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Folding-Generated Molecular Tubes Containing One-Dimensional Water Chains

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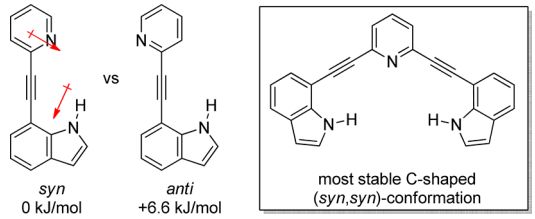
Supporting Information

ABSTRACT: A series of indolocarbazole−pyridine (IP) oligomers were prepared that fold into helical conformations, and their folding features in solution and in the solid state were revealed. Helical folding of these IP foldamers is induced by dipolar interactions through the ethynyl bond and π-stacking between two repeating units. Upon helical folding, ^{1}H NMR signals of aromatic protons were significantly shifted upfield by $\Delta\delta$ = 0.5−2.2 ppm. In addition, hypochromic shifts and fluorescence quenching were observed in the absorption and emission spectra. X-ray crystal structures clearly demonstrated that IP foldamers folded to helical structures with cylindrical internal cavities wherein 3 or 5 water molecules were occupied by hydrogen-bonding interactions in a 1-D array, reminiscent of transmembrane water channels, called aquaporins.

Molecular or supramolecular tubes with internal cylindrical cavities have been intensively studied in recent years for the development of synthetic ion channels, pores, sensors, vessels, and sieves.[1,2] A convenient synthetic strategy is the non-covalent assembly of well-designed molecular components such as macrocycles with internal voids and rod-shaped molecules.[3] Alternatively, molecular tubes can be produced from helical folding of linear oligomers by a combination of intramolecular non-covalent interactions and solvent effects.[4,5] Due to the repulsive interactions between functional groups converging in close proximity upon folding, it is challenging to prepare foldamer-based molecular tubes with a narrow cavity that allows passage of only water or small ions.[6] We herein have prepared indolocarbazole−pyridine (IP) oligomers **4**−**7** that adopt helical conformations to render molecular tubes with internal pores as proven in solution and in the solid state. X-ray structures of **6** and **7** show that the pores are occupied by 3 and 5 water molecules in 1-D chains, respectively.

The IP oligomer design is based on conformational preference driven by dipolar interactions between two aromatic rings connected through ethynyl bonds which have frequently been used in the elongation of aromatic foldamers due to its conformational simplicity, low rotational barrier, and synthetic ease.[4a,7] When indole and pyridine are connected through an ethynyl bond, *syn*-conformation with the indole NH proton oriented on the same side of the pyridyl nitrogen is more stable than the corresponding *anti*-conformation by 6.6 kJ/mol (MacroModel 9.1, MMFFs force field), due to dipolar interactions between indole and pyridine (Chart 1).[8] Likewise,

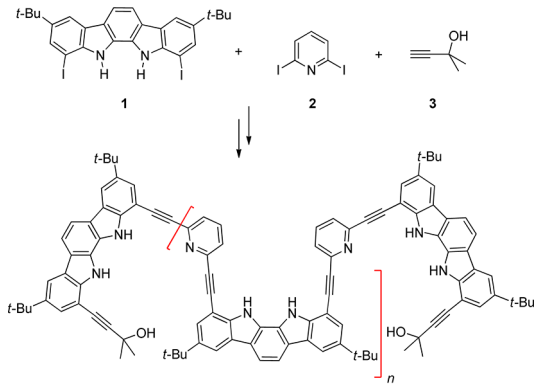
Chart 1. Conformational Preference of Aryl Ethynes



when two indole rings are introduced to the 2,6-positions of pyridine, a C-shaped (*syn*, *syn*)-conformation is more stable than any other possible conformation. Application of this conformational propensity leads to the design of new helical foldamers, IP oligomers **4**−**7**, which consist of two repeating monomers, indolocarbazole and pyridine.

The syntheses of **4**−**7** are straightforward (Scheme 1). Repetitive Sonogashira coupling reactions[9] followed by proto-

Scheme 1. Synthesis of IP Oligomers 4−7



4 (*n*=0, trimer); **5** (*n*=1, pentamer); **6** (*n*=2, heptamer); **7** (*n*=3, nonamer)

desilylation using diiodo-substituted monomers **1** and **2**, 2-methylbut-3-yn-2-ol (**3**), and 1-(trialkylsilyl)ethyne were carried out to prepare **4**−**7**. The synthetic details are described in the Supporting Information. The oligomers are simply named based on their number of the monomeric units; e.g., heptamer is comprised of 3 pyridines and 4 indolocarbazoles. Terminal dimethylcarbinol groups were found to play important roles in the crystal packing structures and also in the kinetic measurements of exchange rates between left- (*M*) and right-handed (*P*) helices (vide infra).

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Evidence for the helical folding of oligomers **5**−**7** was first investigated by ^{1}H NMR spectroscopy, which showed strongly solvent-dependent chemical shifts. For example, the ^{1}H NMR spectra of heptamer **6** in DMSO-d_6 and CD_2Cl_2 are remarkably different from each other, as shown in Figure 1. In DMSO-d_6, the

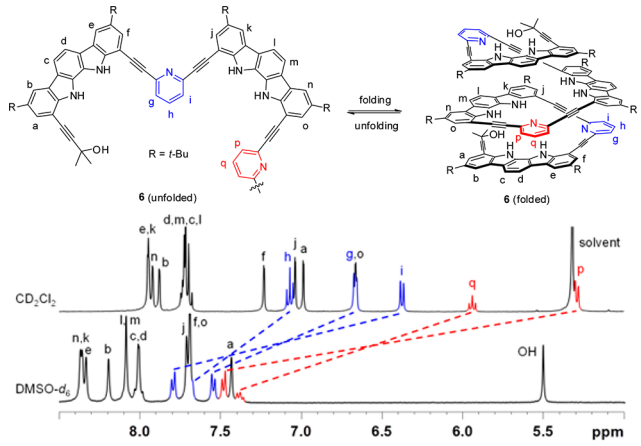

Figure 1. Partial ^{1}H NMR spectra (400 MHz, 25 °C) of **6** (4.0 mM) in DMSO-d_6 (lower) and CD_2Cl_2 (upper). Red- and blue-colored peaks correspond to CH signals of central and outer pyridine(s), respectively.

aromatic signals of **6** appear between 7.3 and 8.5 ppm at room temperature. These are similar to chemical shifts of the corresponding monomeric units, indicative of no appreciable stacking under the given conditions. In sharp contrast, all aromatic signals are dramatically shifted upfield by $\Delta\delta = \delta$ (DMSO-d_6) − δ (CD_2Cl_2) = 0.5−2.2 ppm. It should be emphasized that the CH signals of central pyridine were shifted more upfield ($\Delta\delta$ = 2.21 and 1.45 ppm) than those of the two outer pyridines ($\Delta\delta$ = 1.41, 0.89, and 0.65 ppm). Likewise, the longer nonamer **7** displayed the same pattern of characteristic upfield shifts in CD_2Cl_2 (Figure S4 and Table S2). The ^{1}H NMR signals of the two inner pyridines also showed more pronounced upfield shifts ($\Delta\delta$ = 2.34, 2.04, and 1.30 ppm) than those of the two outer pyridines ($\Delta\delta$ = 1.50, 1.13, and 0.71 ppm). These observations clearly indicate that **6** and **7** fold to helical conformations in CD_2Cl_2. It is noted that intermolecular aggregation of these oligomers can be negligible because identical ^{1}H NMR spectra were observed without any chemical shift change over 0.25−5 mM concentrations (Figure S5). When folded, inner pyridines are sandwiched by two indolocarbazole planes located above and below, while the outer pyridines stack with 1 indolocarbazole. As a consequence, the CH hydrogen atoms in the inner pyridine(s) are expected to experience much stronger shielding effects exerted by aromatic ring currents. In addition, 2D-ROESY experiments showed characteristic NOE correlations between indolocarbazoles and remote pyridines, all consistent with the helically folded structures (Figures S6 and S7). It should be emphasized that residual water molecules in deuterated CD_2Cl_2 play a key role in the helical folding of IP oligomers. In carefully prepared anhydrous CD_2Cl_2, the ^{1}H NMR spectrum of **6** was complicated without characteristic upfield shifts (Figure S8). Upon standing the anhydrous solution in air, new ^{1}H NMR signals corresponding to the helically folded structure appeared and eventually became exclusive. This observation indicates clearly that water molecules are inevitable for the helical folding of **6**. Water molecules may solvate the in situ generated internal cavity to stabilize the helical structure, as supported by NOE cross peaks between water and all NH protons in the 2D-ROESY experiment (Figure S9).

The ^{1}H NMR spectra of IP oligomers **5**−**7** were also examined in other organic solvents (Figures S10−S12). In nonpolar solvents such as CD_2Cl_2, $CDCl_3$, and C_6D_6, the aromatic signals of **5**−**7** were significantly upfield-shifted as a result of helical folding. Interestingly, similar upfield shifts were also observed in a protic solvent CD_3OH. A possible explanation is that a small protic solvent CD_3OH may solvate the internal cavity at least partially by hydrogen bonds. On the other hand, there were no appreciable upfield shifts of aromatic signals in deuterated DMSO, THF, and acetone which all contain only good hydrogen-bonding acceptors. In IP oligomers, each indolocarbazole possesses two convergent NH protons that can form bifurcated hydrogen bonds with these solvent molecules. Provided that the internal cavities generated as a result of helical folding are too small to accommodate bulky solvent molecules, the helical structures would be destroyed unless the folding forces overcome the strength of hydrogen bonds between IP oligomers and solvent molecules. This is possible with the solvent bearing strong hydrogen-bonding acceptors such as DMSO, THF, and acetone. Moreover, dipolar interactions become weakened in more polar solvents, thus reducing the relative stabilities of helical structures.

The absorption and emission spectra of IP oligomers also support the helical folding of oligomers in CH_2Cl_2 (Figure S17). The UV−visible spectra of compounds **S3** and **4**−**7** were recorded in DMSO and CH_2Cl_2. The repeating indolocarbazole unit has strong absorption bands for π−π^* transitions around λ_{max} = 360 nm. In DMSO, the molar extinction coefficients of absorption bands are linearly proportional to the number of indolocarbazole moieties in the IP oligomers, obeying Beer's law. The normalized molar extinction coefficients per indolocarbazole chromophore (ε_N) are 2.4(±0.1) × 10^4 $M^{-1}\cdot cm^{-1}$ for all compounds, regardless of chain length. In CH_2Cl_2, however, the molar extinction coefficients decrease as chain length increases. The ε_N values decrease by ∼20%, varying from 2.1 × 10^4 $M^{-1}\cdot cm^{-1}$ for dimer **S3** to 1.6 × 10^4 $M^{-1}\cdot cm^{-1}$ for heptamer **6** and nonamer **7**. This hypochromic effect in absorption spectra has been used as a convenient tool to monitor the formation of helical structures in DNA and synthetic supramolecules.[7,10] In addition, compounds **5**−**7** are fluorescent in DMSO upon irradiating at λ_{max} = 360 nm but their fluorescence was completely quenched in CH_2Cl_2 (Figure S18). This fluorescence quenching is also an important indicator for aromatic stacking,[11] concomitant with the helical folding of oligomers.

Folding into helical conformations in the solid state was unambiguously proven by the single-crystal X-ray structures of **6** and **7** (Figures 2, S19, and S20). There are some noticeable features in the crystal structures. As anticipated, repeating indolocarbazole and pyridine monomers connected through ethynyl bonds all adopt *syn*-conformations due to long-range dipolar interactions, leading to the helical folding of **6** and **7**. In addition, two repeating units with the opposite dipolar directions become stacked with each other, providing additional stabilizing forces for the helical conformations.[12] Interplanar distances between aromatic rings in neighboring turns were measured to be an average value of ∼3.6 Å, in good agreement with the closely packed π-stacking distances reported in the literature.[13]

Heptamer **6** forms a helix of ∼3 turns and a helical length of ∼10.8 Å, while nonamer **7** makes ∼3.5 turns. In the folded conformations of **6** and **7**, cylindrical cavities are created in which

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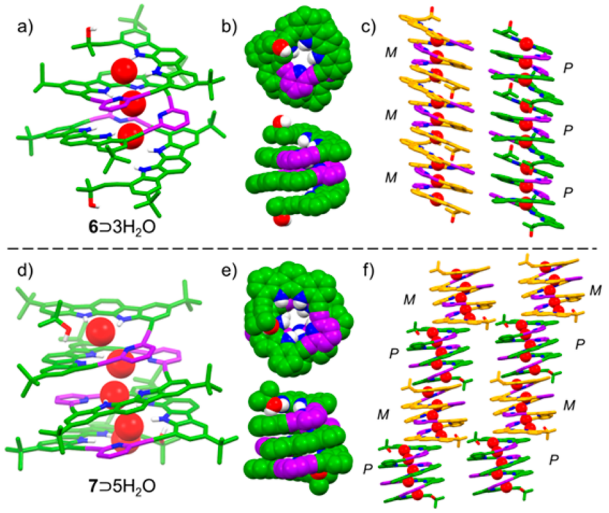

Figure 2. X-ray crystal structures of (a) **6**⊃3H_2O and (d) 7⊃5H_2O, along with two space-filling (CPK) views of (b) **6** and (e) 7 and packing structures of (c) **6**⊃3H_2O and (f) 7⊃5H_2O. Indolocarbazoles are shown in green (*P*) or yellow (*M*), and pyridines are shown in purple. Both water molecules and *tert*-butyl side chains are not shown in (b) and (e), and *tert*-butyl side chains are not shown in (c) and (f). In all cases, hydrogen atoms attached to carbon atoms are omitted for clarity.

all the existing pyridyl nitrogens and indolocarbazole NH protons are convergent. Moreover, 3 and 5 water molecules occupy the cavities of **6** and **7**, respectively, by forming multiple cooperative hydrogen bonds with functional groups in the cavities. Diameters of the internal tubes were measured as 5.6 ± 0.2 Å. The entrapped water molecules are held in 1-D chains, as observed in transmembrane water channels, called aquaporins.[14] Another noticeable difference in the crystal structures of **6** and **7** is the direction of the terminal hydroxyl groups. In the former, hydroxyl groups are directed outward to form cooperative hydrogen bonds with pyridyl nitrogen in a neighboring helix as well as with the water oxygen entrapped in the neighboring helix. On the other hand, hydroxyl groups in the latter are pointed inward to exert OH···π interactions with stacked indolocarbazole planes.

Both oligomers **6** and **7** fold to afford a racemic mixture of two enantiomeric helices, left- (*M*) and right-handed (*P*) isomers, but their packing patterns are remarkably different from each other. In **6**, helical isomers of the same orientation are stacked together to render a supramolecular polymeric helix with a long cylindrical cavity occupied by water molecules. In sharp contrast, two opposite helical isomers of **7** are stacked alternatively in a slipped manner to give a distorted supramolecular helix. The reason for differences in the packing arrays of **6** and **7** is not clear because 3-D packing patterns in the solid state are very sensitive to subtle changes in molecular structures. In the case of **6**, forming slightly less than 3 turns, the starting point of the turn of the next helix is identical to that of the initial one. Consequently, the helices match perfectly to exhibit the stacked array as if a long-chain single oligomer folded into a single-stranded helix. Such packing is impossible in **7**, which contains ~3.5 turns.

Finally, the kinetic stabilities of helical conformations in the oligomers were studied. Due to the intrinsic chirality of a helical structure, two methyl groups at the ends of oligomers are diastereotopic when folded. As a consequence, they may show separate ^{1}H NMR signals. Indeed, the methyl signals in **6** and **7** appear as two separated singlet peaks in CD_2Cl_2 at room temperature, but one singlet peak is observed in the shorter oligomer **5** due to fast exchange (Figure 3). It is noteworthy that

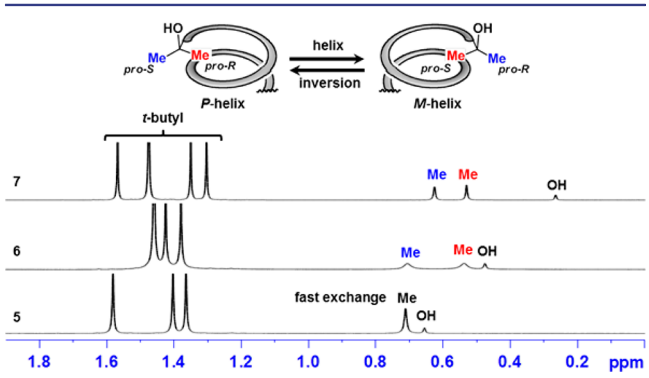

Figure 3. Partial ^{1}H NMR spectra (400 MHz, 25 °C) of **5**−**7** (4.0 mM) in CD_2Cl_2 saturated with water.

all oligomers **5**−**7** show single methyl signals without splitting when unfolded in DMSO-d_6 (Figure S13). Of particular interest is that the two methyl groups of *pro-R* and *pro-S* are exchangeable via inter-conversion between *M* and *P* helices. This phenomenon allows for the measurement of their exchange rates which reflect the stabilities of helical conformations; the more stable the helices, the slower the exchange rates. According to 2D-EXSY experiments at 25 °C, exchange rates were 25 s^{-1} for **6** and 0.5 s^{-1} for **7** in CD_2Cl_2 saturated with water, corresponding to activation free energies ($\Delta G^{\ddagger}$) of 15.6 and 17.9 kcal·mol^{-1}, respectively. For pentamer **5**, the coalescence temperature for the two methyl groups was estimated to be −32 °C in CD_2Cl_2 saturated with water, yielding $\Delta G^{\ddagger}$ = 11.5 kcal·mol^{-1} (Table 1 and Figures

Table 1. Rate Constants and Activation Free Energies for Exchange of *M* and *P* Helical Isomers

	method	T (°C)	k_{ex} (s^{-1})	$\Delta G^{\ddagger}$ (kcal·mol^{-1})
5	coalescence	−32	196	11.5
6	EXSY	25	25 ± 7	15.6 ± 0.2
7	EXSY	25	0.5 ± 0.1	17.9 ± 0.2

S14−S16). These results clearly indicate that the stability of helical structures increases as chain length increases. As mentioned earlier, the helical conformations of IP oligomers are induced and stabilized by local dipolar interactions through ethynyl bonds and π-stacking between helical turns. Moreover, stability is further enhanced by entrapped water molecules that form multiple hydrogen bonds with the helix interior. These key interactions add up more and more in longer oligomers to enhance the stability of helices.

In conclusion, we have for the first time prepared a new kind of aromatic foldamers that consist of indolocarbazoles and pyridines linked alternatively through ethynyl bonds and can fold into helical structures by dipolar interactions. Upon helical folding, internal cylindrical cavities have been generated wherein water molecules are occupied in 1-D arrays by forming multiple hydrogen bonds.[14] These IP oligomers have great potentials to function as synthetic water channels or ion transporters in the lipid and cellular membranes. To demonstrate this possibility, we are currently modifying the oligomers to modulate their lipophilicity and hydrophilicity by incorporating proper functional groups at the side chains such as the *para*-position of pyridine units.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11808.

Crystallographic data for **6** (CIF)
Crystallographic data for **7**(CIF)
Synthetic procedures, and Tables S1−S6 and Figures S1−S20, with analytical and spectral characterizations of **4**−**7** (PDF)

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Notes

The authors declare no competing financial interest.

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