an α-helical secondary structure. If one replaces the endocyclic nitrogen atom of 6-alkoxy-5-aminopicolinic acid by an exocyclic methoxy hydrogen-bond acceptor, a similar motif can be envisaged (Figure 6, e). This monomer has been prepared by Gong et al. and has been combined with other monomers in bent structures,[9] but linear oligomers of this kind have not yet been reported. Similarly, one may design linear oligoamides from *para*-substituted aromatic amino acids derived from pyridazine or pyrazine (Figure 6, f and g).

Linear oligomers may be divided into two classes: those in which hydrogen bonding takes place on both sides of the molecular strand, and are expected to be strictly linear (Figure 6, a−c, g), and those which exhibit a facial polarity because hydrogen bonding takes place on only one side of the strand (Figure 6, d−f). In the latter case, the strand is not expected to be strictly linear and a slight curvature is indeed observed.[27] The facial polarity of such strands can be exploited in molecular recognition,[27] or be transformed into facial amphiphilicity.[33]

3.5 Bent Oligomers and Helices

Bending of aromatic oligoamide strands is achieved when the orientation of amine and acid substituents define an angle smaller than 180°. Typically, this has been implemented using *meta*-substituted, six-membered, aromatic amino acids, as in the oligoamides of 2,6-diaminopyridine and/or 2,6-pyridinedicarboxylic acid,[15−27,36] and oligoamides of 4,6-dialkoxy-3-aminobenzoic acid[9,10] (Figure 7, a and b; Figure 8). Examples are found in the literature of oligomers consisting of the repetition of the same unit, and also of oligomers consisting of the alternation of different subunits.

For short oligomers, no contact between units remote from each other in the sequence is expected. The structures are bent and essentially planar with a "crescent" shape. Longer oligomers are bent in the same way, and slightly deviate from planarity so as to form helices (Figure 7). The diameter and number of units per turn of the helices may vary widely, but in all cases the pitch remains equal to the thickness of one aromatic ring, ca. 3.4 Å. The deviation from planarity is accommodated by slight changes of the torsional angles of each aryl−amide bond. When one helical turn comprises many units, this torsion is minimal, because it is distributed over several rotatable bonds (Figure 7, a).[9] For highly curved helices with only a few units per turn (Figure 7, d),[15] the torsions are larger.

Intramolecular overlap between aromatic rings is associated with the helical shape. It gives rise to π−π interactions that bring about significant additional stabilization of the structures. However, it has not been observed that these interactions alter the bending of the strand. The comparison between the crystal structures of short crescent oligomers and longer helical oligomers of the same family shows identical curvature.[8,15,20] This implies that intramolecular aromatic stacking in the helices either happens to be at an optimum in the position set by hydrogen bonding, or that it provides too small a gain in the interaction energy to perturb the hydrogen bonds and force the curvature to change to a position where stacking would be more favorable. Computational studies have not yet been performed to assess the strength and position dependence of intramolecular π−π interactions in these systems.

As illustrated by the variety of structures shown in Figure 7, which are all made of 8−11 units, the diameter of the helices and the number of units per turn may be tuned very simply using the following three parameters:

1) The factor that has the strongest impact on the helix diameter is the relative orientation between the amine and acid substituents. As shown by Gong et al., the alternate incorporation of *para*-substituted and *meta*-substituted units may generate helices with very large hollows (Figure 9, a), that may in principle be tuned by simply varying the ratio between the *meta*- and *para*-substituted monomers.[9,10] At the other end of the scale, units where the

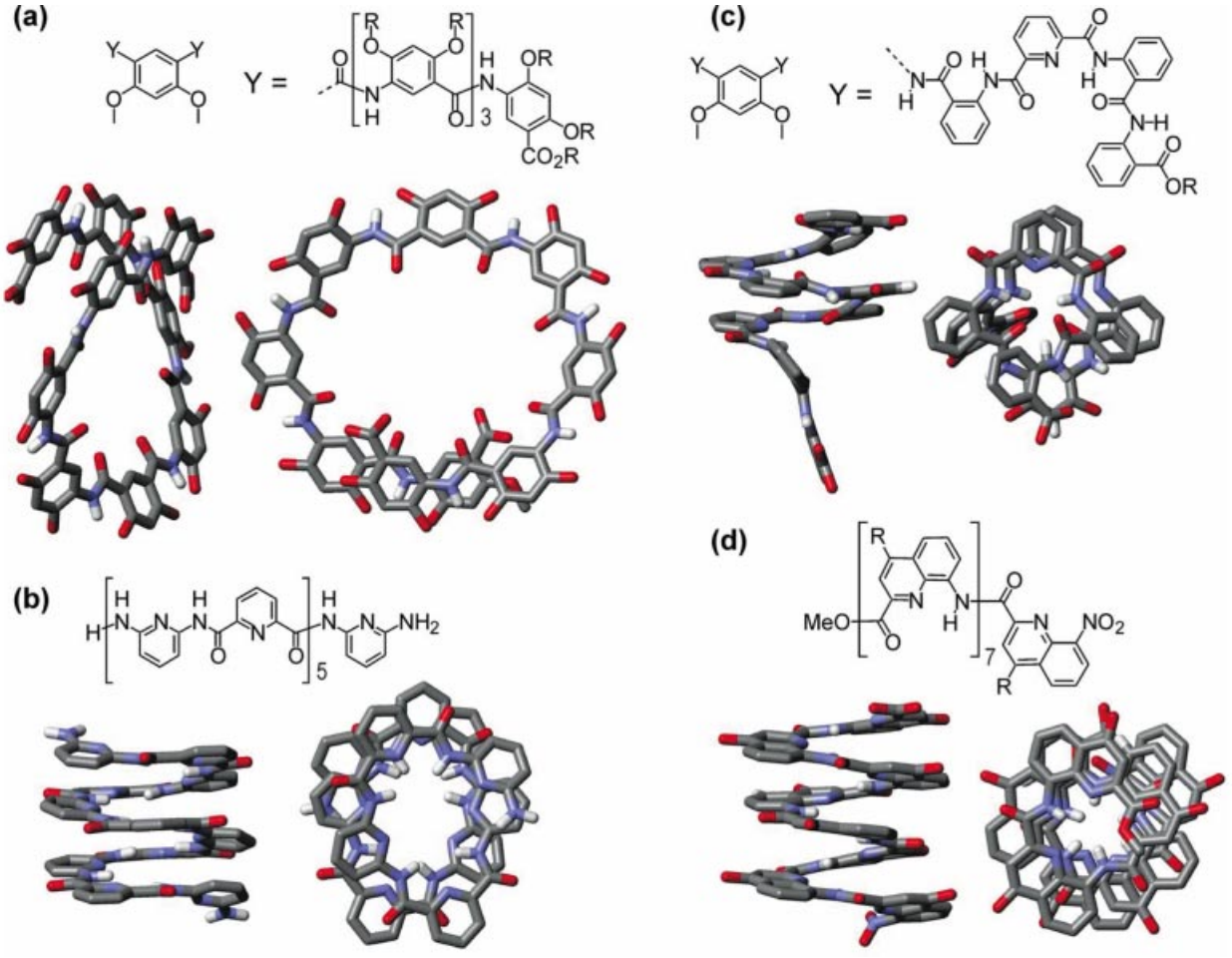

Figure 7. Structures in the solid state of four aromatic oligoamides comprising 8−11 units; the four compounds are represented on the same scale; for clarity, non-amide hydrogen atoms, alkyl groups and included solvent molecules have been omitted; structures (a), (b), (c), and (d) are described in refs.[9,18,28,13]

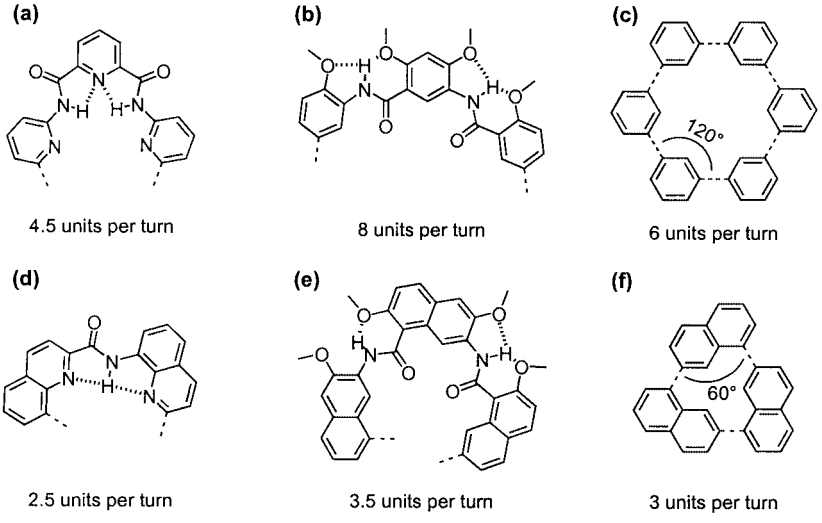

Figure 8. Bending of aromatic oligomers depends on intramolecular hydrogen bonds on the inner or outer rim of the oligomer, and on the substitution motif (*ortho*, *meta*, ...) of aromatic rings

amine and acid groups define an angle of 60° give rise to highly curved helices (Figure 7, c and d; Figure 8, d and e).[15,29]

2) The second factor to tune the diameter of the helices is the size of the units. For a given orientation of the amine and acid substituents, for example 120°, large units induce

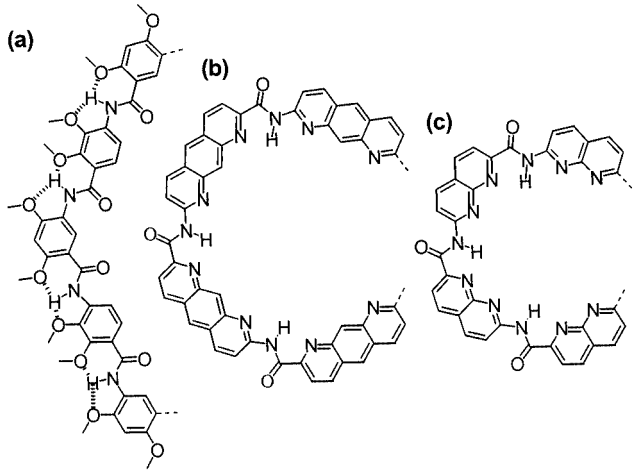

Figure 9. Tuning strand bending

large diameters and small units induce smaller diameters (Figure 9, b and c; Figure 8, a).[48] The size of the aryl groups does not influence the number of units per turn.

3) Finally, the diameter also depends on the position of the hydrogen bonds. If one considers *meta*-substituted aromatic amino acids with an angle of 120° between the amine and acid substituents, six units per turn are expected (Figure 8, c). In practice, the strand is pinched when the hydrogen bonds form at the inner rim of the helix (Figure 7, b; Figure 8, a), and only 4.5 units are necessary for one turn. Conversely, the strand is partly straightened when the hydrogen bonds form at the outer rim of the helices (Figure 7, a; Figure 8, b), leading to about 8 units per turn. The same applies when the amine and acid substitutents are oriented at 60° (Figure 8, d−f; the number of units per turn may then vary between 2.5[15] and 3.5) or when they are oriented at 180° (the strand does not have to be strictly linear; Figure 6, d−f).[27]

The possibility to tune these parameters opens the door to many applications. Helices with a large diameter (Figure 7, a) define a cylindrical channel that may be used for recognition, transport or catalysis.[49] For example, the helices formed by oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acids contain a polar hollow in which several water molecules are bound (Figure 10).[20] On the other hand, helices with very few units per turn permit easy access to objects with a high aspect ratio at minimal synthetic effort.[15] In this respect, the shape of the structure shown in Figure 7 (d) sharply contrasts with that shown in Figure 7 (a).

4. Syntheses and Characterization of the Oligomers

The ease of synthesis of aromatic oligoamide foldamers is one of the attractive aspects of this field. Research groups have usually applied similar simple synthetic strategies. Although solid-supported synthesis of aromatic oligoamides has been reported,[50] a convergent solution-phase strategy is generally adopted. Carboxylic acids are activated as high-yielding acid chlorides before couplings are performed. They are protected as esters, which can be easily saponified

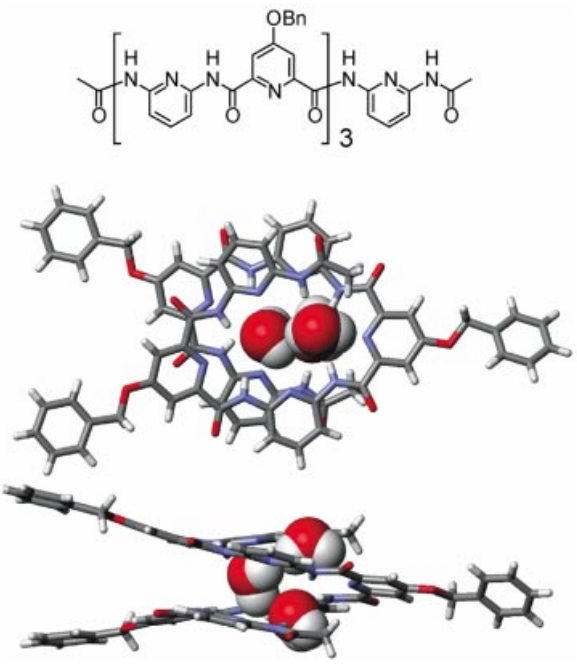

Figure 10. Crystal structure of an oligomer showing water molecules included in a polar helix groove

in the presence of several aromatic amide bonds. Amines may be obtained from the reduction of nitro groups, or from the deprotection of simple carbamates (Fmoc, Cbz). A convergent segment-doubling strategy is generally adopted,[51] where a dimer is obtained from two monomers, a tetramer from two dimers and so on. More than two blocks may also be assembled in one step as in a convergent dendrimer synthesis. For example, two oligomers bearing a free amine group may be coupled to a diacid chloride core. This way, molecular weights of 5000 g/mol and above have been attained after a limited number of steps.[9,23] That the amide groups are involved in stable intramolecular hydrogen bonds results in relatively low polarities, high R_f values on silica gel, and facile chromatographic separation.

Among the synthetic difficulties encountered is the fact that folding occurs in the reaction media. For helical structures, this may result in serious steric hindrance of the reactive functions, and lower yields. Longer reaction times and denaturing conditions (polar solvents and high temperatures) help improve the yields, but ideal conditions cannot always be found. Another problem is that aromatic oligoamides sometimes strongly bind to water and become difficult to dry.

The folded structures have proven particularly easy to characterize. This arises mainly from the fact that the preferred conformations are well defined and stable. As is already obvious from Section 3, aromatic oligoamide foldamers crystallize easily. Therefore, the main technique of characterization is single-crystal X-ray diffraction. However, crystallinity often requires the absence of long alkyl chains and is not always compatible with high solubility, so structural studies in solution are performed using NMR spectroscopy. The well-defined conformations give rise to

sharp spectra, from which deshielding of hydrogen-bonded amide groups and/or shielding of aromatic protons involved in π−π stacking are easily observable. A detailed conformational analysis in solution using the NMR techniques developed for peptides cannot be used in every case because the spectra are not always easy to assign completely. The spin systems of each aryl group are readily reconstituted, but their sequence within the strand is difficult to build when the amide protons do not correlate with a proton of each neighboring spin system as is the case in aliphatic peptides.

Molecular modeling is often used to predict the conformations. The methods employed are generally rudimentary (simple energy minimizations and Monte-Carlo searches), but the predictions of modeling studies have proven to be reliable as they match remarkably well with the structures observed in the solid state.

5. Conformational Transitions

Large structures may undergo conformational changes of large amplitude. Such transitions may be uncontrolled and belong to the intrinsic dynamics of the oligomers. They may also be triggered by external stimuli. Interest in these molecular motions is fueled by their relation to important natural phenomena (molecular motors), and by the prospect of elaborating useful chemical devices.

5.1 Intrinsic Dynamics of the Oligomers

The most common conformational transition of aromatic oligoamide foldamers is helix inversion (Figure 11). Most helices reported thus far bear no asymmetric center. In solution, they exist as a balanced mixture of right- and left-handed mirror-image conformers. In the solid state, the two enantiomers cocrystallize and spontaneous resolution (conglomerate) has yet to be reported. The right- and left-handed helices can be revealed in solution by NMR spectroscopy using chiral shift reagents, and because it often results in diastereotopic splitting of numerous NMR signals.[15] The temperature of the coalescence of these signals allows one to estimate the rate of inversion of the helix, and thus its stability relative to a partially unfolded state. This rate varies with the chemical nature of the oligomer, with its length, and with the solvent. The overall picture however, is that helices of aromatic oligoamides tend to be much more stable than those of α-peptides and their aliphatic homologues. For example, short oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acids are helically folded in water.[20] Molecular dynamic simulations show that in this series, folding of an extended linear heptameric strand should occur within 1 ns.[19] Even more striking is the fact that the helical structure of the quinoline-derived octamer shown in Figure 7 (d) is unaltered at 120° in DMSO![15]

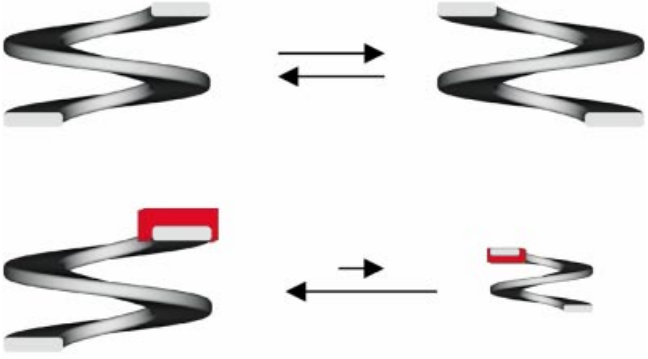

Figure 11. Schematic representation of the equilibria between enantiomeric left- and right-handed helices (top), and between diastereomeric left- and right-handed helices (bottom)

There are several reasons for the enhanced stability of aromatic oligoamide helices with respect to aliphatic peptide helices: (i) as previously mentioned, the conjugation of π orbitals make the rotation about aryl−amide bonds intrinsically more restricted than the rotation about alkyl−amide bonds; (ii) the overlapping aryl and amide units provide additional stabilizing π−π interactions; (iii) in aromatic oligoamide foldamers, hydrogen bonds occur between consecutive units (thus, a heptamer gives rise to six hydrogen bonds, instead of three for the α-helix of an α-heptapeptide); (iv) in some cases hydrogen bonds are directed towards the helix groove and are shielded from the solvent; (v) hydrogen bonds in helical aromatic oligoamides are perpendicular to the helix axis, which allows the helix to breathe and extend like a spring, with minor distortions of the hydrogen bonds (described in Section 6).

A few examples of helical aromatic oligoamides bearing asymmetric centers have been reported. In the presence of a chiral center, the right- and left-handed helices become diastereoisomers, and their proportions may differ (Figure 11). In one case, no chiral induction of the handedness was observed, and the two helical diastereoisomers actually cocrystallized.[40] In the case of the oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acids, induced circular dichroism (CD) was indeed observed in the chromophore of the oligomer showing that one helical form is favored.[30] Further studies along this line show that both intramolecular and intermolecular chiral induction is possible with these compounds.[48] Chirality was also induced in aromatic oligoamide dendrimers,[23,41] and in stacks of branched oligomers.[32] These phenomena, combined with the slow rate of helix inversion mentioned above, may have applications in the construction of chiroptical devices capable of storing transient chiral stimuli.[52]

5.2. Controlled Structural Changes

Controlled conformational transitions of aromatic oligoamides rely on the possibility of triggering a *syn*-to-*anti* or *anti*-to-*syn* 180° rotation. This occurs upon protonation of 2-pyridinecarboxamide and of 2-(carbonylamino)pyridine units (Figure 1, d and g; Figure 2, e and f).[30,37,38] Moreover, it occurs selectively in the presence of acids of various strengths. For instance, trifluoroacetic acid protonates 2-(carbonylamino)pyridines and not 2-pyridinecarboxamides whilst triflic acid protonates both. It follows that in oligomers where the two units are assembled alterna-

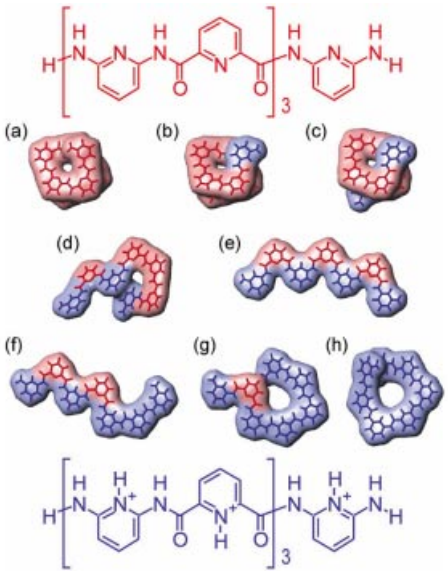

Figure 12. Energy-minimized structures of the various protonated states of an oligoamide comprising four 2,6-diaminopyridine units alternating with three 2,6-pyridinedicarbonyl units; the protonated rings are shown in blue while rings which are not protonated are in red

tively, selective protonations induce selective *syn-anti* rotations that results in the unfolding of the initial helix (Figure 12, a) into a linear strand (Figure 12, e). Further protonation causes the refolding of the strand into another helix (Figure 12 h).[30]

A transition between a helical and a linear conformation has also been described in oligomers of 1,8-naphthyridines linked in positions 2 and 7 by urea functional groups.[53,54] Contrary to the 2-(carbonylamino)pyridines which have a strong preference for one conformation (Figure 2, e), 2-ureopyridines may exist as two *cis* and *trans* conformers (Figure 13, a). In oligomers, the balance between the two conformers results in an equilibrium between intermolecular hydrogen-bonded linear dimers, and intramolecular hydrogen-bonded helical monomers (Figure 13, b). By comparison, the conformation of 2-pyridinecarboxylic acid hydrazides is biased in favor of the *trans* conformer (Figure 13, c) and no *cis* conformer is observed.[55]

Among other means that could be envisaged to trigger conformational transitions of aromatic oligoamides are metal coordination[56] and tautomeric equilibria such as the lactim-lactam equilibrium of 2- and 4-hydroxypyridines (Figure 14). Tautomeric equilibria convert endocyclic and exocyclic hydrogen-bond acceptors into hydrogen-bond donors that may induce a *syn-anti* 180° rotation of an adjacent aryl−amide bond. However, it appears that the equilibria are generally strongly shifted in one direction and do not allow a conformational change. For example, 2-hydroxy-3-pyridinecarboxamide has a strong preference for the lactam tautomer (Figure 14, a),[57] whereas 4-hydroxy-2-pyridinecarboxamide is in the lactim form (Figure 14, c).[20] The lactim form also prevails for 2-(carbonylamino)-4-hydroxypyridine (Figure 14, d).[58] The question remains open for 2-(carbonylamino)-6-hydroxypyridine (Figure 14, b), for which we could not find literature data indicating a clear preference for one tautomer.

6. Supramolecular Assemblies Using Oligoamide Foldamers

Aromatic oligoamide foldamers possess multiple hydrogen-bonding functions and extended flat aromatic surfaces that can both be involved in intermolecular interactions and promote specific and nonspecific aggregation. Linear oligomers exhibit facial recognition elements that may be used for protein surface recognition,[27] or for association with biological membranes.[33] Hydrogen-bonded mediated assemblies may occur at the sites which are not involved in intramolecular hydrogen bonds and give rise to linear homo- and heterodimers (Figure 4, a and b; Figure 13, b).[7,8,36,53]

In branched, cyclic, and helical oligomers, hydrogen bonds may help binding guests in the hollow(s) of the structures (Figure 10).[20,24,46,49] However, this possibility has not often been exploited until now. Hydrogen bonds in these structures are mainly intramolecular and essential to stabilize the conformation of the oligomer. Contrary to hydrogen bonding, aromatic stacking allows extensive intermolecular contacts. For example, all oligomers undergo nonspecific aggregation at high concentration and/or low temperature,

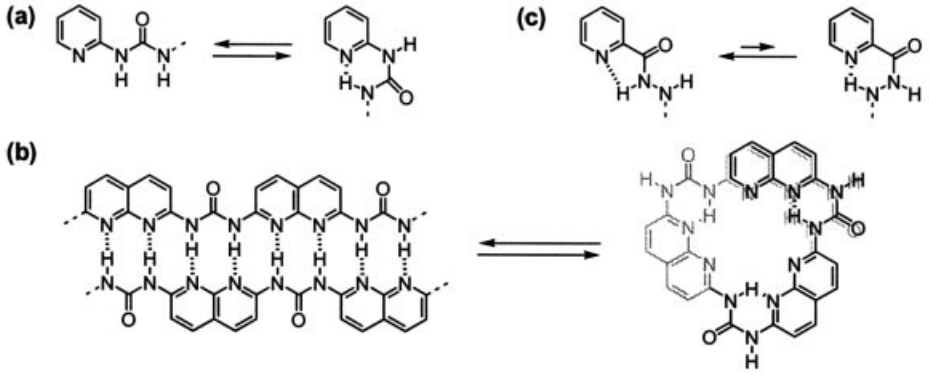

Figure 13. a) *cis-trans* equilibrium of 2-ureopyridines; b) equilibrium between intramolecularly hydrogen-bonded linear and helical monomers; c) for comparison the *cis-trans* equilibrium for 2-pyridinecarboxylic acid hydrazide

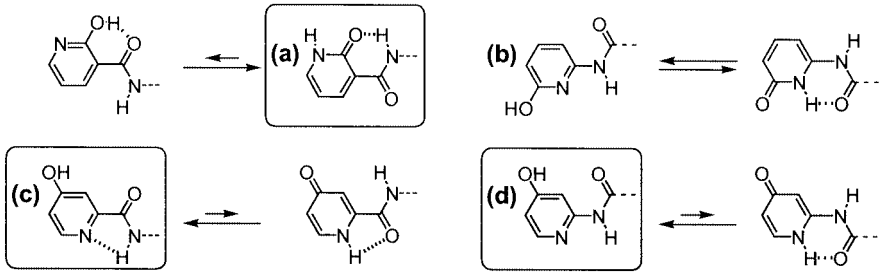

Figure 14. Lactam-lactim tautomerization

characterized by a broadening and a shift to higher field of the NMR signals. This appears to be particularly significant for large structures such as dendrimers.[23,24] Selective aromatic stacking occurs with aromatic "discs" such as the branched oligomers shown in Figure 5 (b), which pile up into columnar aggregates. In principle, helical oligomers may pile up in a similar manner. The area of intermolecular $\pi-\pi$ interactions would then be limited to the cross-section of the helix. But helices may also intertwine and form double-helical structures which permit much more extensive intermolecular stacking interactions (Figure 15).

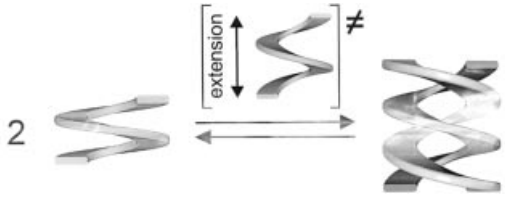

Figure 15. The intertwining equilibrium of helices

An example of an entwined dimer is shown in Figure 16, which results from the assembly of two of the second-generation dendrimers of Figure 5 (a).[24] Intertwining allows some aryl groups to undergo stacking interactions on both of their faces, as can clearly be seen from the side view of the dimer, whilst it involves only two molecules. Compared to the simple piling up of numerous aromatic units, intertwining maximizes the interactions and minimizes the entropic cost.

Extensive $\pi-\pi$ stacking interactions also drive the assembly of oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid into double-helical dimers.[21,22] Three crystal structures of these double helices are shown in Figure 17 and reveal that the relative positions of the two strands in the dimers may vary significantly. The surface involved in intermolecular $\pi-\pi$ contacts is higher for the dimers shown in Figure 17 (a and b) than in the dimer shown in Figure 18 (c) in which the two strands are offset. The formation of these dimers illustrates the possibility of extending helical aromatic oligoamide foldamers like a spring (Figure 15). Such an extension can be accommodated by slightly increasing the dihedral angles at each aryl–amide bond. This results in a minor lengthening of the intramolecular hydrogen bonds, and can thus be effected at a small energetic cost. The price for this distortion is apparently well compensated by the intermolecular interactions in the dimer.

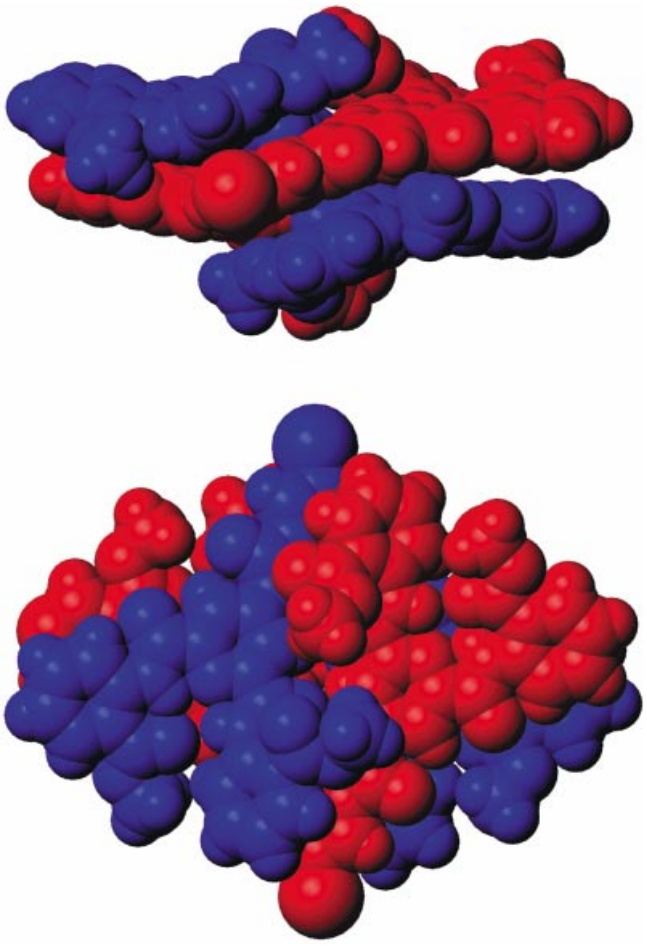

Figure 16. Side and top views of the intertwined dimer of the second-generation dendrimer represented in Figure 5 (a)

Hybridization is easily observed in solution. Since the single-helix and double-helix equilibrium is often slow on the NMR timescale, both species give rise to distinct signals.[21,22] Dimerization constants higher than 5×10^5 mol^{-1} have been measured.[48] Dimerization depends on the nature of the solvent and the presence of water which causes duplex dissociation. Electron donors in position 4 of the pyridine rings result in a dramatic enhancement of dimerization (by up to three orders of magnitude).[21,22]

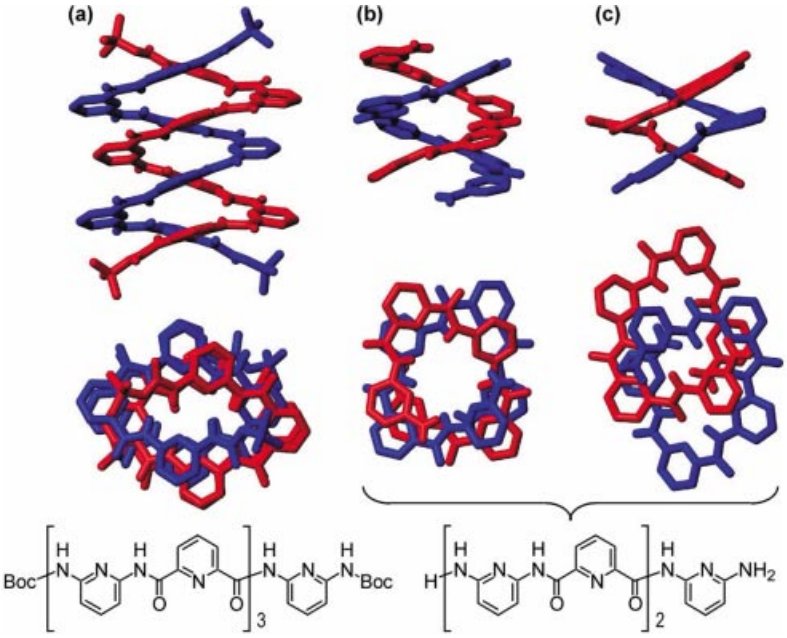

Figure 17. Side (top) and top (center) views of three crystal structures of two oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (bottom); the three structures are represented on the same scale; non-amide hydrogen atoms and included solvent molecules have been omitted for clarity

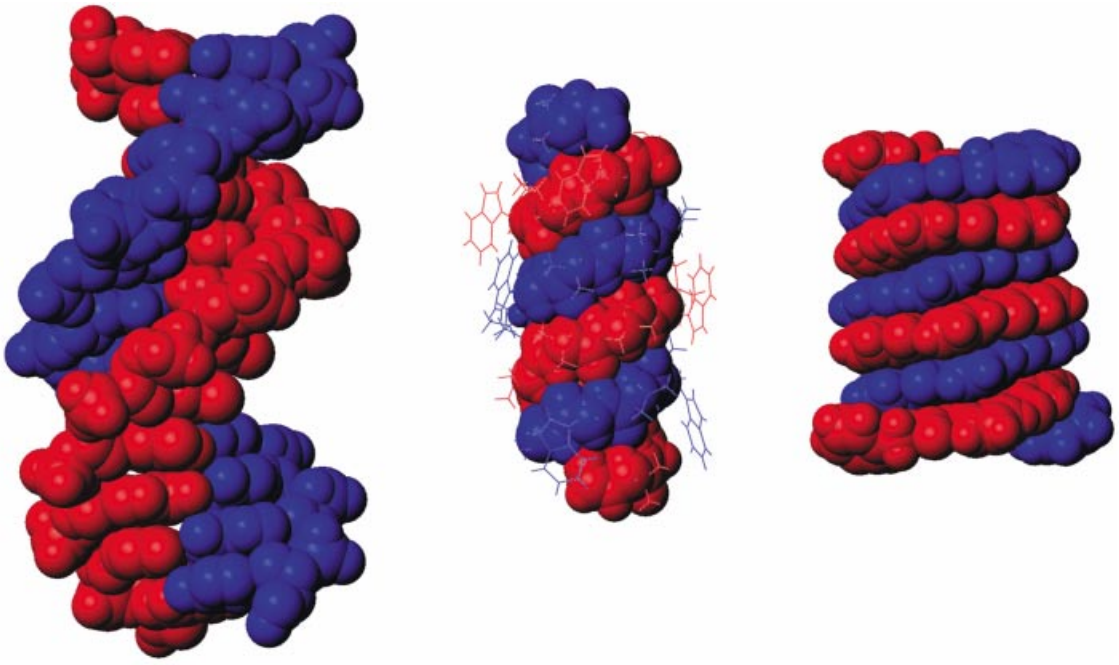

Figure 18. Representation at the same scale of the B-form of double-helical DNA (left), an X-ray structure of double-helical Gramicidin D (center), and a double helix of pyridine oligoamide foldamers

These double helices are unusual and unexpected structures. Indeed, whilst single-helical oligomers and polymers are common both in natural and synthetic systems, double-helical motifs held by direct interactions between the two strands are rare and almost all known cases are of natural origin (Figure 18). Besides the double helices DNA, RNA and their synthetic analogues such as PNA, some bacterial peptides such as Gramicidin D also dimerize as double helices (Figure 18).[59] The structure of the double helices of oligoamide foldamers show that their diameter is between that of DNA and that of Gramicidin D. Their double-helical pitch of about 7 Å corresponds to the thickness of two aromatic rings, and is probably the smallest possible pitch for a doubly stranded structure (Figure 18). It will be inter-

esting to see whether such artificial structures can be endowed with the functions of natural double helices.

Conclusion

This review is aimed at showing that aromatic oligoamide foldamers are efficiently designed and easy to synthesize; they also allow one to reach a wide range of stable folded states. Though they have received much less attention than their aliphatic counterparts, these compounds also possess a high potential for mimicking the secondary structures of biopolymers. An expected development of this field is a rapid increase in the size and complexity of the foldamers, and a progressive shift from peptidomimetics to proteomimetics − mimics of tertiary and quaternary structures. This will require improvements of the stepwise synthesis of high molecular weight molecular strands, which will certainly benefit from the experience acquired in dendrimer synthesis. It will also require further adaptations of the tools of structural biology to the purification and structural study of fully synthetic large objects. Another essential development is the endowment of these structures with functions. Though truly efficient artificial enzymes seem to remain a long-term endeavor, large synthetic folded structures open the way to new recognition, transport, and vectorization schemes of proteins, nucleic acids and membranes.

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