Cylindrical sheet formation of oligo-*meta*-aniline foldamers†

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***Ortho*-nitro- and *ortho*-alkoxy-oligo-*meta*-aniline units fold in solution through hydrogen bonds and aromatic stacking into compact structures that were characterized in the solid state as cylindrical β-sheet like structures.**

During the last decade, efforts have been made to develop new organic oligomers backbones that adopt specific predefined architectures. These oligomers known as foldamers are designed to mimic natural biomolecule secondary structures such as β-sheets and helices.[1] Two different approaches have been used for the design of such compounds: (i) the "top-down approach", which involves structural variation of parent chain molecules to create peptidomimetic[2] or nucleotidomimetic[3] foldamers, and (ii) the "bottom-up approach" which involves abiotic backbones. This class of foldamers often takes advantage of the rigidity and solvophobicity of aromatic units. Aromatic units can be directly connected to each other through C–C bonds[4] and C–N bonds[5] or using amide,[6] urea[7] or hydrazide[8] functions. These functional groups are used to facilitate the synthesis of long oligomers and to induce the folding of the molecule through hydrogen bonds.

In this paper, we present a new class of aromatic oligoamine foldamers that adopt compact folded structures in solution through hydrogen bonds and aromatic stacking. These foldamers show cofacial architectures, in the solid state, that can be compared to cylindrical β-sheets.

Our design is based on the use of alternating 1,5-diamino-2,4-dinitrobenzene units and 1,5-diamino-2,4-dialkoxybenzene units (Fig. 1). The *ortho* position of the amine and the nitro groups allows the formation of a six-membered hydrogen bond ring between the amine proton and the oxygen of the nitro group. The *ortho* position of the amine and the alkoxy group leads to the formation of a five-membered hydrogen bond ring between the same amine proton and the oxygen of the alkoxy group.

This hydrogen bond pattern when applied to a three-aromatic unit oligomer **1** gives rise, in the solid state, to a pseudo-planar crescent shape molecule (Fig. 2(a)). Downfield chemical shift of the amine proton NMR signal (δ = 9.73 ppm in $CDCl_3$, Fig. 3(a)), that reflect its implication in strong hydrogen bonds, and observation of a NOE correlation between H4 and H5 protons on the two adjacent rings are in agreement with a similar structure of **1** in solution.

A shift from planarity of terminal aromatic units is observed in the crystal, probably caused by the repulsion of the close aromatic protons inside the curved molecule (d_{H-H} = 2.09 Å). This tilting provokes an elongation of the structuring hydrogen bonds NH···OAr (d_{H-O} = 2.23 Å).[9]

Helical structures are expected for longer oligomers since a fourth aromatic unit cannot lie in the same plane as the three first units. To allow the n and n + 3 units to overlap and to keep the hydrogen bonds network, an overall elongation of each hydrogen bond should occur.

The NMR spectrum of the oligomer **2** (Fig. 3(b)), constituted of five aromatic units, shows downfield amine proton signals (δ = 9.68 ppm in $CDCl_3$), which reflect the involvement of these protons in hydrogen bonds. An upfield shifting of aromatic protons signals of **2** compared to **1** (for example H5 shifts from δ = 6.61 ppm in **1** to δ = 6.41 ppm in **2**) is observed, and can be explained by an increase of the aromatic stacking, consistent with a compact structure of **2**. To overcome problems due to superimposition of NMR signals on 2D-ROESY spectrum, selective 1D-ROESY experiments were performed on **2** (see ESI†). Selective pulse on H5 proton signal shows correlations with H4 and H7 proton signals, indicating the spatial proximity of H5 with H4 and H7. This result confirms the presence of a stable folded structure in solution that may have an helical architecture.

However, in the solid state, the expected helical organization of the oligomer **2** is not observed. The pseudo-planar organization of the three first units observed in **1** is conserved but the fourth unit lies perpendicular to this initial plane (Fig. 2(b)). In this structure, no hydrogen bond is formed

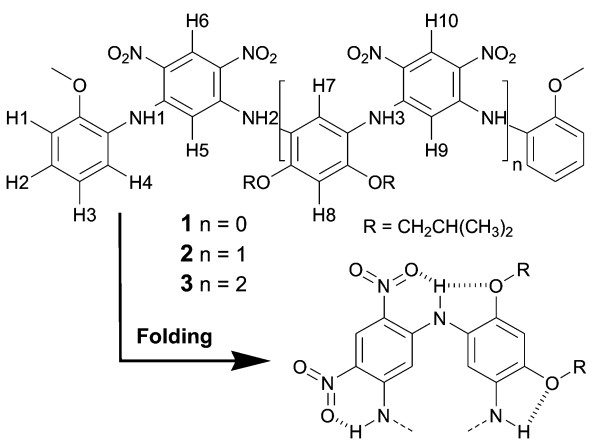

Fig. 1 Structures and folding of the oligomers through intramolecular hydrogen bonds.

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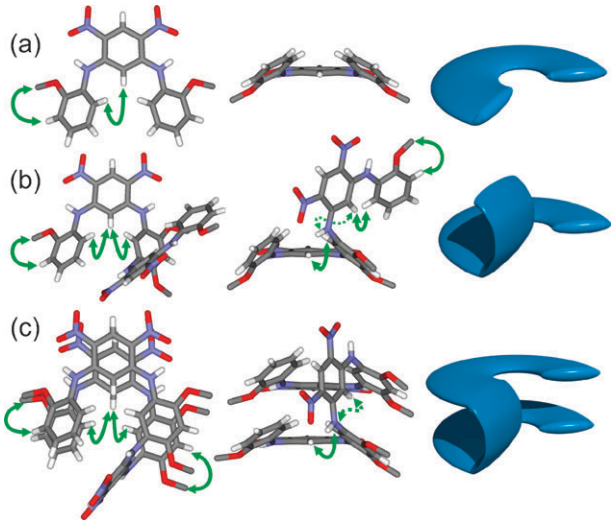

Fig. 2 Top and side view of crystal structures‡ and schematic representation of their spatial organisation of: (a) **1** (crystal grown from nitrobenzene–methanol), (b) **2** (crystal grown from chloroform–methanol) and (c) **3** (crystal grown from chloroform–methanol). Arrows show NOE effects observed by NMR. Included solvent molecules, alkyl chains and hydrogens have been omitted for clarity.

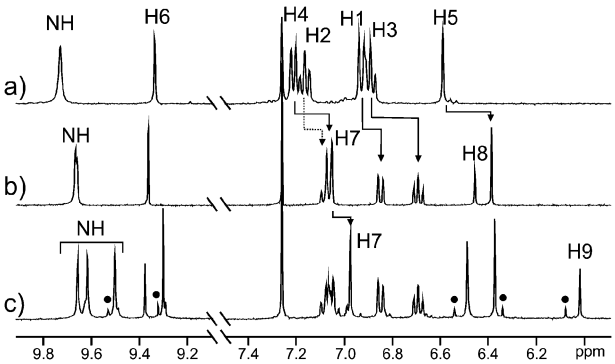

Fig. 3 Part of the ^{1}H NMR spectra of (a) **1**, (b) **2** and (c) **3** at room temperature in $CDCl_3$. The symbol ● indicates an impurity in compound **3**.

between the amine proton and the oxygen of the alkoxy group of the third unit, which results in a non-symmetrical architecture. The disruption of the hydrogen bond network may emerge from crystal packing effects since the fourth aromatic unit is involved in π–π stacking interactions with its neighbour molecule and in an intermolecular hydrogen bond through its nitro group (Fig. 4).

Moreover, loss of the NH···OR hydrogen bond in the solid state can be explained by three different factors: (i) the strong repulsion of the aromatic protons inside the hollow of the expected helix (this steric hindrance was already observed in **1**); (ii) the hydrogen bond of the six-membered ring between the amine proton and the nitro group is too strong to allow its elongation, indeed the pseudo-sp^2 hybridization of the nitrogen and oxygens allows the optimal orientation of the hydrogen bond; (iii) the hydrogen bond of the five-membered ring is long and too weak to overcome its required elongation for the formation of the helix (the lone pair of electrons of the sp^3 oxygen is not well oriented for hydrogen bonding). In addition to crystal packing constraints, these effects trigger the loss of the structuring hydrogen bond in the solid state.

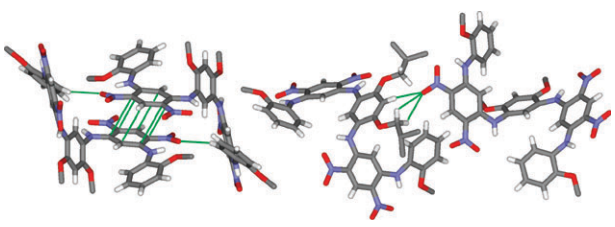

Fig. 4 View of intermolecular interactions of **2** in the crystal.

In the crystal, the oligomer **3** composed of seven aromatic units adopts a compact structure, again different from the expected helical conformation (Fig. 2(c)). Like in **1** and **2**, extremities are pseudo-planar. These extremity planes are involved in strong intramolecular π–π stacking interactions ($d_{plane-plane} \approx 3.5$ Å), and are organized in an anti-parallel way. The fourth unit, that is the central one, stands perpendicular to these planes and induces a β-turn like structure. This turn results from a similar hydrogen bond disruption observed in **2**, between the oxygen of the alkoxy group of the third unit and the amine proton of the fourth unit. Unlike **2**, no intermolecular interactions are observed in the solid state for **3** but crystal packing and optimization of the orientation of the intramolecular π–π stacking interaction could be the driving force for this organization.

The solution ^{1}H NMR spectrum of **3** (Fig. 3(c)) shows a strong upfield shifting of the H9 signal compared to the H5 signal. This shielding is in agreement with its position between the two aromatic rings in the crystal structure but could also be explained by its position in the hollow of the expected helix. 2D-ROESY NMR experiment shows strong cross-peaks between protons of adjacent aromatic units, inside the curved structure: H4 ↔ H5 ↔ H7 ↔ H9 (Fig. 5), which are in agreement with a compact folded organization in solution. Other weak NOE correlations are observed between these aromatic protons and their respective neighbouring amine hydrogens: NH1 ↔ H5 ↔ NH2 ↔ H7 ↔ NH3 ↔ H9. These correlations result from the fact that during the mixing time of the NMR experiment these protons are close enough in space to allow polarisation transfer. This indicates a temporary loss of structuring hydrogen bonds and the presence of a dynamic equilibrium of the compact structure with an unfolded conformation. However, the intensity of these cross-peaks are, on average, 10 times weaker than the NOE correlations described earlier, indicating that the oligomer adopts preferentially a folded structure in solution. Additional structural analysis is required to determine which organization prevails in solution: the sheet conformation or the helical structure.

In summary, a surprising non-conventional sheet structure was observed in the solid state for these *ortho*-hydrogen bond acceptor-*meta*-aniline oligomers. Propagation of this motif that may arise from crystal packing can be expected for longer oligomers. In solution, we have shown that these oligomers adopt stable compact folded structures, and therefore represent a new class of foldamers. These oligomers enrich the scope of abiotic backbones that could be used for the design of more complex and functional molecular architectures, such as previously suggested: synthetic receptors, enzyme mimics, molecular devices or tunable materials.[1]

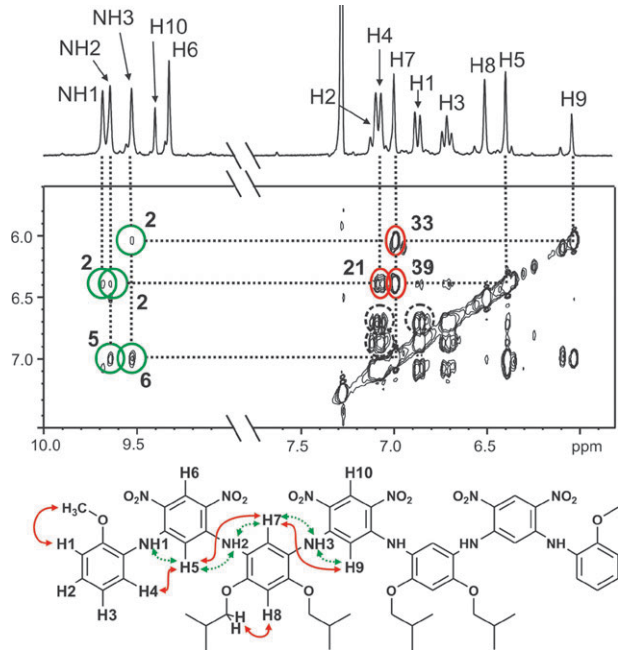

Fig. 5 2D-ROESY spectrum of the aromatic and amine proton region of **3** in $CDCl_3$. Values indicated on the spectrum are integration values of cross-peaks. Red circles and arrows show strong NOE correlations compatible with a folded organisation. Green circles and arrows show very weak NOE correlations compatible with an unfolded conformation. Dashed circles show COSY correlations.

Notes and references

‡ *Crystal data*: **1**: $C_{20}H_{18}N_4O_6$, M = 410.38, orthorhombic, space group *Pnma*, a = 19.9110(18), b = 23.1854(3) Å, c = 4.0727(14) Å, V = 1880.1(7) Å^3, T = 293(2) K, Z = 4, λ = 0.154180 nm, reflections measured = 23 008, 1849 unique (R(int) = 0.0369), final R indices were R_1 ($I > 2\sigma(I)$) = 0.0452, $wR2$ (all data) = 0.1197. **2**: $C_{41}H_{43.8}Cl_3N_8O_{13.40}$, M = 969.39, monoclinic, space group $P2_1/a$, a = 15.4253(9), b = 16.0157(8), c = 18.8913(8) Å, β = 89.956(4)°, V = 4667.0(4) Å^3, T = 193(2) K, Z = 4, λ = 0.154180 nm, reflections measured = 26 487, 4076 unique (R(int) = 0.1282), final R indices were R_1 ($I > 2\sigma(I)$) = 0.0996, $wR2$ (all data) = 0.2987. The poor quality of this structure is due to disordered solvent molecules and crystal decomposition during measurement. **3**: $C_{60}H_{66}N_{12}O_{18}$, M = 1243.25, monoclinic, space group $C2/c$, a = 18.0066(9), b = 33.8684(11), c = 20.2630(10) Å, β = 92.719(2)°, V = 12343.6(10) Å^3, T = 193(2) K, Z = 8, λ = 0.154180 nm, reflections measured = 85 375, 11 511 unique (R(int) = 0.0751), final R indices were R_1 ($I > 2\sigma(I)$) = 0.0778, $wR2$ (all data) = 0.2655.

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9 1,3-Di(aminophenyl)-4,6-dinitrobenzene (CCDC 740015) was prepared and crystallized to enlighten the influence of the methoxy group. The dihedral angle of the terminal aromatic units and the dinitro unit are around 50°, compared to 28° in **1** (see ESI†).

