Novel Folding Patterns in a Family of Oligoanthranilamides: Non-Peptide Oligomers That Form Extended Helical Secondary Structures

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Abstract: Anthranilamide derivatives are used as the basis for a series of novel oligomers that fold into helical secondary structures in the solid state. When combined with pyridine-2,6-dicarboxylic acid and 4,6-dimethoxy-1,3-diaminobenzene subunits, oligoanthranilamides can be induced to take up a coiled conformation corresponding to two turns of a helix. X-ray crystallography shows that intramolecular hydrogen bonding and $\pi-\pi$ stacking interactions are important in stabilizing the extended helical structures. Furthermore, both experimental and calculated ^{1}H NMR methods indicate that related conformations are taken up by the oligomers in chloroform solution.

The remarkable diversity of protein form and function lies in the link between primary amino acid sequence and the formation of defined secondary, and thence tertiary, structure. The combination of conformational preference, side-chain−side-chain interactions and intramolecular hydrogen bonds leads to the formation of ordered regions of structure, of which α-helices and β-sheets are the most common.[1] In recent years there has been intense interest in the design of non-peptide oligomers that fold into well-defined secondary structures. Such materials might then be applicable to the formation of new functional polymers with interesting catalytic or recognition properties. Various approaches to folding structures have been taken, involving primarily the use of intramolecular hydrogen bonding[2−4] or donor−acceptor interactions.[5,6] We have previously shown that simple anthranilamide derivatives can be combined to form oligomers which take up linear strand or single turn helical structures, stabilized by intramolecular hydrogen bonding and $\pi-\pi$ stacking interactions.[7−11] In this paper we report a further development of this approach with the formation of extended, multiturn helical oligomers.

Our underlying strategy is based on the ability of anthranilamide derivatives to form intramolecular hydrogen bonds between adjacent amide-NH and -CO groups. This leads not only to a stabilization of the planar arrangement of the substituents but also to the possibility of further hydrogen bonds to neighboring basic or acidic groups (as shown in Figure 1A). If the adjacent residues are anthranilamides a linear strand structure is produced, stabilized by intra-anthranilamide hydrogen bonds (Figure 1B).[8] When two anthanilamides are linked through a pyridine-2,6-carboxylic acid unit, a turn is introduced, and the resulting molecule is forced, by hydrogen bonds to the pyridine-N, to position the two carboxamide substituents above and below each other in a helical conformation (Figure 1C).[7,8] It is critical for the more general application of this strategy that we show that more extended secondary structural features representing large molecular surface areas (>100 Å^2) can be formed by the combination of simple components. We demonstrate here that the coupling of several anthranilamide groups[12] with 2,6-pyridinedicarboxamide[13−15] and 4,6-dimethoxy-1,3-diaminobenzene subunits leads to oligomers with extended secondary structure corresponding to two turns of a helix.

The syntheses of the oligomers involve a series of iterative condensation steps and are outlined in Scheme 1. The coupling

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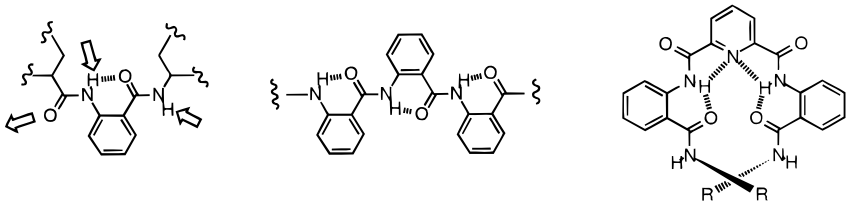
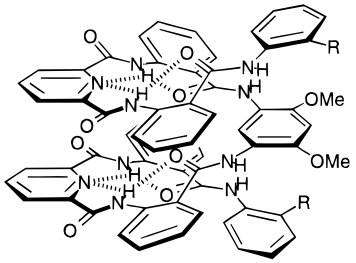


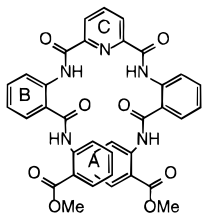
A B C

Figure 1. Hydrogen bonding options with oligoanthranilamides.

between pyridinedicarboxylic acid mono benzyl ester **1**[16] and dianthranilamide **2a**[8] using pivaloyl chloride gave **3a** (59%). This was followed by hydrogenation on palladized charcoal to remove the benzyl ester and form pyridinecarboxylic acid **4a** (89%). Bisanthranylphenylenediamine **7** was synthesized from dimethoxydinitrobenzene **5**[17] by hydrogenation to dimethoxyphenylenediamine, coupling with 2-nitrobenzoyl chloride to dinitro compound **6** and reduction of the nitro groups using catalytic hydrogenation (73% for two steps). Diamine **7** and 2 equiv of **4a** were coupled by the mixed anhydride method using pivaloyl chloride to give anthranilamide-based oligomer **8a** in 61% yield. The more soluble hexyl ester analog **8b** was prepared by an analogous route. Our expectation was that **8a** and **8b** would take up a coiled structure involving two helical turns, as shown **9**. This conformation should be favored by the stabilizing effects of intramolecular hydrogen bonding between amide-NH and adjacent pyridine-N or amide-CO groups and $\pi-\pi$ stacking between aromatic rings as well as the destabilization of alternative, unwanted conformations.[8,14] In order to investigate these points, a series of comparison molecules, **10**−**12**, containing isolated regions of the extended helical structure was prepared by similar routes.[18]



9a R = COOMe
9b R = COOHx-n



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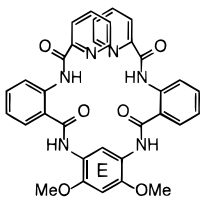

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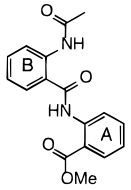

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Two different crystals were obtained for **8a** from the same solvent system (trace CH_2Cl_2 + $CHCl_3$ + AcOEt/hexanes). The first was a clear, triclinic crystal with a $P\bar{1}$ space group that had no included solvent and showed all 12 of the expected hydrogen bonds (Figure 2 and Table 1). The structure deviates from the idealized one (shown in **9a**) by an increased nonplanarity of the N−Ph_b linkage (the dihedral angle of Ph_b1C-Ph_b-2C-N_b-CO_c was 138.2°, instead of the expected 180°). This feature directs the first anthranilamide ring (ring A, viewed from the top of Figure 2a) away from the tight coiled structure and is reminiscent of the fraying that occurs at the end of α-helix secondary structures in peptides.[19] Otherwise, the extended helical structure is maintained by a network of intramolecular hydrogen bonds and extensive $\pi-\pi$ interactions. Figure 2 shows that eight of the nine aromatic rings are paired in close stacked arrangements. For example, the two pyridine rings (C−C′) take up an offset face-to-face structure[20] with ring center-to-center and closest edge-to-edge distances of 3.82 and 3.47 Å, respectively. In a similar way ring pairs D−B′, E−A′, and B−D′ stack with closest approach (carbon−carbon) distances of 3.48, 3.80, and 3.83 Å, respectively. In the last case the distortion of ring A causes a more edge-to-face orientation of the rings to occur.

The second, triclinic crystal was yellow with a $P\bar{1}$ space group and contained 1 equiv of CH_2Cl_2 (Figure 3). The overall shape of the structure is of two turns of an extended helix and, indeed, 11 out of the 12 expected hydrogen bonds were formed (Table 1). However, one hydrogen bond within the third anthranilamide ring (ring D viewed from the top of Figure 3a) between the amide-CO and amide-NH is broken. Also, the dihedral angle defining the phenyl and carbonyl planes [O=C_d-Ph_d1C-Ph_d2C(N_dH)] widens considerably to 142.2° compared to the corresponding angle in the clear polymorph (Figure 2a, 24.8°). As a result the developing left-handed helix about the first pyridine dicarboxamide (Figure 3a, viewed form the top) reverses across the phenylenediamine unit to terminate in a right-handed helix centered on the second pyridine ring. Despite this reversal of the helix turn, a compact folded structure is formed in the solid state with intramolecular hydrogen bonding and aromatic stacking interactions playing an important stabilizing role. Unlike Figure 2, the two pyridine rings are far apart in this structure. However, an offset face-to-face interaction occurs at the center of the structure in which phenylenediamine ring E is sandwiched between anthranilamide rings B and A′ with closest edge distances of 3.61 and 3.63 Å, respectively.

The crystal structures of both polymorphs of **8a** confirm that, in the solid state, the oligoanthranilamide does take up a compact two-turn helical conformation. In the first structure (Figure 2) the two turns are of the same helical sense, and an extended coiled conformation is formed. The unit cell contains both right- and left-handed helical molecules. In the second polymorph the structure contains one turn of a right- and one turn of a left-handed helix linked through the phenylenediamine spacer. In both cases, it was the bifurcated hydrogen bond areas about the pyridine carboxamide-NH that failed to control the orientation of key anthranilamide rings (ring B in Figure 2 and ring D in Figure 3) and led to deviation from the idealized helical conformation shown in **9a**.

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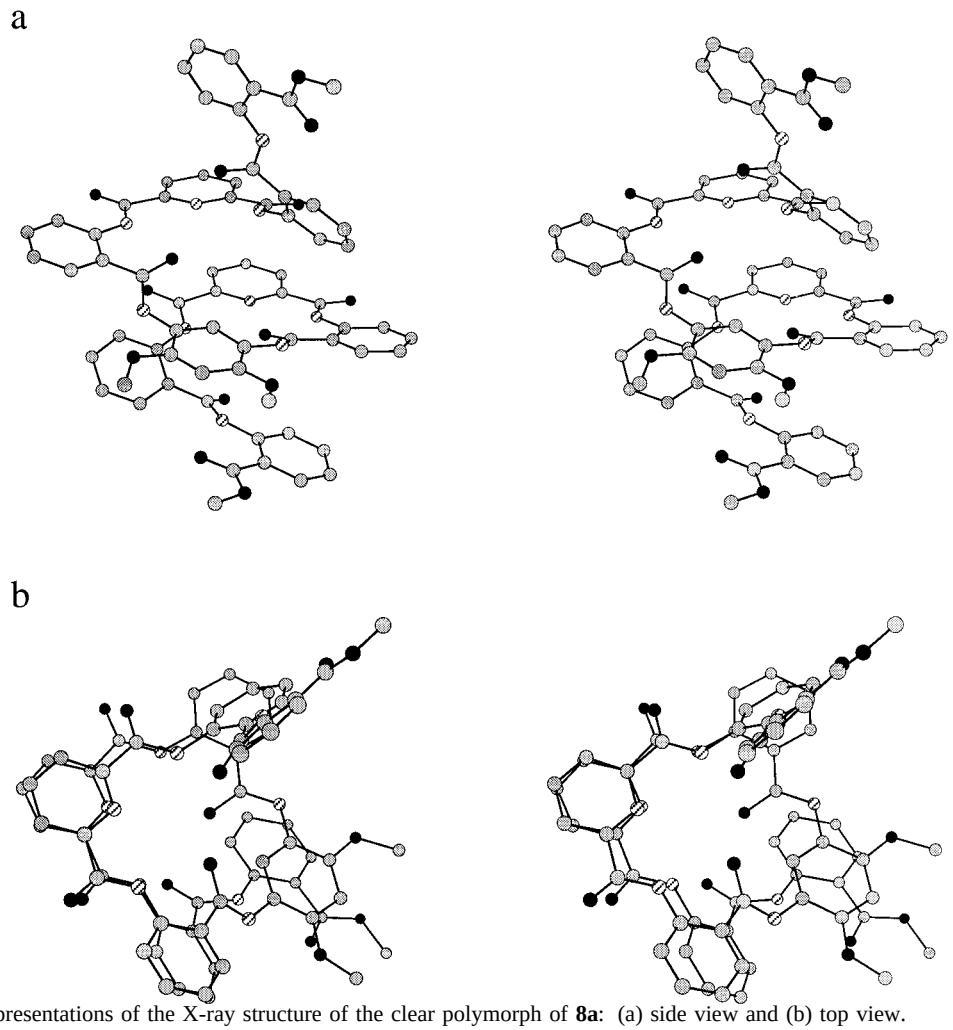
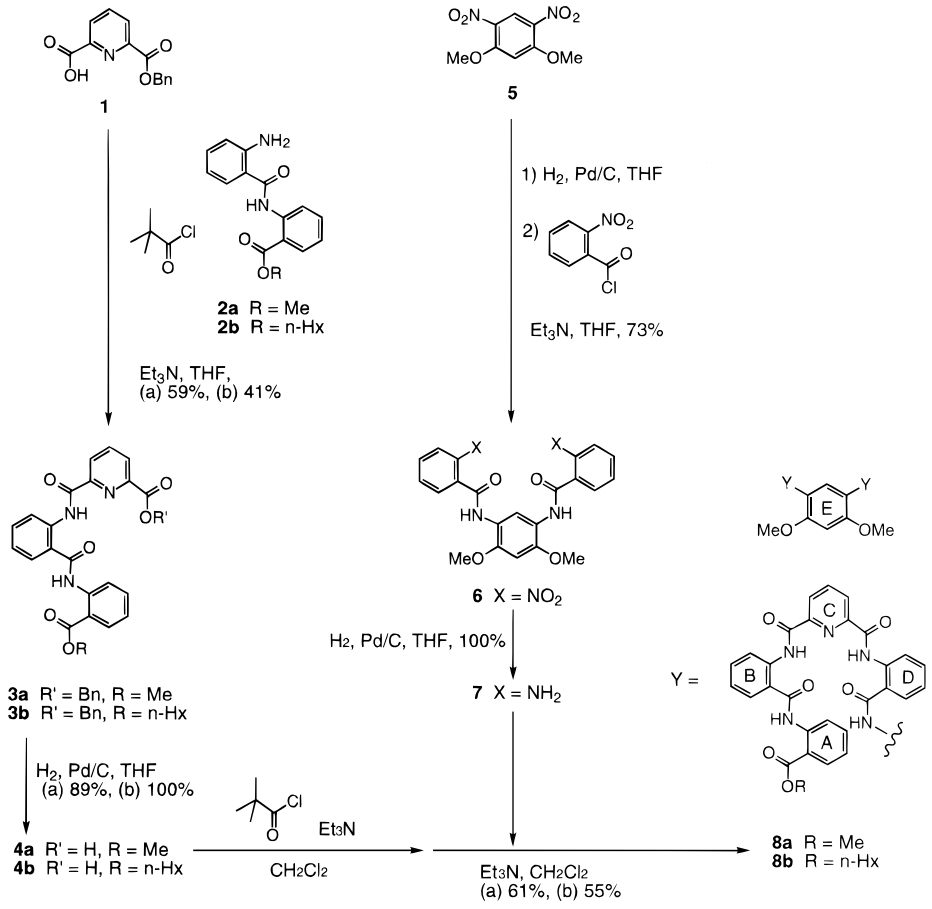


Figure 2. Stereo representations of the X-ray structure of the clear polymorph of **8a**: (a) side view and (b) top view.

Scheme 1



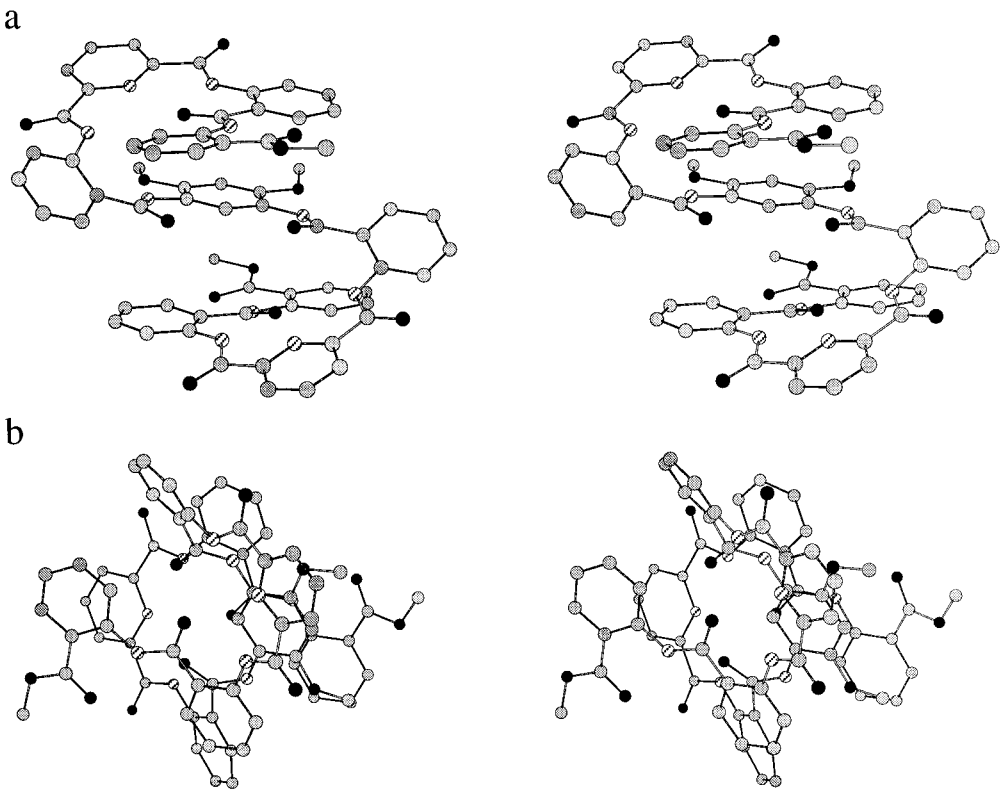


Figure 3. Stereo representations of the structure of the yellow polymorph of **8a** viewed from (a) the side and (b) the top.

Table 1. X-ray Crystal Structure Data

crystal	$NH_a\cdots OC$	$NH_b\cdots OC$	$NH_b\cdots Nc$	$NH_d\cdots Nc$	$NH_d\cdots OC$	$NH_e\cdots OMe$
8b	1.88	2.27	2.27	2.22	1.83	2.32
(clear)	1.81	2.16	2.34	2.31	1.96	2.27
8b	1.84	1.94	2.17	2.26	2.32	2.11
(yellow)	1.88	1.90	2.12	2.21	3.85	2.16
10[7]	1.88	2.02	2.21			
	1.92	1.82	2.12			

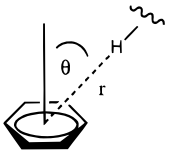
Table 2. Selected ^{1}H NMR Chemical Shifts in $CDCl_3$ of **8b** and Reference Molecules (**10**−**12**)

	NH_a	Ph_a3H	Ph_a4H	Ph_a5H	Ph_a6H	NH_b	Ph_b3H	Ph_b4H	Ph_b5H	Ph_b6H
8b	11.48	8.30	6.71	6.85	7.84	12.70	8.76	7.63	7.26	7.42
10	11.60	8.50	6.70	6.89	7.90	13.08	8.88	7.64	7.22	7.58
12	12.07	8.78	7.64	7.18	8.11	11.17	8.67	7.54	7.24	7.87

	Py_c3H	Py_c4H	Py_c5H	NH_d	Ph_d3H	Ph_d4H	Ph_d5H	Ph_d6H	NH_e	Ph_e3H	Ph_e6H
8b	8.46	8.02	8.14	12.54	8.30	7.07	6.88	7.45	7.44	8.80	5.99
10	8.46	8.13	8.46	13.08	8.88	7.64	7.22	7.58			
11	7.30	7.80	8.24	12.77	8.85	7.54	7.16	7.76	8.23	9.04	6.45

The solution conformation of **8b** was investigated by ^{1}H NMR ($CDCl_3$) and IR (CH_2Cl_2). By analogy to **10** and related structures[7,8] the extended helical conformation should be characterized by downfield shifts of all hydrogen bonded protons and large upfield shifts of certain aryl proton resonances due to ring current effects from stacked adjacent rings. The ^{1}H NMR chemical shifts of **8b** and reference molecules, **10**, **11**, and **12**, are listed in Table 2. The proton resonances of the terminal benzene rings of **8b** (Ph_a3H-Ph_a6H) are very similar to those of **10** and are upfield shifted compared to **12**, indicating that in both **10** and **8b** terminal benzene rings are likely to be located above other ring currents. The small upfield shifts of Ph_b3H, Ph_b6H, Pyc4H, and Py_c5H in **8b** compared to the equivalent resonances in **10** may indicate weak $\pi-\pi$ stacking interactions between rings B, C, and other rings. The signals for the protons on rings D and E in **8b** are shifted upfield ($\Delta\delta$ = 0.55, 0.47, 0.28, 0.31 ppm for D and 0.24, 0.46 ppm for E, respectively) compared to the corresponding signals in **11**, consistent with their proximity to other rings in the helical conformation. Despite repeated attempts, efforts to observe NOEs between protons on different aryl rings in **8b** were unsuccessful. This failure may reflect the formation of a conformation in solution with interproton distances of >4 Å or an equilibrium among several conformations. Nonetheless, the absence of specific NOE effects prevents us from firmly establishing the extent of helix formation in solution.

In order to investigate further the relationship between the conformation in solution and that in the solid state, an estimation of the anisotropic effect of the nearby aromatic rings on individual protons in the anthranilamide oligomers was carried out using X-ray structure coordinates and the equivalent dipole model of ring current induced shifts developed by Abraham (Figure 4),[21] where $\Delta\delta_{calcd}$ is the chemical shift change due to a nearby aromatic ring current, θ is the angle between the normal and a line from the center of the aromatic ring to the hydrogen in question, and r is the distance between the ring center and



$$\Delta\delta_{calcd} = 27.6\ (1 - 3\cos^2\theta)\ /\ r^3 \qquad (1)$$

Figure 4. Estimation of ^{1}H NMR chemical shift changes as a result of the anisotropic ring current of a nearby benzene ring.

Table 3. Selected ^{1}H NMR Chemical Shifts of **10** and **12** in $CDCl_3$ and the Observed and Calculated Chemical Shifts Changes by Aromatic Ring Current

	Ph_a3H	Ph_a4H	Ph_a5H	Ph_a6H
10	8.50	6.70	6.89	7.90
12	8.78	7.64	7.18	8.11
$\Delta\delta_{obsd}$	−0.28	−0.94	−0.29	−0.21
$\Delta\delta_{calcd}$	−0.53	−1.10	−0.22	−0.08

the hydrogen. In this way, the position of a proton relative to nearby aromatic rings can be determined from the X-ray crystal structure coordinates and the expected ring current induced shifts can be calculated using eq 1, assuming that a similar conformation is maintained in the solid state and in solution. Deviations in the direction and size of the calculated and experimentally determined ring current induced shifts give a measure of the differences between solid state and solution structures.

The approach was first tested using the single turn helical derivative **10** and its control molecule **12** which has a planar conformation.[8] Combining eq 1 with the X-ray coordinates of **10** gives a reasonable correlation between calculated and experimental chemical shift changes (Table 3), strongly suggesting that a similar helical conformation is taken up in solution.

The small deviations between $\Delta\delta_{obsd}$ and $\Delta\delta_{calcd}$ are probably due to minor differences between the average structure in solution and that in the solid state, caused by crystal packing effects. One interesting finding from this analysis is that the large upfield shift of Ph_a4H in **10** is not due to the ring current of the other ring A but to that of ring B on the other arm of the molecule.

The method was next used to investigate the conformation of **8b** in solution (Table 4). The anisotropic effects were calculated using coordinates from the two different crystal structures of **8a**. Comparison of the two analyses (Table 4) shows that while both predicted the general trend of solution chemical shift changes there were significant deviations between calculated and observed values, particularly for Ph_a4H and Py_c5H. Use of coordinates from the clear polymorph of **8a** (Figure 2) underestimated the anisotropic effect on Ph_a4H, due to the fraying visible at the one end of the helix, and overestimated the effect on Py_c5H, due to the close proximity of the two pyridine rings in the crystal structure. Calculations based on the coordinates of the yellow polymorph of **8a** (Figure 3) predicted too large an upfield shift for Ph_a4H, due to the ring current from ring D (similar to **10**), and too small a shift for Py_c5H, since the two C rings are far apart. These results suggest that neither of the solid state helices alone (Figure 2 or 3) gives an adequate description of the solution conformation of **8b**. However, the average of the two calculated $\Delta\delta$ values provided a remarkably good match to the observed ring current induced shifts in solution (Table 4). This observation, therefore, lends support to the possibility that the two solid state structures resemble two low energy conformations of **8b** that are populated to similar extents and are rapidly interconverting in solution.

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Further support for the role of intramolecular hydrogen bonding in stabilizing the solution conformation comes from infrared spectroscopy. The IR spectrum of **8b** shows two N−H stretch peaks at 3424 cm^{-1} due to free N−H and at 3300−3100 cm^{-1} from hydrogen bonded N−H groups in an area ratio of about 1:9.[22] As there are 10 NH groups and 12 potential hydrogen bonds per molecule (as in **9b**), on average only one NH hydrogen per molecule is not involved in a hydrogen bond in CH_2Cl_2 solution.

In summary, we have shown that a series of simple molecular components based on anthranilamides can be used to form oligomers with novel folding properties. When pyridine-2,6-dicarboxamide and 1,3-diaminobenzene derivatives are used to introduce turn regions into the oligomers, extended helical structures are formed. X-ray crystallographic studies show that two distinct helical structures are taken up in the solid state, each stabilized by extensive intramolecular hydrogen bonding and $\pi-\pi$ stacking interactions. NMR analysis supports the formation of related structures in solution.

Experimental Details

General Methods. CH_2Cl_2 was obtained from Fisher and distilled from P_2O_5. Et_2O and THF were obtained from Fisher and distilled from sodium benzophenone ketyl. All other reagents, unless otherwise noted, were obtained from the Aldrich Chemical Company and used without further purification.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz). NMR chemical shifts are reported in ppm downfield from internal TMS. FT-IR spectra were obtained on Mattson Cygnus 100 instrument. CaF_2 IR cell having a path length of 1.0 mm was used. Mass spectra were determined at the Department of Chemistry, University of Pittsburgh. EI and low resolution FAB mass spectra were obtained using a Varian MAT CH-5 or VG 7070 mass spectrometer under the direction of Dr. Kasi V. Somayajula. High resolution FAB mass spectra were obtained by the Nebraska Center for Mass Spectrometry. Melting points were determined using an Electrothermal capillary melting point apparatus and are uncorrected.

Analytical thin layer chromatography (TLC) was conducted using PolyGram 0.25 mm silica gel precoated plates with fluorescent indicator UV_{254}. Silica gel 60 (particle size 0.063−0.200 mm, 70−230 mesh ASTM) (EM Science) was used for flash chromatography.

2,6-Pyridinecarboxylic Acid Mono Benzyl Ester (1). A mixture of 2,6-pyridinecarboxylic acid (11.5 g, 69 mmol) and ion exchange resin DOWEX 500-X8 H+ 20−50 mesh (4.50 g) in BnOH (120 mL) was refluxed for 1.5 h. The mixture was cooled to room temperature. The ion exchange resin was filtered off and washed with toluene. The filtrate was extracted with saturated aqueous $NaHCO_3$ (4 × 400 mL). The aqueous layers were combined, acidified with H_2SO_4, and extracted with CH_2Cl_2 (2 × 250 mL). The organic layers were combined, washed with brine (400 mL), dried over $MgSO_4$, and evaporated in vacuo to give the crude product as an oil. The crude product was recrystallized from AcOEt (150 mL) and hexane (750 mL) to obtain the titled product as a white powder (4.93 g, 28%): mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (m, 2H), 8.12 (t, J = 7.8 Hz, 1H), 7.45 (m, 5H), 5.47 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 163.7, 163.5, 146.8, 146.5, 139.6, 135.0, 128.9, 128.7 (two different C's), 128.6, 126.9, 68.0; HRMS *m/e* calcd for $C_{14}H_{11}NO_4$ (M^+) 257.0688, found 257.0696.

6-(2-(2-Methoxycarbonylphenylcarbamoyl)phenylcarbamoyl)-pyridine-2-carboxylic Acid Benzyl Ester (3a). A solution of 2,6-pyridinecarboxylic acid mono benzyl ester (1.81 g, 7.0 mmol), trimethylacetyl chloride (928 mg, 7.7 mmol), and TEA (780 mg, 8.4 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature for 3 h. To a solution of **2a**[8] (1890 mg, 7.0 mmol) and TEA (1560 mg, 16.8 mmol) in dry CH_2Cl_2 (50 mL) was added the mixture of the acid anhydride, and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 (100 mL) was added to the mixture which was then washed with 1 N HCl (100 mL), aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and evaporated

(22) For a discussion of IR interpretation, see: Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054−1062.

Table 4. Selected ^{1}H NMR Chemical Shifts of **8b** and Reference Molecules (**10**−**12**) in $CDCl_3$ and the Observed and Calculated Chemical Shifts Changes by Aromatic Ring Current

	Ph_a3H	Ph_a4H	Ph_a5H	Ph_a6H	Py_c3H	Py_c4H	Py_c5H	Ph_e3H	Ph_e6H
8b	8.30	6.71	6.85	7.84	8.46	8.02	8.14	8.80	5.99
ref	8.78	7.64	7.18	8.11	8.46	8.13	8.46	9.04	6.45
	(**12**)	(**12**)	(**12**)	(**12**)	(**10**)	(**10**)	(**10**)	(**11**)	(**11**)
$\Delta\delta_{obsd}$	−0.48	−0.93	−0.33	−0.27	0.00	−0.11	−0.32	−0.24	−0.46
$\Delta\delta_{calcd}$ with clear	−0.30	−0.55	−0.20	−0.12	0.11	−0.09	−0.92	−0.18	−0.57
$\Delta\delta_{calcd}$ with yellow	−0.72	−1.38	−0.31	−0.22	−0.06	0.03	−0.02	−0.34	−0.71
$\Delta\delta_{calcd}$ av	−0.51	−0.97	−0.26	−0.17	0.03	−0.03	−0.47	−0.26	−0.64

in vacuo to give the crude product as a yellow oil. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to obtain the desired product as a pale yellow powder (2.11 g, 59%): mp 184−185 °C; ^{1}H NMR ($CDCl_3$) δ 13.24 (s, 1H, amide), 12.07 (s, 1H, amide), 8.97 (td, J = 8.0, 0.6 Hz, 2H), 8.48 (dd, J = 7.8, 0.9 Hz, 1H), 8.28 (dd, J = 7.7, 0.8 Hz, 1H), 8.05 (m, 2H), 7.96 (d, J = 6.9 Hz, 1H), 7.60 (m, 3H), 7.35 (m, 5H), 7.09 (t, 1H), 5.56 (s, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 167.4, 164.5, 162.5, 150.8, 147.1, 141.6, 139.6, 138.6, 135.9, 134.6, 132.9, 130.9, 128.6, 128.2, 128.0, 127.5, 125.8, 123.8, 122.9, 122.3, 121.8, 120.8, 115.5, 67.4, 52.6; HRMS *m/e* calcd for $C_{29}H_{23}N_3O_6$ (M^+) 509.1587, found 509.1600.

6-(2-(2-Methoxycarbonylphenylcarbamoyl)phenylcarbamoyl)-pyridine-2-carboxylic Acid (4a). A solution of **3a** (533 mg, 1 mmol) and 10% Pd/C (50 mg) in dry THF (30 mL) and MeOH (5 mL) was prepared in a 100-mL round-bottomed flask containing a magnetic stirrer. H_2 was introduced after removal of air by an aspirator, and the solution was stirred vigorously for 5 h at room temperature. The compound was isolated from the catalyst using a Soxhlet apparatus with CH_2Cl_2 (200 mL). The solvent was removed in vacuo, and the desired compound was obtained as a white powder (371 mg, 89%): mp 254−256 °C; ^{1}H NMR (DMSO-d_6) δ 13.28 (broad s, 1H, acid), 12.34 (s, 1H, amide), 11.50 (s, 1H, amide), 8.60 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.36 (d, J = 6.6 Hz, 1H), 8.26 (m, 2H), 7.98 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.69 (m, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 3.80 (s, 3H); HRMS *m/e* calcd for $C_{22}H_{17}N_3O_6$ (M^+) 419.1117, found 419.1122.

2-(2-Nitrobenzoylamino)benzoic Acid 1-Hexyl Ester. A solution of 2-nitrobenzoic acid (5.01 g, 30 mmol) and oxalyl chloride (4.19 g, 33 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature. DMF (0.1 mL) was added through a silica gel filter, and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated in vacuo to obtain the acid chloride as a yellow oil. 2-Aminobenzoic acid hexyl ester (6.64 g, 30 mmol) and pyridine (2.61 g, 33 mmol) were dissolved in dry CH_2Cl_2 (25 mL). The 2-nitrobenzoyl chloride in CH_2Cl_2 (25 mL) was added, and the mixture was stirred at room temperature for 30 min. CH_2Cl_2 (200 mL) was added to the mixture which was then washed with 1 N HCl (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give the crude product as a yellow oil. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to obtain the desired product as a yellow oil (7.79 g, 70%): mp 62−63 °C; ^{1}H NMR ($CDCl_3$) δ 11.61 (s, 1H, amide), 8.82 (d, J = 8.4 Hz, 1H), 8.09 (m, 2H), 7.72 (m, 2H), 7.63 (m, 2H), 7.16 (td, J = 7.7, 1.2 Hz, 1H), 6.64 (m, 2H), 4.28 (t, J = 6.6 Hz, 2H), 1.76 (quint, J = 7.0 Hz, 2H), 1.34 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 164.3, 146.9, 141.0, 134.7, 133.7, 132.9, 130.8 (2C), 128.3, 124.7, 123.3, 120.6, 115.6, 65.7, 31.3, 28.4, 25.6, 22.5, 13.9; HRMS *m/e* calcd for $C_{20}H_{22}N_2O_5$ (M^+) 370.1529, found 370.1542.

2-(2-Aminobenzoylamino)benzoic Acid 1-Hexyl Ester (2b). A solution of 2-(2-nitrobenzoylamino)benzoic acid 1-hexyl ester (3.70 g, 10 mmol) and 10% Pd/C (370 mg) in dry THF (25 mL) was prepared in a 100-mL round-bottomed flask containing a magnetic stirrer. H_2 was introduced after removal of air by an aspirator and the solution was stirred vigorously at room temperature for 2 h. The catalyst was removed by filtration through Celite. The filtrate was evaporated in vacuo to give the desired compound as a yellow wax (3.02 g, 89%): ^{1}H NMR ($CDCl_3$) δ 11.87 (s, 1H, amide), 8.82 (d, J = 8.1 Hz, 1H), 8.08 (dd, J = 7.8, 1.5 Hz, 1H), 7.73 (dd, J = 7.8, 1.2 Hz, 1H), 7.59 (td, J = 8.0, 1.5 Hz, 2H), 7.26 (td, J = 7.8, 1.5 Hz, 1H), 7.11 (td, J = 7.7, 1.1 Hz, 1H), 6.77 (td, J = 7.5, 1.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 2H), 5.76 (s, 2H, amine), 4.34 (t, J = 6.6 Hz, 2H), 1.79 (quint, J = 7.4 Hz, 2H), 1.35 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H).

6-(2-(2-(1-Hexoxycarbonyl)phenylcarbamoyl)phenylcarbamoyl)-pyridine-2-carboxylic Acid Benzyl Ester (3b). This was prepared by a route analogous to **3a** from **1** (1.29 g, 5.0 mmol), trimethyacetyl chloride (663 mg, 5.5 mmol), **2b** (1.70 g, 5.0 mmol), and TEA (1.21 g, 12 mmol) in dry CH_2Cl_2 (55 mL). The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to obtain the desired product as a yellow solid (1.18 g, 41%): mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 12.65 (s, 1H, amide), 12.11 (s, 1H, amide), 8.97 (m, 2H), 8.48 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 7.5 Hz, 1H), 8.03 (m, 3H), 7.59 (m, 3H), 7.35 (m, 5H), 7.09 (t, J = 7.7 Hz, 1H), 5.56 (s, 2H), 4.34 (t, J = 6.6 Hz, 2H), 1.79 (quint, J = 7.4 Hz, 2H), 1.35 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 167.3, 164.4, 162.4, 150.7, 147.0, 141.4, 139.6, 138.5, 135.8, 134.4, 132.8, 130.8, 128.5, 128.1, 128.0, 127.4, 125.7, 123.7, 122.8, 122.2, 121.6, 120.8, 115.7, 67.3, 65.7, 31.3, 28.4, 22.5, 14.0; LRMS (FAB, MNBA) *m/e* calcd for $C_{34}H_{33}N_3O_6$ ($M + H^+$) 579, found 579.

6-(2-(2-(1-Hexoxycarbonyl)phenylcarbamoyl)phenylcarbamoyl)-pyridine-2-carboxylic Acid (4b). This was prepared by a method analogous to **4a** from **3b** (870 mg, 1.5 mmol) and 10% Pd/C (90 mg) in dry THF (10 mL) to give the desired compound as a yellow cotton (733 mg, 100%): mp 210−211 °C; ^{1}H NMR ($CDCl_3$) δ 13.13 (s, 1H, acid), 12.45 (s, 1H, amide), 11.60 (s, 1H, amide), 8.92 (dd, J = 8.30, 0.8 Hz, 1H), 8.86 (d, J = 8.1 Hz, 1H), 8.51 (d, J = 7.2 Hz, 1H), 8.42 (dd, J = 8.1, 0.9 Hz, 1H), 8.19 (t, J = 7.8 Hz, 1H), 8.13 (dd, J = 8.1, 1.5 Hz, 1H), 8.01 (dd, J = 7.8, 1.1 Hz, 1H), 7.75 (td, J = 7.5, 1.2 Hz, 1H), 7.64 (t, J = 8.7 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 4.37 (6.6, 2H), 1.80 (quint, J = 7.1 Hz, 2H), 1.38 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H); LRMS (FAB, MNBA) *m/e* calcd for $C_{27}H_{28}N_3O_6$ ($M + H^+$) 490, found 490.

1,3-Dinitro-4,6-dimethoxybenzene (5).[17] To a suspension of 1,3-difluoro-4,6-dinitrobenzene (4.08 g, 20 mmol) in TEA (4.45 g, 44 mmol) was added MeOH (1346 mg, 42 mmol), and the mixture was stirred at room temperature for 30 min. CH_2Cl_2 (80 mL) was added to the reaction mixture which was then washed with 1 N HCl (80 mL), aqueous $NaHCO_3$ (80 mL), and brine (80 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give the crude product (4.38 g). The crude product was recrystallized from CH_2Cl_2 and EtOH to obtain the desired product as a yellow powder (3.92 g, 86%): mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 8.77 (m, 1H), 6.63 (s, 1H), 4.10 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.0, 130.3, 124.7, 99.6, 57.9; HRMS *m/e* calcd for $C_8H_8N_2O_6$ (M^+) 228.0382, found 228.0390.

1,3-Bis(2-nitrobenzoylamino)-4,6-dimethoxybenzene (6). To a solution of 2-nitrobenzoic acid (371 mg, 2.2 mmol) and oxalyl chloride (380 mg, 3.0 mmol) in dry THF (10 mL) was added DMF (0.025 mL) through a silica gel filter, and the mixture was stirred at room temperature for 20 min. The reaction mixture was evaporated in vacuo to obtain the acid chloride.

A solution of **5** (228 mg, 1.0 mmol) and 5% Pd/C (50 mg) in dry THF (15 mL) was prepared in a 50-mL round-bottomed flask containing a magnetic stirrer. H_2 was introduced after removal of air by an aspirator, and the solution was stirred vigorously at room temperature for 30 min. The catalyst was removed by filtration through Celite. The filtrate was directly introduced into a solution of the acid chloride and pyridine (475 mg, 6.0 mmol) in dry THF (20 mL), and the mixture was stirred at room temperature for 20 min. To the reaction mixture was added CH_2Cl_2 (50 mL), and the mixture was washed with 1 N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude product was recrystallized from THF

(150 mL) and hexane (100 mL) to obtain the desired compound as a yellow solid (340 mg, 73%): mp 237−239 °C; ^{1}H NMR (DMSO-d_6) δ 9.89 (s, 2H, amide), 8.14 (s, 1H), 8.10 (d, J = 8.1 Hz, 2H), 7.83 (t, J = 7.5 Hz, 2H), 7.72 (m, 4H), 6.83 (s, 1H), 3.85 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 164.4, 150.1, 146.8, 133.9, 132.9, 130.7, 129.4, 124.1, 121.0, 118.6, 97.2, 56.2; HRMS *m/e* calcd for $C_{22}H_{18}N_4O_8$ (M^+) 466.1125, found 466.1106.

1,3-Bis(2-aminobenzoylamino)-4,6-dimethoxybenzene (7). A solution of **6** (533 mg, 1.0 mmol) and 5% Pd/C (50 mg) in dry THF (30 mL) and MeOH (5 mL) was prepared in a 100-mL round-bottomed flask containing a magnetic stirrer. H_2 was introduced after removal of air by an aspirator, and the solution was stirred vigorously at room temperature for 5 h. The catalyst was removed by filtration through Celite, and the filtrate evaporated in vacuo to give the desired compound as a yellow solid (465 mg, 100%): ^{1}H NMR (DMSO-d_6) δ 9.17 (s, 2H, amide), 7.83 (s, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.18 (t, J = 7.5 Hz, 2H), 6.81 (s, 1H), 6.72 (d, J = 8.1 Hz, 2H), 6.56 (t, J = 7.5 Hz, 2H), 6.39 (s, 4H, amine), 3.85 (s, 6H).

1,3-Bis((6-(2-(2-methoxycarbonylphenylcarbamoyl)phenylcarbamoyl)pyridine-2-carbonylamino)phenylcarbamoyl)-4,6-dimethoxybenzene (8a). To a solution of **4a** (168 mg, 0.4 mmol) and TEA (40 mg, 0.4 mmol) in dry THF (10 mL) was added trimethylacetyl chloride (96 mg, 0.8 mmol), and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated to give the mixed anhydride. The evaporated residue was dissolved in dry THF (20 mL) and then added to **7** (81 mg, 0.2 mmol). The mixture was refluxed for 5 h, and then the reaction mixture was evaporated in vacuo. CH_2Cl_2 (50 mL) was added to the mixture which was then washed with 5% citric acid (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give the crude product. The crude product was purified by preparative thin layer chromatography (silica gel, 1/20 = MeOH/$CHCl_3$) to obtain the desired product as a pale yellow powder (147 mg, 61%): mp 291−193 °C; ^{1}H NMR ($CDCl_3$) δ 12.89 (s, 2H, amide), 12.42 (s, 2H, amide), 11.34 (s, 2H, amide), 8.82 (m, 3H), 8.45 (d, J = 7.5 Hz, 2H), 8.29 (d, J = 8.1 Hz, 4H), 8.00 (m, 4H), 7.77 (d, J = 7.8 Hz, 2H), 7.61 (t, 2H), 7.29 (m, 8H), 6.97 (t, 2H), 6.79 (m, 4H), 6.65 (t, J = 8.1 Hz, 2H), 5.99 (s, 1H), 3.65 (s, 6H), 3.44 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.3, 166.1, 164.1, 162.3, 161.3, 149.3, 149.0, 144.9, 141.2, 138.8, 138.7, 138.6, 134.0, 132.1, 131.7, 130.3, 127.4, 127.0, 124.8, 124.7, 123.3, 123.1, 122.9, 122.2, 122.1, 121.9, 120.2, 119.6, 114.5, 113.4, 93.4, 55.3, 52.1; HRMS (FAB, MNBA) *m/e* calcd for $C_{66}H_{52}N_{10}O_{14}Na$ ($M + Na^+$) 1231.3562, found 1231.3546.

1,3-Bis((6-(2-(2-(1-Hexoxycarbonyl)phenylcarbamoyl)phenylcarbamoyl)-pyridine-2-carbonylamino)phenylcarbamoyl)-4,6-dimethoxybenzene (8b). This was prepared by a method analogous to **8a** from **4b** (98 mg, 0.2 mmol), TEA (26 mg, 0.25 mmol) in dry THF (5 mL), trimethylacetyl chloride (27 mg, 0.23 mmol), and **7** (38 mg, 0.094 mmol) in dry THF (5 mL). The crude product was purified by preparative thin layer chromatography (silica gel, 1/20 = MeOH/$CHCl_3$) to obtain the desired product as a yellow foam (70 mg, 55%): mp 229−231 °C; ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 2H, amide), 12.54 (s, 2H, amide), 11.48 (s, 2H, amide), 8.78 (m, 3H), 8.46 (dd, J = 7.7, 0.8 Hz, 2H), 8.30 (d, J = 8.4 Hz, 4H), 8.14 (d, J = 7.8 Hz, 2H), 8.02 (t, J = 7.7 Hz, 2H), 7.84 (dd, J = 7.8, 1.5 Hz, 2H), 7.63 (t, J = 7.7 Hz, 2H), 7.43 (m, 6H, 2H amide + 4H aromatic), 7.26 (t, 2H), 7.07 (t, J = 7.8 Hz, 2H), 6.86 (m, 4H), 6.69 (t, J = 7.2 Hz, 2H), 5.99 (s, 1H), 4.08 (t, J = 6.6 Hz, 4H), 3.41 (s, 6H), 1.64 (m, 4H), 1.31 (m, 12H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 168.0, 166.3, 164.2, 162.3, 161.4, 149.2, 149.1, 145.1, 141.2, 138.9, 138.7, 138.3, 134.0, 132.1, 131.8, 130.3, 127.7, 127.2, 124.9, 124.8, 123.8, 123.6, 123.0, 122.3, 121.9, 120.4, 119.7, 115.0, 113.7, 93.4, 65.4, 55.2, 31.4, 28.4, 25.6, 22.5, 14.0; IR (2 mM in CH_2Cl_2) 3424, 3325, 3261, 1688, 1600, 1586, 1535, 1458, 1274, 1234 cm^{-1}; HRMS (FAB, MNBA) *m/e* calcd for $C_{76}H_{72}N_{10}O_{14}$ (M^+) 1348.5229, found 1348.5243.

1,3-Bis(2-((pyridine-2-carbonyl)amino)phenylcarbamoyl)-4,6-dimethoxybenzene (11). To a solution of picolinic acid (74 mg, 0.6 mmol) and oxalyl chloride (102 mg, 0.8 mmol) in dry CH_2Cl_2 (3 mL) was added DMF (25 μL) through a silica gel filter, and the mixture was stirred at room temperature for 5 min. The reaction mixture was evaporated in vacuo to obtain the acid chloride. To the acid chloride was added a solution of **7** (101 mg, 0.2 mmol) and DIPEA (129 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was charged with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was separated, evaporated, and triturated with hexanes. The crude product was purified by column chromatography (SiO_2, first 1/20 = MeOH/CH_2Cl_2, later 1/3 = MeOH/CH_2Cl_2) to obtain the desired compound (137 mg, 89%): mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 12.77 (s, 2H), 9.04 (s, 1H), 8.85 (d, J = 8.1 Hz, 2H), 8.62 (d, J = 4.5 Hz, 2H), 8.23 (m, 4H), 7.78 (m, 4H), 7.54 (7.8, 2H), 7.30 (m, 2H), 7.16 (t, J = 7.5 Hz, 2H), 6.45 (s, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.4, 163.5, 150.4, 148.9, 147.5, 138.9, 137.2, 127.5, 126.2, 123.3, 122.9, 122.4 (2C), 121.5, 119.3, 117.1, 94.9, 56.0; IR (2 mM in CH_2Cl_2) 3420, 3255, 1682, 1583, 1538, 1515, 1460, 1244, 1205 cm^{-1}; HRMS *m/e* calcd for $C_{34}H_{28}N_6O_6$ (M^+) 616.2070, found 616.2062.

Computational Approach for Calculating Ring Current Induced Shifts. A program that can calculate the anisotropic effect of nearby aromatic rings on individual protons was written in QuickBasic using the equivalent dipole model of the ring current[22] and the X-ray structural coordinates of the molecule in question. First, the program reads the coordinates of atoms that form the aromatic ring system. Second, the program calculates the geometrical relationship of the proton relative to all of the aromatic rings in the molecule (i.e., values of r and θ as defined in eq 1, Figure 4). Third, individual values of $\Delta\delta$ for the effect of all aromatic rings on the proton are calculated using eq 1 and the geometrical coordinates. The overall predicted ring current induced shift for a given proton is obtained from the sum of all individual $\Delta\delta$ values, except those from the ring to which the proton is attached and its directly linked neighbor. The $\Delta\delta$ values from these two rings were ignored because their effect will be cancelled when the experimental $\Delta\delta_{obs}$ values are obtained by the comparison of the helical structures (e.g., **10**) with their control molecules (e.g., **12**). The procedure was repeated for all protons of interest. The source file for this program can be found in the Supporting Information.

Note Added in Review. While this manuscript was under review Seebach,[23] Gellman,[24] Lehn,[25] and Moore[26] reported the formation of extended helical oligomers based on β-alanine, trans-2-aminocyclohexanecarboxylic acid, pyridine-pyrimidine, and phenylacetylene units, respectively.

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Supporting Information Available: Crystallographic details for the two polymorphs of **8a** (Figure 2) and (Figure 3) including tables of atomic coordinates, thermal parameters, bond angles and bond lengths, and also an example of the use of the ring current calculation program to predict the aromatic induced shifts in **10** (23 pages). See any current masthead page for ordering and Internet access instructions.

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