# Foldamers with unusual structural architecture from spirobi(indane) building blocks†

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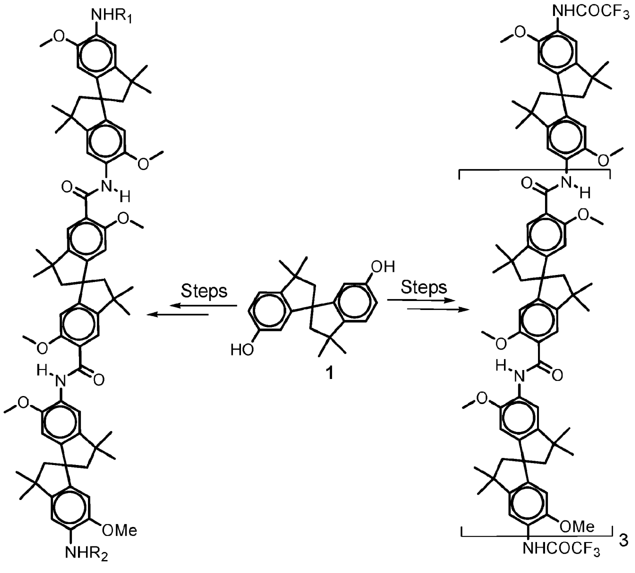
**This communication demonstrates the utility of inherently rigid building blocks such as 1,1′-spirobi(indane) for generating conformationally ordered synthetic oligomers with structural architectures distinct from those classically observed.**

Conformationally ordered synthetic oligomers, called "foldamers", have attracted considerable attention in recent years primarily due to their enormous ability to display discrete folding propensities similar to biopolymers.[1] The initial efforts ushered by Seebach and Gellman showed that oligomers made from β-amino acids form stable secondary structures, akin to the conformations displayed by native peptides and proteins.[1,2] Subsequent studies revealed that oligomers of the higher homologous γ- and δ-amino acids are also able to form definite secondary structures.[3] To extend the repertoire of foldamer design, oligomers containing different residues of independent conformational preferences have been suggested. For instance, several groups demonstrated that α,β-, α,γ- and β,γ-hybrid peptides composed of the corresponding amino acids in alternate order adopt special helix types.[4] Interestingly, such oligomers are resistant against proteases and some of them display promising biological activities.[5] In a related development, several researchers utilized sugar amino acids in the design and development of stable protein secondary structure mimics. Studies from various laboratories have convincingly demonstrated the enormous potential of sugar building blocks to breed structural architectures reminiscent of protein structures.[2a,6] The search for building blocks to construct synthetic oligomers with predefined conformational preference has also led to the discovery of a myriad of molecules with aromatic frameworks showing intriguing structures and properties.[7,8]

In this article, we report on foldamers containing 1,1′-spirobi(indane) building blocks as subunits. 1,1′-Spirobi(indanes)[9] are aromatic–aliphatic spiro systems characterized by a highly rigid framework. Owing to the periplanar arrangement of the aromatic rings, they have certain similarities to binaphthols (BINOLs),[10] but are conformationally much more rigid due to the spiro-annulated rings that prevent rotation of the aryl rings. Considering the high conformational stability and the ease of their synthesis, we anticipated that 1,1′-spirobi(indane) building blocks might find application in foldamer design after introduction of suitable alkoxy groups into the aromatic rings to exert hydrogen-bonding-mediated directional effects in the foldamer conformation (Fig. 1).

The foldamer building blocks were synthesized starting from the precursor **1**, which is easily available in multi-gram quantities by the one-step acid-mediated rearrangement of bisphenol A (details in Experimental section in ESI†).

All oligomers were highly resistant to crystallization, which is a known, but not really understood serious problem associated with large foldamers. However, at least in the case of the shorter oligomer **3**, crystals suitable for single-crystal X-ray studies were obtained by slow evaporation from ethyl acetate–petroleum



**2** R1 = R2 = COCF$_3$
**3** R1 = H, R2 = COCF$_3$

**4**

**Fig. 1** 1,1′-Spirobi(indane)-derived oligomers synthesized in this study.

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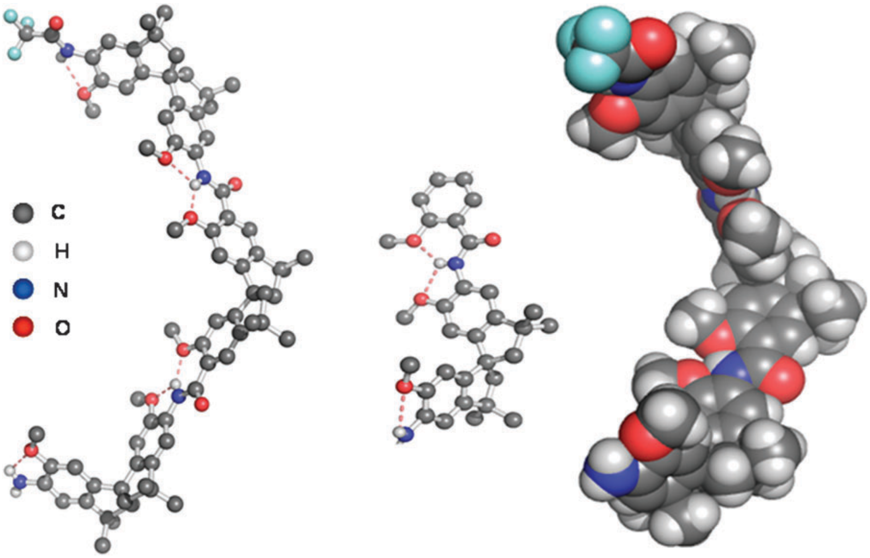

**Fig. 2** X-Ray crystal structure of the oligomer **3** in ball-and-stick (left) and sphere representations (right). A detailed view (middle) shows the bifurcated H-bonding interactions and the periplanar arrangement of the aryl rings in the 1,1′-spirobi(indane) building block. Hydrogens, other than at the hydrogen bonding sites have been deleted for clarity in the ball-and-stick representation.

ether (4 : 1). Analysis of the crystal structure revealed the presence of one molecule of **3**, three partially occupied cyclohexanes and one partially occupied methyl propanoate in the asymmetric unit of the triclinic $P\bar{1}$ cell.‡ The anticipated bifurcated hydrogen bonding interactions involving the characteristic S(5) and S(6) arrangements[11] are clearly evident (Fig. 2). Another quickly visible feature is the periplanar arrangement of the aryl rings on which the chain propagating groups are appended. Indeed, this arrangement paves the way for the unique conformation observed for this oligomer.

The crystal structure of the trimer **3** is perfectly reproduced by *ab initio* MO theory at the HF/6-31G* level as it is shown by the overlay of the crystal structure and the *ab initio* structure (Fig. S1, S33, ESI†). The excellent agreement can presumably be referred to the exceptional conformational rigidity of the foldamer backbone containing the inherently constrained 1,1′-spirobi(indane) building blocks that precludes alternative conformers. The presence of stronger bifurcated hydrogen bonding interactions involving the characteristic S(5) and S(6) arrangements[11] contributes to a further restriction of the conformational space. However, conformational and shape diversity could essentially be extended by sequential alteration of the stereochemistry of the foldamer building blocks. Thus, we were recently able to demonstrate in BINOL-based oligomers that conformational and shape diversity can enormously be increased by changing the chirality of the two-dimensional building blocks along the sequence.[12]

The good agreement between theoretical and experimental structural data for **3** confirms the reliability of *ab initio* MO theory for the prediction of foldamer structures as has been frequently found in the description of the conformational characteristics of numerous other foldamers in the past.[13] Thus, we employed *ab initio* MO theory for the description of the conformational features of the higher oligomers. In order to draw a close comparison with the crystal structure of **3** and also to probe the effect of a growing foldamer chain on the overall shape, we performed computational studies on the pentamer with five, and the heptamer **4** with seven 1,1′-spirobi(indane) building blocks, for which we did not get single crystals. Whereas the HF/6-31G* level was maintained for the geometry optimization of the pentamer, the lower HF/3-21G level was employed for the heptamer due to its enormous size. The comparison of the trimer, pentamer and heptamer structures in Fig. 3 provides insight into the helical architecture of the growing foldamer chain. The onset of helicity is clearly evident already in the shorter oligomer **3** (Fig. 3, left). As the oligomer length increases, the termini come closer together, as seen in the *ab initio* structure of the theoretical pentamer (Fig. 3, middle). The heptamer **4** adopts a fully helical architecture.

Hydrogen bonding interactions, in particular intramolecular hydrogen bonding, play a crucial role in the conformational ordering of synthetic oligomers.[1a] Experimental support for the prevalence of intramolecular hydrogen bonding interactions in solution-state came from [D$_6$]DMSO titration studies of the oligomers **2** and **4** (ESI,† S65–68). Notably, all the amide NHs participating in bifurcated intramolecular H-bondings [S(5)–S(6)]-type][11] appear at far downfield region ($>$10.5 ppm) and show little shift ($\Delta\delta < 0.03$ ppm) when solutions of oligomers **2** and **4** in CDCl$_3$ were titrated gradually with [D$_6$]DMSO. This observation suggested their strong involvement in intramolecular hydrogen bonding interactions. The chemical shift data and DMSO data are consistent with the X-ray crystal structure of **3**. However, the terminal NHs that do not participate in bifurcated H-bonding interactions showed relatively larger shift ($\Delta\delta < 0.20$ ppm), presumably because of their weak S(5)-type interaction. The bifurcated hydrogen bonding interactions were further confirmed by the observed dipolar couplings from 2D ROESY NMR spectra of the oligomers (ESI,† S69–72). The most characteristic NOEs observed that supported the bifurcated H-bonding arrangements, as observed in the crystal structure of **3**, were between

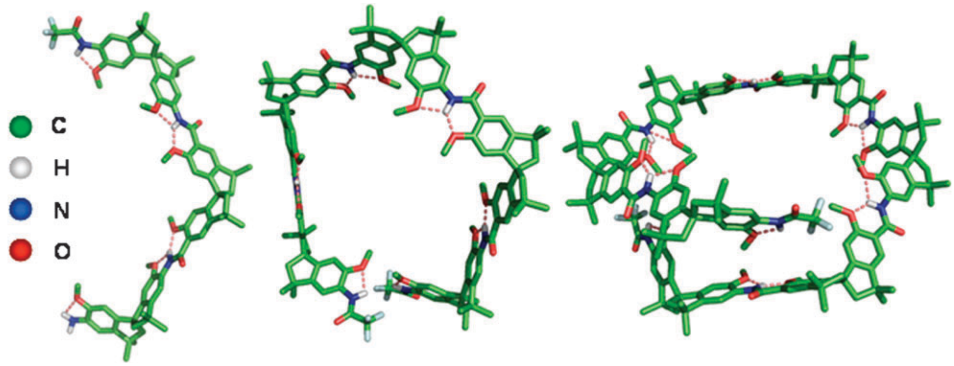

**Fig. 3** Optimized structures obtained by *ab initio* MO theory of the trimer **3** (left, HF/6-31G*), pentamer (middle, HF/6-31G*) and heptamer **4** (right, HF/3-21G). Hydrogens, other than at the hydrogen bonding sites, have been omitted for clarity. The internal diameter of **4** is measured as ~15 Å.

the amide NHs and the adjacent methoxyls (NH *vs.* adjacent methoxy $CH_3$s), taking part in S(5)–S(6)-type bifurcated H-bonding interactions.[11] The majority of other NOE contacts were between the vicinal groups/protons of the adjacent spirobiindane building blocks.

Our results demonstrate the utility of highly rigid 1,1′-spirobi(indane) building blocks in the design and development of novel conformationally ordered synthetic oligomers. The striking feature of this foldamer class is their propensity to adopt unusually large helical structures.[14] Thus, rigid building blocks of 1,1′-spirobi(indanes) could become the starting point for novel ordered synthetic oligomers with structural architectures distinct from those classically observed. Currently we are working towards generating hetero-foldamer-based novel structural architectures containing 1,1′-spirobi(indane) building blocks.

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## Notes and references

‡ *Crystal data* for **3**. $C_{80.52}H_{98.04}F_3N_4O_{10}$: $M$ = 1338.78, crystal dimensions 0.62 × 0.57 × 0.37 mm, triclinic, space group $P\bar{1}$, $a$ = 10.861(4), $b$ = 18.959(7), $c$ = 23.398(9) Å, $\alpha$ = 85.319(7), $\beta$ = 80.280(7), $\gamma$ = 84.741(7)°; $V$ = 4718(3) Å$^3$; $Z$ = 2; $T$ = 100(2) K, $D_c$ = 0.927 g cm$^{-3}$, $\mu$(Mo-K$\alpha$) = 0.065 mm$^{-1}$, $F$(000) = 1396, $2\theta_{max}$ = 50.00°, 45149 reflections collected, 16471 unique, 6779 observed ($I > 2\sigma(I)$) reflections, 904 refined parameters, $R$ value 0.1546, $wR2$ = 0.3704 (all data $R$ = 0.2679, $wR2$ = 0.4358), $S$ = 1.206, minimum and maximum transmission 0.9609 and 0.9764, respectively, maximum and minimum residual electron densities +0.603 and −0.345 e Å$^{-3}$.

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