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Computational prediction and experimental verification of pyridine-based helical oligoamides containing four repeating units per helical turn†

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Aided by high level *ab initio* computational modeling, we successfully designed and experimentally proved a new set of backbone-rigidified pyridine-based folding oligoamides that require approximately four repeating units to form a helical turn.

A highly effective means to restrict the conformational freedom of diverse folding backbones explores the uses of hydrogen bonding (H-bonding) forces of varying types. The robustness, predictability and directionality of H-bonds have allowed a reliable creation of diverse helically folded unnatural backbones.[1,2] Compared to the H-bonded helically folded aliphatic foldamers, H-bonded aromatic helical foldamers have remained much less studied and their backbone diversity has been mostly limited to the examples reported by Hamilton *et al.*,[2a–c] Lehn *et al.*,[2d–f] Gong *et al.*,[2g–k] Zimmerman *et al.*,[2l] Huc *et al.*,[2m–p] Li *et al.*,[2q–t] and others.[2u–w]

We have recently reported a series of folding molecules with their repeating units represented by pentamer **1a** and hexamer **1b** (Fig. 1a) and with their folded structures enforced by internally placed continuous H-bonding networks.[3a–e] Examining these folding molecules by both solid state and solution studies reveals an intrinsic unusual peculiarity requiring five identical repeating units to form either a macrocycle[3a–c] or a helical turn,[3d,e] which has been rarely observed before by others among unnatural foldamers. We postulated that by replacing the methoxy benzene units in **1a** or **1b** with the pyridine units the same peculiar requirement shall still remain in pyridine-containing aromatic foldamers such as **1c–1e** (Fig. 1b). More specifically, the internally H-bonded pyridine oligomers **1c–1e** containing no end groups (*i.e.*, ester, nitro, *etc.*) should adopt a planar conformation rather than a helical geometry provided that pyridine nitrogen atoms and amide protons are able to form stabilizing intramolecular H-bonds to constrain the aromatic backbone.

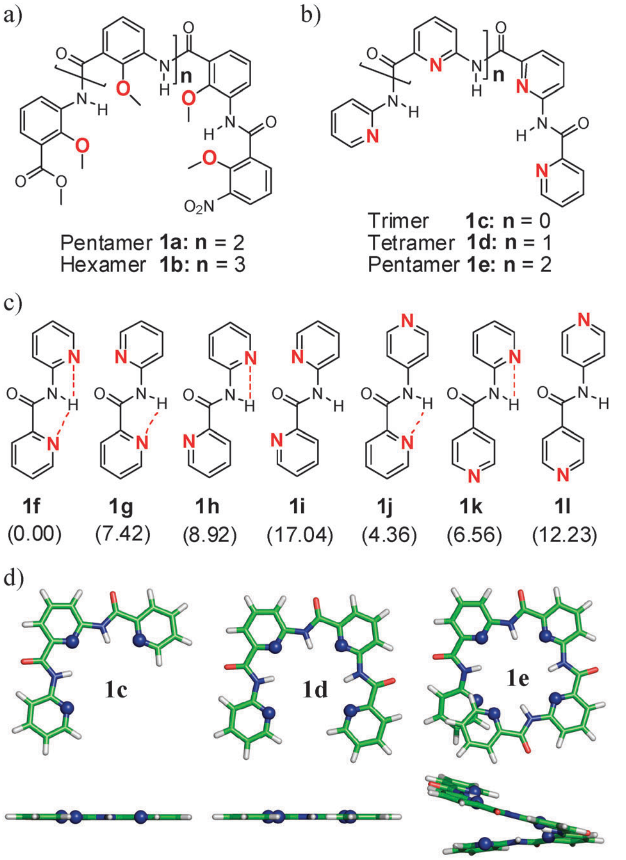

Fig. 1 (a) Methoxybenzene-based pentamer **1a** and hexamer **1b**,[3d,e] (b) pyridine-derived oligoamides **1c–1e**, (c) pyridine dimers used for *ab initio* computational modelling and (d) their computationally optimized geometries at the B3LYP/6-31G* level. Values in parentheses shown in (c) are the relative energies in kcal mol^{-1} computed at the level of B3LYP/6-311+G(2d,p) and normalized against the most stable conformer **1f**.

Using the density functional theory at the level of B3LYP/6-311+G(2d,p), our calculations on dimer **1f** with different conformations and on dimers **1j–1l** reveal **1f** to be perfectly planar (ESI†) and the most stable (Fig. 1c). The high stability of **1f** primarily derives from the two stabilizing cooperative

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† Electronic supplementary information (ESI) available: Synthetic procedures and a full set of characterization data including $^{1}H/^{13}C$ NMR, MS, 2D NOESY, and molecular modelling. [CCDC NUMBER(S)]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11532d

intramolecular H-bonds worth of $\sim$10.92–12.23 kcal mol^{-1}. The unfavorable repulsive forces between oxygens and nitrogens deduced by comparing the relative energies of **1g–1i** with **1j–1l** further increase the stability of **1f** by $\sim$4.81–5.42 kcal mol^{-1}.

Prompted by the high strength of intramolecular H-bonds in **1f**, higher oligomers **1c–1e** were subjected to the theoretical scrutinies at the B3LYP/6-31G* level (Fig. 1d). While trimer **1c** and tetramer **1d** both are crescent-shaped as expected, pentamer **1e** surprisingly takes up a helical structure. A closer look into **1c–1e** shows that each pyridine-based repeating unit corresponds to a 84° turn in the helix, and therefore, rather than five residues per helical turn as in **1a** and **1b**,[3d,e] only 4.3 residues are required to furnish a helical turn.

We were perplexed by this seemingly contradictory finding and intrigued to find out if this can be experimentally verified or not. For this purpose, pyridine oligoamides from dimer **2** to pentamer **5** were made (Fig. 2)† with an overall yield of $\sim$1% for **5** after 12 steps, and they were then subjected to study using X-ray crystallography and 2D NOESY spectroscopy.

Crystals of oligomers **2–5** suitable for X-ray structure determination were obtained by slow evaporation or diffusion methods at room temperature. The top and side views of the determined crystal structures (Fig. 2) demonstrate that with the increasing addition of pyridine-based building blocks into the aromatic backbone, the elongated backbone becomes increasingly curved in one direction. This is a result of the stabilizing forces from the progressively lengthened intramolecular H-bonding network that comprises up to nine intramolecular H-bonds (pyridine N$\cdots$H of amide groups = 2.101–2.394 Å). While shorter oligomers **2** and **3a** adopt a crescent formation, tetramer **4** starts to become helically shaped due to the steric hindrance from the end ester and Cbz groups, and pentamer **5** is clearly helically folded whereby the two end pyridine rings almost can be superimposed over each other (Fig. 2e). In **5**, each repeating unit in average corresponds to an $\sim$84° turn and so 4.3 such units are needed to furnish a helical turn, remarkably identical to the computationally determined value. For comparison, helical turns in some well-known H-bonded aromatic folding helices with a homogeneous backbone have been reported to contain $\sim$2.5 residues,[2m,w] $\sim$4 residues,[2p] between 4–5 residues,[2k] 5 residues,[3d,e] and between 6–6.5 residues.[2g,h] On the other hand, most aliphatic helices contain less than four repeating units per helical turn.[1l] Of further interest to note is the aliphatic π-helices containing 4.3 residues per helical turn.[1l] The ability to fine-tune the helicity parameters should enable us to systematically and precisely control the 3D spatial orientation of the exterior side chains for functional diversification of helically folded aromatic foldamers.[2q,s,t,4]

A 2D NOESY study was employed to examine if the crescent-shaped or helical conformations seen in oligomers **3b**, **4** and **5** in solid states also persist in solution. Given that the NOE contacts seldom become detectable if the inter-atomic distance is over 5 Å. The experimentally observed NOE contacts therefore would provide evidence for the distance between two interacting protons and accordingly the conformations in solution.

As revealed from the crystal structure of **3a**, the inter-atomic distances between adjacent amide protons, and between the end ester and Cbz groups are of 3.35 Å to 3.50 Å, an indication of a possibility to observe NOE contacts among them. The ^{1}H NMR signal overlaps due to the repetitive nature of **3b** were overcome by performing the NOESY study at 263 K. At this temperature, amide proton d was well separated from the aromatic protons, permitting us to confidently analyze the NOE patterns. The observation of (1) the expected NOE cross-peaks between proton c and b or d and (2) the end-to-end NOE contacts between end methoxy protons a and Cbz protons g or h provides the convincing evidence for the folded crescent-shaped structure of **3b** in solution (Fig. 3a). Additionally, in **3b**, the NOE intensities among amide protons b, c and d (distances = 3.40 and 3.50 Å) were stronger than that between protons d and g (4.16 Å, Fig. 3a). This comparison provides further evidence on the existence of intramolecular

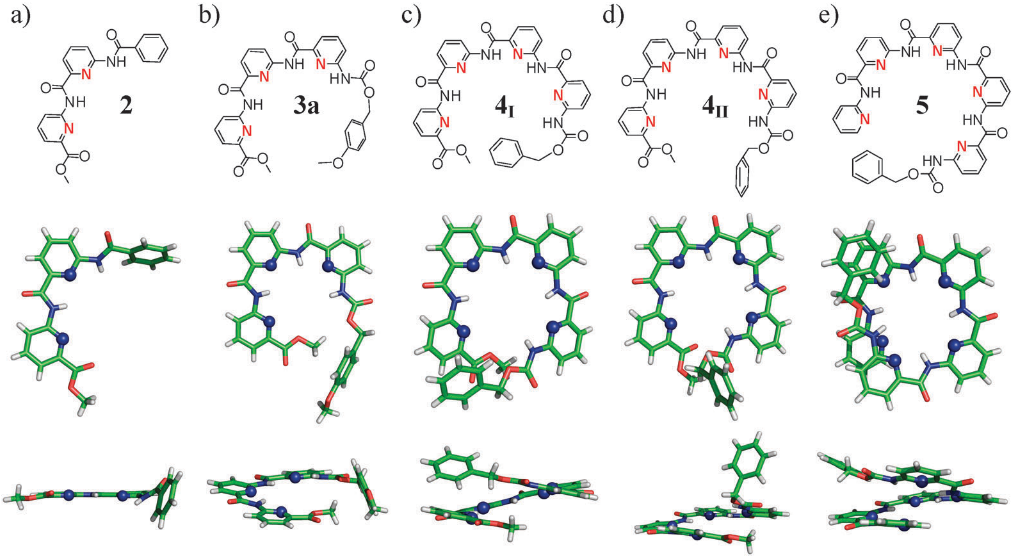

Fig. 2 Top and side views of crystal structures of (a) dimer **2**, (b) trimer **3a**, (c) tetramer $\mathbf{4_{I}}$, (d) tetramer $\mathbf{4_{II}}$, and (e) pentamer **5**. Tetramer **4** exists in two different conformations in the solid state that are designated as $\mathbf{4_{I}}$ where the *N*-terminal benzene ring is roughly coplanar with other pyridine rings and $\mathbf{4_{II}}$ where the *N*-terminal benzene ring is roughly perpendicular to other pyridine rings. It can be seen that the backbone becomes increasingly curved from dimer **2** to pentamer **5** and about 4.3 repeating units are required to make up one helical turn in pentamer **5**.

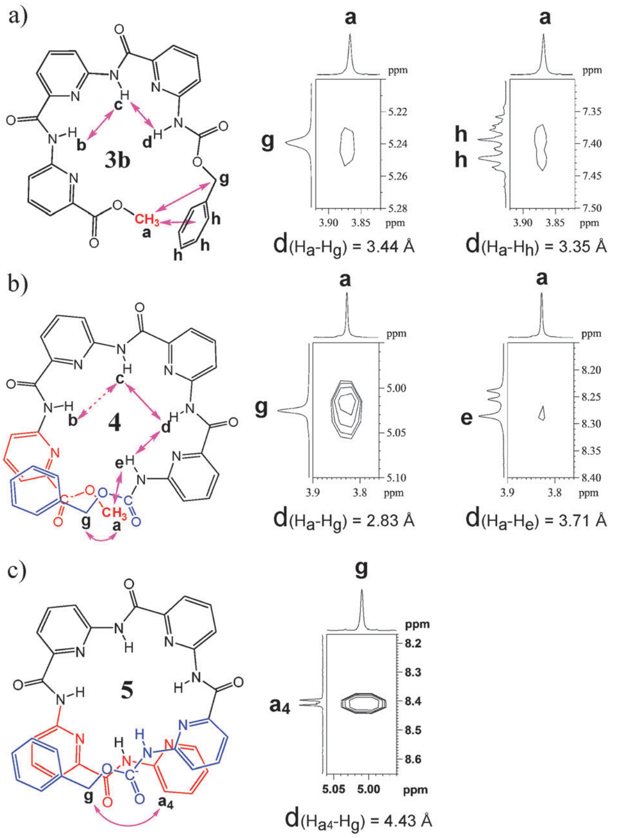

Fig. 3 Observed NOE contacts in $CDCl_3$ illustrated by double headed purple arrows in (a) trimer **3b**, (b) tetramer **4**, and (c) pentamer **5**.† The selected end-to-end NOE cross-peaks with their corresponding shortest inter-atomic distances from the crystal structures of **3b**, **4**, and **5** are shown to the right. The dotted arrow in (b) indicates a much weaker NOE contact seen between protons b and c.

H-bonds that restrict the conformational freedom of amide bonds. If one of the amide bonds in **3b** is flexibly allowed to flip to the other side by 180°, the distance between this flipped amide proton and its neighboring amide protons will become larger than 5 Å, a distance that allows the observation of either much weakened NOEs or no NOEs at all.

Similar to **3b** and consistent with the inter-atomic distances from 2.83 to 3.77 Å found in tetramer **4** (Fig. 3b),† NOE cross-peaks between amide protons b and c, and between d and e were observed, suggesting the close proximity of these amide protons in space and the folded conformation for tetramer **4**. The helically folded geometry adopted by both tetramer **4** and pentamer **5** is unambiguously confirmed by the end-to-end NOE contacts seen between protons a and e or g for **4** (Fig. 3b), and between protons a_4 and g for **5** (Fig. 3c). As a result of extensive ^{1}H NMR signal overlaps, all the other NOE cross-peaks seen in **5** cannot be unambiguously assigned.†

In summary, we show that the high level *ab initio* models enable us to rationally design and experimentally demonstrate by both solution and solid state characterizations a new class of helical aromatic foldamers, requiring ~4.3 residues per helical turn that closely mimics the helicity requirement by π-helices. The availability of these diverse helical foldamers should greatly facilitate the design of function-oriented aromatic foldamers.[2q,s,t,4]

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