Pyridine–imide oligomers†

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Pyridine–imide oligomers created by incorporating imide and pyridine units alternatively in sequence were successfully synthesized and found to form highly compact and stable helical conformations contributed by intramolecular H-bonds between the imide and both adjacent pyridines, and by the structural characteristics of the imide units.

The α-helix widely occurs in nature and is related to the extensive biological functions of proteins. Foldamers have been created with chemically diverse units from aliphatics to aromatics in the past decades to mimic α-helices in either structure or function.[1] In contrast to the aliphatic homologues,[2,3] which may tightly pack into highly compact structures such as the α-peptides, most of the reported aromatic oligoamides (AOAs)[1c,4,5] are still far from high compactness although the AOAs possess advanced structural features such as structural predictability and canonical helical conformations. Considering the rigidity and high coplanarity of the aromatics, there remain challenges to create highly compact helical conformations for AOAs. Reported cases include those generated by adjusting the relative orientations of substituted amine and acid groups from 120° (at pyridine) to 60° (at quinoline[6] or benzene[4d]).

As H-bonding functional linkages, amide units have been widely used in constructions of AOAs as the NHCO–aryl rotation may be restricted into a strong preference of *anti*- or *syn*-conformation with H-bonds. Other linkages such as urea[5c,7] and hydrazide[8] have also been reported. 2-Ureopyridine may exist as a balance between *cis* and *trans* conformers, which may result in an equilibrium for oligomers between the intermolecularly H-bonded linear dimers and intramolecularly H-bonded helical monomers. Although hydrazide was found to favor a *trans*-conformation, the oligomers seem to adopt linear conformations rather than helical conformations. In contrast, imide groups are rarely utilized as linkages (three reported cases were related to N-substituted imidyl–benzene and –naphthalene based oligomers[9,10]). Most importantly, how the imide groups act as H-bonding linkages to regulate dynamics, conformations, and structures of the oligomers is as yet unknown.

In this communication, we introduce imide as a functional H-bonding unit incorporated with pyridine together to develop pyridine–imide oligomers with highly compact and stable helical conformations (Fig. 1). The imide-NH was found to H-bond with both adjacent pyridine nitrogen atoms intramolecularly and then produce consecutive bends along the strand. The high compactness is contributed from both intramolecular H-bonds and structural characteristics of the imide itself.

The oligomers were successfully synthesized by refluxing the corresponding primary amide and acid chloride prepared from commercial 2,6-pyridinedicarboxylic acid. In brief, refluxing of 2-ethoxycarbonyl-6-pyridinoyl chloride (**1**) and 2-ethoxycarbonyl-6-pyridinoyl amide (**2**) in toluene gave **PIO1**, while **PIO2** was obtained from **2** and 2,6-pyridinoyl dichloride (**3**). **PIO3** was obtained from the **PIO1**-monoamide and **PIO1**-monoacyl chloride converted from **PIO1** as starting materials (Fig. 2).

^{1}H NMR studies in $CDCl_3$ solution (Fig. 3) show the imide protons of **PIO1** are deshielded at 12.96 ppm, much more downfield of values characteristic of intramolecularly non-H-bonded or H-bonded imide protons,[11] or H-bonded amide protons of dimeric pyridine–oligoamides.[12] This strongly suggests that the imide-protons intramolecularly H-bond to both adjacent pyridine nitrogen atoms, as further supported by the slight upfield shifting (0.3 ppm) of the imide-protons in d_6-DMSO. Moreover, it is surprising that the intramolecularly H-bonded imide-protons are remarkably stable to DIEA

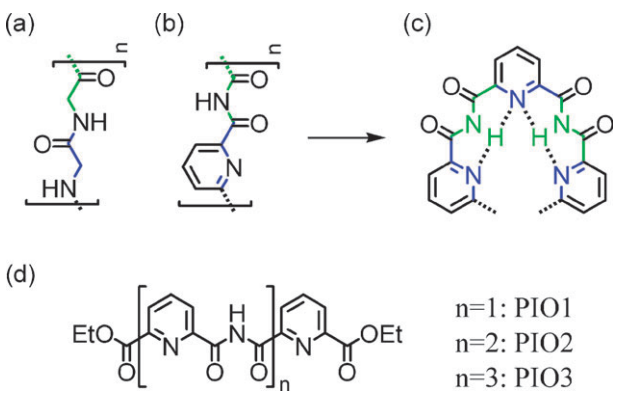

Fig. 1 Comparison of (a) α-peptide and (b) pyridine–imide oligomers: alternative three-atom sequences are colored blue and green along the backbone direction (in the inner rim). (c) A helical structure showing intramolecular H-bonds between imide-NH and both adjacent pyridine nitrogen atoms. (d) Chemical structures of pyridine–imide oligomers.

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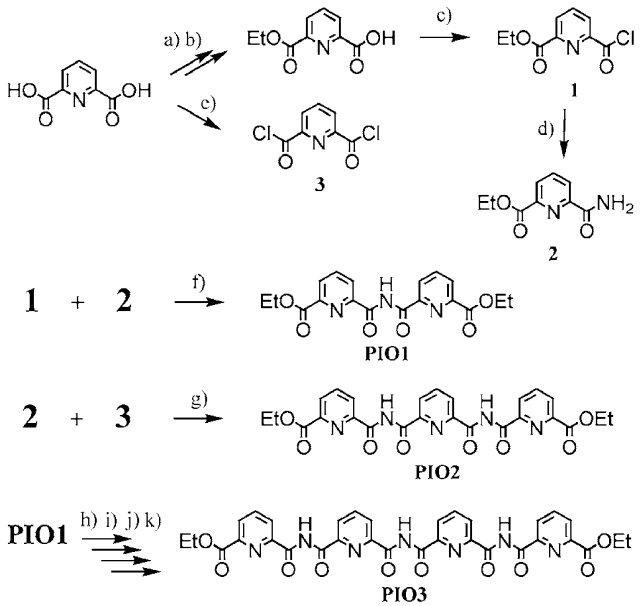

Fig. 2 Synthetic procedure for pyridine–imide oligomers. *Reagents and conditions*: (a) ethanol, H_2SO_4, reflux, 8 h, 94%; (b) NaOH, ethanol, 1,4-dioxane, 70–80%; (c) $SOCl_2$; (d) NH_3/CH_2Cl_2, RT, 95%; (e) $SOCl_2$; (f) toluene/reflux, 8 h, 80–95%; (g) toluene/reflux, 8 h, 10–20%; (h) NaOH, 1,4-dioxane, 25–35%; (i) $SOCl_2$; (j) NH_3/CH_2Cl_2, RT, 90%; (k) toluene/reflux, 8 h, 10–15%.

(diisopropylethyl amine), as revealed by ^{1}H NMR study on adding DIEA into the **PIO1**/$CDCl_3$ solution.

With chain length increase from **PIO1** to **PIO2** to **PIO3**, both similarities and distinct differences were observed in the ^{1}H NMR spectra (Fig. 3). **PIO1**, **PIO2** and **PIO3** all show sharp signals and no indications of double-helix formation or other types of aggregates, even at temperatures down to 223 K (Fig. 4). This is different from the behavior of pyridine–oligoamides,[4] but similar to that of quinoline–oligoamides.[6] On the other hand, the protons of **PIO1**, **PIO2** and **PIO3** show distinct shifting in the NMR range, a reflection of helical conformations, for example, the upfield shifting of both ethyl-protons of **PIO2** or **PIO3** and terminal imide protons (appearing at 12.64 ppm) of **PIO3**, evidenced shielding effects from the pyridines in a helical structure. The helical conformations are further confirmed by NOE experiments, particularly, by the strong NOE contacts between terminal ethyl protons or imide-protons and pyridine-protons for both **PIO2** and **PIO3** and the contacts between central and terminal imide-protons for **PIO3**, an obvious reflection of the formation of compact helical conformations (Fig. 5).

All the ^{1}H NMR data above are consistent with compact helical conformations in solutions. Crystals suitable for the single-crystal X-ray diffraction analysis were obtained for both **PIO2**[13] and **PIO3**.[14] The resolved structures agree well with molecular modeling (Gauss MM2) and solution structures. As expected, the imide units show high coplanarity. The imide C–N lengths are nearly identical in the range of 1.368–1.388 Å with the C═O bond lengths ranging from 1.196 to 1.207 Å, indicating high electron delocalization and double-bond character of the C–N bond. The imide-NH forms into two intramolecular H-bonds with both adjacent pyridine nitrogen atoms, generating consecutive bends along the strand. The bending curvature is also contributed from the structural characteristics of the imide groups, as indicated by the bond angles of ∠C(imide)–N(imide)–C(imide) (126.25–129.48°) and ∠N(imide)–C(imide)–C(pyridine) (111.55–113.78°). Interestingly, the crystal structures give three surprising findings. The first is that **PIO2** crystallises in a chiral space group, in which a crystal cell accommodates four left-handed helices. This suggests that the racemic oligomers undergo spontaneous resolution into the two enantiomers. This feature is very uncommon in helical molecules. The second is that the imide groups in **PIO3** have higher coplanarity than in **PIO2**, as revealed by the torsion angles of O(imide)–C(imide)–N(imide)–C(imide). The third is that **PIO3** exhibits a more bent conformation than **PIO2**. For example, the ∠C(imide)–N(imide)–C(imide)s are nearly 0.6–3.2° smaller in **PIO2** (126.25 and 127.83°) than in **PIO3** (128.41, 128.99, 129.48°). The ∠N(imide)–C(imide)–C(pyridine) angles are in the range of 112.54–113.64° in **PIO2**, while decrease to 111.55–112.47° (with an exception of 113.78°) among six values in **PIO3**, although they are

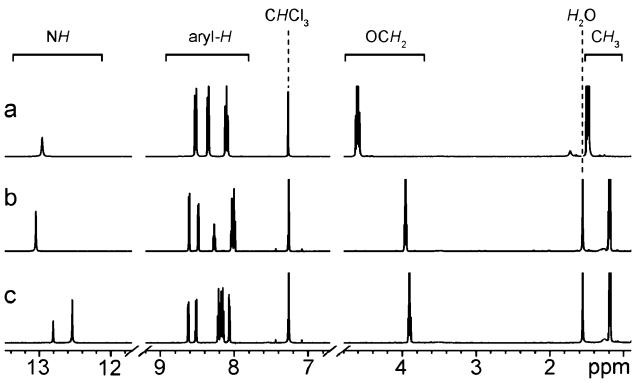

Fig. 3 Part of the 400 MHz ^{1}H NMR spectra of **PIO1** (a), **PIO2** (b) and **PIO3** (c).

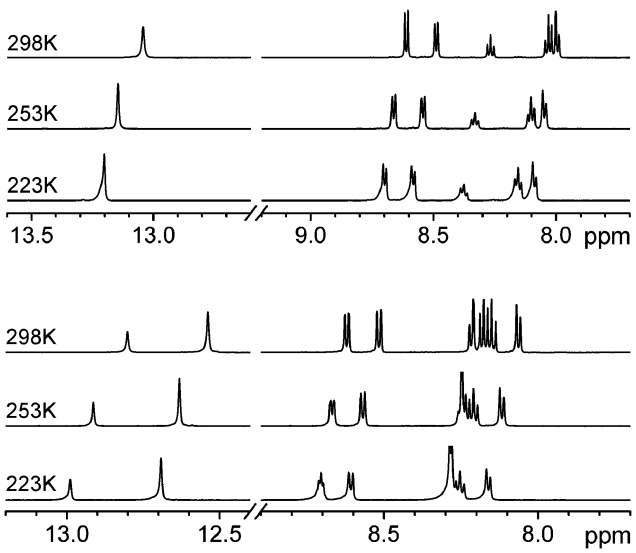

Fig. 4 Partial 600 MHz ^{1}H NMR spectra of **PIO2** (upper) and **PIO3** (lower) at three different temperatures.

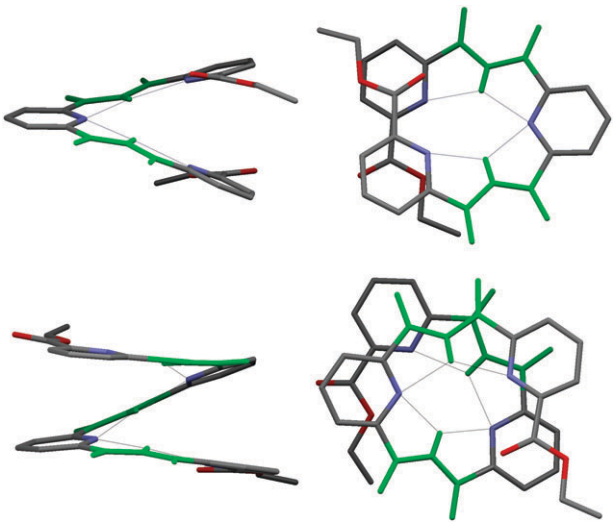

Fig. 5 Solid-state structures of **PIO2** (upper) and **PIO3** (lower): side-view (left) and top-view (right) with the imide units colored in green. The hydrogen atoms except for the imide protons are omitted for clarity.

dependent on either the position in the sequence or the chain length. The above two structural differences between **PIO2** and **PIO3** are likely due to the "structural tunability"—the bond and torsion angles—of the imide unit, which is sensitive to interactions between the stacking units in the helical structures, for example, the *i* imide is shown to stack partially with the pyridine positioning at $i + 5$ and partially with another imide at $i + 4$.

As expected, the pyridine–imide oligomers possess compact helical conformations with every five units constituting a helical turn, that is each turn contains about 15 atoms along the backbone (in the inner rim). Considering the coplanarity and rigidity of the constituent units, this corresponding to the highest curvature reached by AOAs. The imide protons all fill the helix hollow and prevent solvent molecules penetrating through it. All imide oxygen atoms position outward the helix. Additionally, the homologous units positioning at *i* and $i + 5$ sites in sequence are arranged in an orderly manner along the helical axis, for example, the imide units at 2 and 7 positions. The helical pitch is 3.4 Å, similar to the pyridine–oligoamides and related to the thickness of one aromatic ring. The relative inclinations of the helix are contributed by both the torsions between the pyridine and the imide units and the imide unit itself. The inclinations can be estimated from the torsion angles of each consecutive four-inner-rim-atoms between the nitrogen atoms of two pyridines attached to one imide unit.

In summary, both solution- and solid-state studies reveal the pyridine–imide oligomers form into remarkably stable and compact helical conformations. On basis of the advanced features—stability and compactness, further study will focus on possible bio-applications and electron/energy transfer properties through the bridged oligomeric strand.

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13 *Crystal data* for **PIO2**: crystallization solvent/precipitant: DMF/diethyl ether, orthorhombic, space group $P2_12_12_1$, colorless, a = 7.7201(14), b = 8.3506(15), c = 37.025(7) Å, T = 113(1) K, Z = 4, GOF = 1.037. The final R indices were $R1$ ($I > 2\sigma(I)$) = 0.0312, $wR2$ (all data) = 0.0750.

14 *Crystal data* for **PIO3**: crystallization solvent/precipitant: DMF/diethyl ether, triclinic, space group $P\bar{1}$, colorless, a = 11.556(2), b = 12.222(2), c = 12.249(2) Å, α = 67.75(3), β = 82.17(3), γ = 88.75(3), Z = 2, T = 298 K, GOF = 1.149. The final R indices were $R1$ ($I > 2\sigma(I)$) = 0.0983, $wR2$ (all data) = 0.2085. The poor quality of this structure is due to weak diffraction intensity and disorder of the terminal ethyl units. However, all atoms relative to the backbone of the helix were accurately located.

