Solid Phase Synthesis and Secondary Structural Studies of (1→5) Amide-Linked Sialooligomers[1]

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A series of dimeric through octameric (1→5) amide-linked sialooligomers were prepared using solid-phase peptide methods on Rink resin with Fmoc protecting group chemistry. The oligomers were conjugated to ϵ-amino caproic acid in order to model membrane-bound conformations. The secondary structure of the oliogomers was probed with NH/ND exchange rates determined by NMR, and with circular dichroism. The combined structural studies show that a tetramer is required for ordered secondary structure, and that secondary structure is stabilized upon elongation to pentameric and hexameric species. Interestingly, the heptamer shows rapid NH/ND exchange rates; however, ordered secondary structure is restored in the octamer. These studies provide the first evidence that oligomers composed of constrained carbohydrate-derived amino acids form stable secondary structures in water.

Introduction

In his review on complex carbohydrates, Nathan Sharon pointed out that neuraminic acid (NeuAc) is not only a carbohydrate but it is also a naturally occurring δ-amino acid (Figure 1).[2] That observation inspired our recent studies directed toward using NeuAc as an amino acid equivalent.[3] The idea of using sugar amino acids as both glyco and peptido mimetics has gained considerable interest in the past two years.[4] Amide-linked sugars have been shown to possess important biological[4b,4c] and structural properties[4a] and more recently they have been employed in combinatorial syntheses.[5] Our interest in amide-linked sugars is focused on preparing oligomeric materials that have defined secondary structures in water. The fact that *O*-glycoside oligomers of sialic acid (Figure 2) are helical in solution[6] prompted us to investigate whether amide-linked oligomers derived from NeuAc would also be helical. While the secondary structures derived from *O*-linked and amide-linked sugars would not necessarily be the same, the possibility of creating novel helical structures is an exciting proposition. One important application of these novel materials would be as helical scaffolds in biomolecular recognition events. Therefore we embarked upon an investigation to determine if amide-linked oligomers of NeuAc could be prepared, if higher order constructs would be water soluble, and if so, whether the oligomers would have defined secondary structures in water.

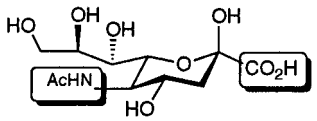

Figure 1. *N*-Acetylneuraminic acid is a naturally occurring amino acid.

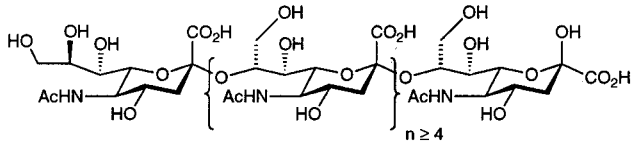

Figure 2. *O*-Linked Oligomers of NeuAc Are Helical in Solution.[6]

We were alerted to the fact that solubility might be a problem since, until very recently,[7] hexameric species were the largest amide-linked pyranoses reported. We reasoned that the pendent side chain of NeuAc would afford greater solubility and thus began synthetic studies

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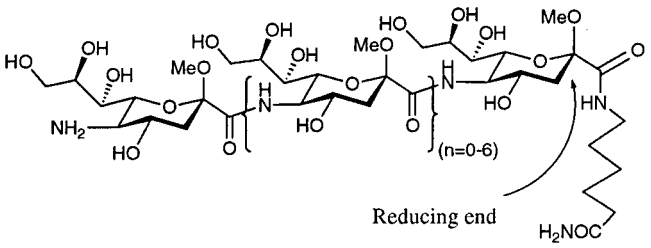

Figure 3. Target amide-linked oligomers.

on the preparation of functionalized sialic acids for incorporation into amide-linked oligomers. Several analogues of NeuAc, capable of undergoing solution phase amidation, were prepared, but the coupling yields were disappointingly low.[3] Therefore we decided to explore solid-phase methods in order to improve efficiency. Reported herein is the solid-phase synthesis and structural studies of amide-linked sialooligomers ranging in size from dimers to octamers.

Results and Discussion

The target molecule for our investigations is shown in Figure 3. Incorporation of an ϵ-amino caproic acid linker at the reducing end was deemed important for several reasons. First, it was reasoned that coupling may be facilitated by placing a linker between the resin and the first residue. Second, the caproamide functionality could serve as a potential site for conjugation of the sialooligomers at a later stage in the synthesis. Finally, and perhaps most importantly, the lipid chain could serve to protect the reducing end amide from fraying when placed in an aqueous environment. In this manner the soluble oligomers would model membrane bound conformations where the reducing end amide would not be exposed to water.

The synthetic route to the target molecule is shown in Scheme 1. β-*O*-Methyl neuraminic acid (**1**)[3a] was treated with 9-fluorenylmethyl chloroformate in dioxane to provide the Fmoc-protected amino acid **2** in 72% yield. This material was coupled to Rink resin, possessing an ϵ-amino caproic acid linker, by activating the acid (1.4 equiv) with BOP (1.4 equiv) and Hünig's base (4 equiv) in NMP. While the linker was designed to serve several different roles, it should be noted that coupling of **3** directly to the Rink resin was also possible. The resin containing the monomeric species was readied for elongation by reaction with hydrazine hydrate in methanol which resulted in removal of the Fmoc protecting group as well as the *O*-acetates. At this point, the beads were split and one portion was cleaved from the resin to give the monomer linked ϵ-amino caproic amide **4** in 62% yield. The other portion was coupled to **3** and the above process reiterated. After removal from the resin, the dimeric species **5** was obtained in 47% yield. The process outlined above was repeated for trimer through octamer syntheses, giving pure products after size exclusion chromatography; the yields ranged from 44 to 55%. Each of the oligomers was soluble in water, methanol, and dimethyl sulfoxide, confirming our expectation that NeuAc analogues would afford greater solubility than glucose-derived amide-linked oligomers.

Recently, Gellman and co-workers demonstrated that differences in amide NH/ND exchange rates are indicative of secondary structure in hexamers composed of *trans*-2-aminocyclohexanoic acid.[8] Our sialooligomers composed of δ-amino acids are closely related to Gellman's β-peptide foldamers except at the ends. Both the carboxy and amino termini of the β-peptides are exposed to solvent, and therefore both ends can fray.[9] In contrast, the carboxy terminus of the sialooligomers is protected by the lipid linker designed to model a membrane-bound oligomer which would not be capable of fraying. The NMR experiments were performed in DMSO-d_6 at room temperature with 10% D_2O added. For the 2−8mers there are four sets of NH protons corresponding to the primary amide (two singlets at 6.7 and 7.3 ppm), the secondary amide (triplet at 8.2) on the caproamide linker, and the internal amides (7.6−7.8 ppm). The half-lives corresponding to NH/ND exchange rates for the oligomers are listed in Table 1. Both of the amides in the lipid linker show pseudo-first-order kinetics as do the internal amides in the dimer and trimer. The internal amide of the dimer has a $t_{1/2} = 0.5$ h. The two internal NH's of the trimer were resolved, and their half-lives were shown to be 1 h and 7 h for the end amide and the end-1 amide, respectively. These data suggest that the amino terminus amide exchanges at comparable rates (0.5−1 h) regardless of oligomer length. The fact that the end-1 amide exchanges slower suggests that it is protected, perhaps through an internal hydrogen bond. The tetramer showed three different internal NH protons, and the half-lives of the slower two (analyzed after the end amide had exchanged) were shown to be 8 h and 6 h for the end-1 and end-2 amides, respectively. The internal amide resonances were not resolved for the 5−8mers, but a pseudo-first-order plot (analyzed after the end amide at exchanged) gave $t_{1/2} = \sim$11 h (Table 1) for these protons except for the heptamer which undergoes relatively fast exchange ($t_{1/2} = 1$ h).

Our interpretation of these data is that the end amide is exposed to solvent and therefore undergoes rapid exchange. The end-1 amide of the trimer is protected from solvent and undergoes slower exchange. The $t_{1/2}$ of the tetramer end-1 amide is 2 h slower than the end-2 amide, suggesting that it is involved in stronger H-bonding interactions which may give rise to secondary structure. Interestingly, the heptamer deviates from the above trends with all internal hydrogens exchanging with a $t_{1/2} = 1$ h.[10] This behavior is difficult to explain without further experimentation, however one possibility is that the heptamer can engage in more than one type of intramolecular hydrogen bonding interaction, creating the opportunity for conformational fluctuation. This behavior is not observed in the octamer which reverts back to an ordered secondary structure.

Circular dichroism studies in water also support secondary structure for higher order constructs (Figure 4). The monomer is distinctly different from the oligomers, suggesting that the strong positive bands and the crossover to negative values is due to the (1→5) amide chromophore. These spectra also show that the ellipticity per residue increases with oligomer length. The most compelling evidence comes from analysis of the difference between the peak and trough ellipticities for each oligo-

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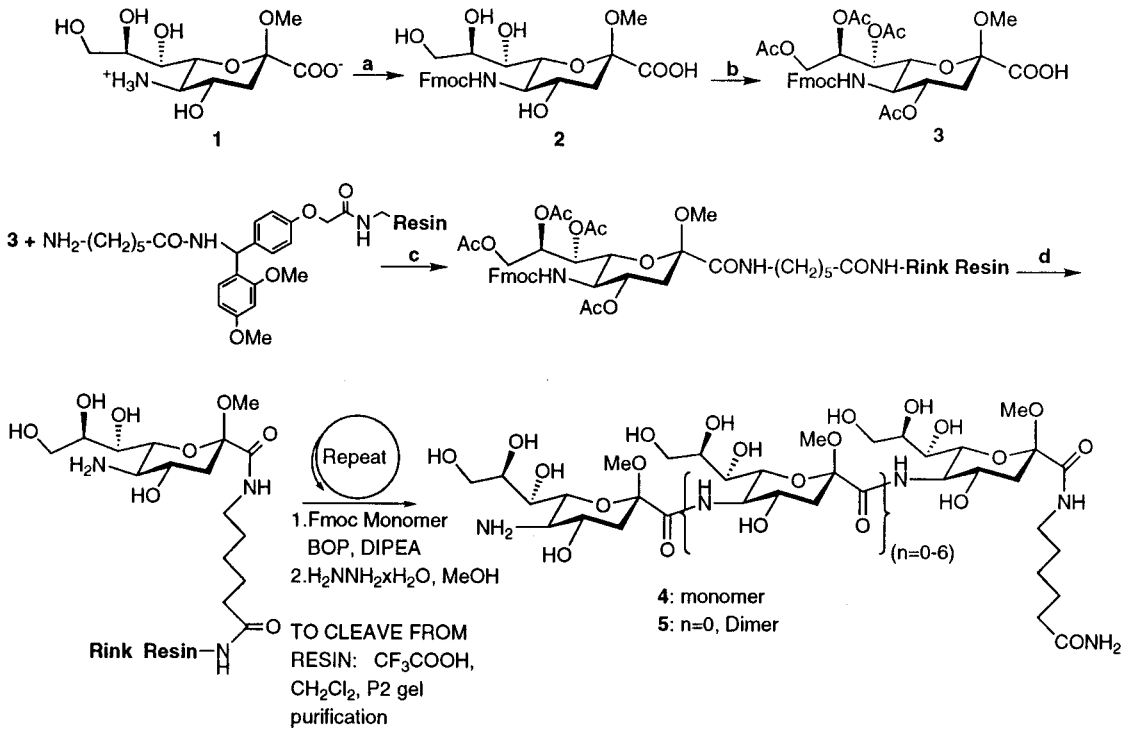
(10) The exchange rates experiments were repeated numerous times with careful control of the pH.

Scheme 1



(a) Fmoc-Cl, $NaHCO_3$, H_2O, dioxane, 0°C. (b) Ac_2O, Pyridine, 0°C. (c) BOP, DIPEA. (d) $H_2NNH_2 \cdot H_2O$, CH_3OH.

Table 1. $t_{1/2}$ (h) As Determined by NH/ND NMR ExchangeExperiments

		internal amides				
oligomer	linker 2° amide	end amide	end-1	end-2	linker 1° amide	linker 1° amide
monomer	43	n/a[a]	n/a	n/a	7.3	7.7
dimer	20	0.5	n/a	n/a	1.8	1.9
trimer	67	1.0	7.0	n/a	5.8	5.3
tetramer	45	1.0	8.3	6.2	4.6	5.0
pentamer	52	n/a	10.8		4.8	4.7
hexamer	63	n/a	11.6		5.0	4.9
heptamer	11	n/a	1.3		2.2	2.6
octamer	58	n/a	10.4		4.8	4.9

[a] n/a = not applicable. Assumed to be consistent.

mer. There is a large increase between dimer and trimer and between trimer and tetramer. Tetramer through hexamer are roughly the same (10.9) but upon going to heptamer another increase is observed (11.5) and still further for the octamer (12.0). These data are consistent with our NMR data and support the possibility that there is a change in secondary structure occurring at the heptamer length. Our interpretation of the combined NMR and CD data is that four residues are required in order to initiate a stable secondary structure. Incorporation of the fifth and sixth residues leads to additional stabilizing interactions. The heptamer may be able to engage in more than one type of H-bonding pattern as evidenced by the change in CD and NMR data. Structural regularity is then restored in the octamer whose secondary structure may differ from the smaller oligomers, perhaps forming a more extended secondary structure.

Conclusion

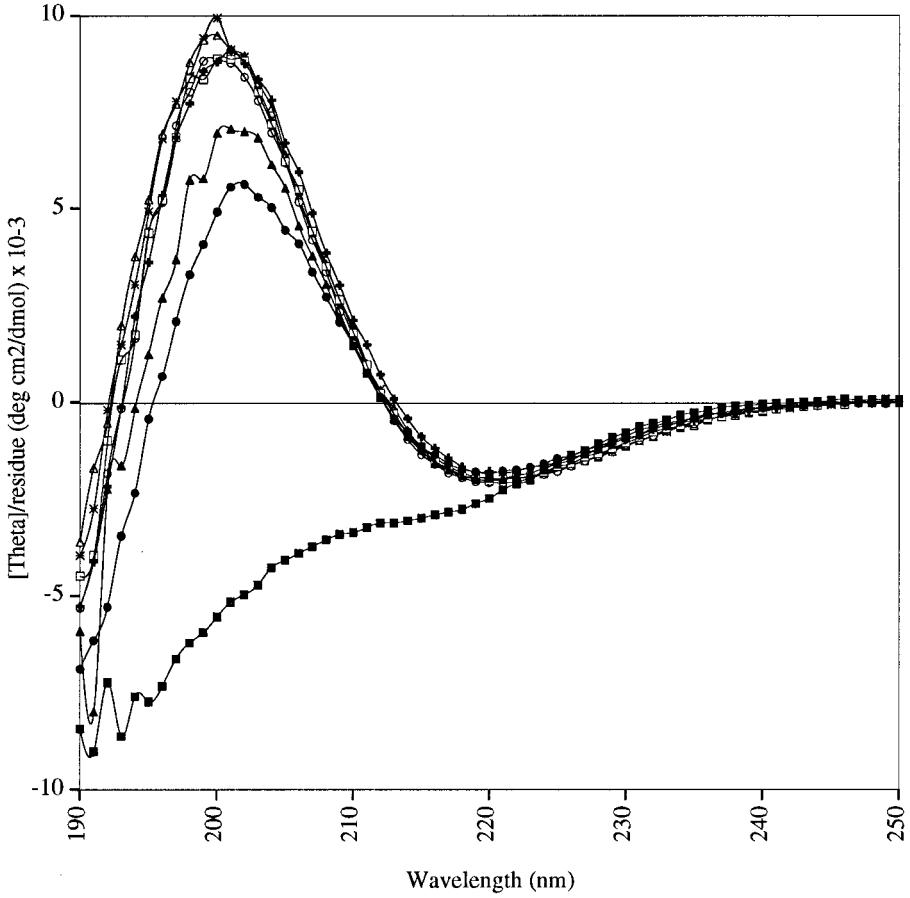
In summary we have demonstrated that (1→5) amide-linked sialooligomers can be efficiently prepared using solid-phase synthetic methods. The oligomers were prepared with lipid linkers to keep the reducing end from fraying (as evidenced by slow exchange of the reducing end amide) in aqueous media as a model for membrane bound oligomers. A series of oligomers were prepared ranging from dimeric to octameric species and all were soluble in water, DMSO, and methanol. Combined NMR and CD data suggest that higher order constructs have defined secondary structural features that may vary with length. Further investigations are underway in our laboratory to unambiguously determine the secondary structures of these novel compounds, and to ascertain whether they are helical.

Experimental Section

General. Resins and Fmoc-amino acids were purchased from Advanced ChemTech. All air and moisture sensitive reactions were performed under an argon atmosphere in flame-dried reaction flasks. CH_2Cl_2 and CH_3CN were dried over P_2O_5, and all solvents were freshly distilled under an argon atmosphere prior to use. For flash chromatography, 400−230 mesh silica gel 60 (E. Merck No. 9385) was employed. All compounds described were >95% pure by ^1H- and ^{13}C NMR.

***β*-*O*-Methylneuraminic Acid.** *β*-*O*-Methyl-*N*-acetylneuraminic acid methyl ester (400 mg) was dissolved in 2 M NaOH water solution (20 mL). The mixture was kept at 90−95 °C for 48 h. After cooling to room temperature, the pH was set to 7 with Dowex H^+ resin. The resin was filtered, and the supernatant was freeze-dried to give brownish amorphous solid. (284 mg, 85.0%). Without any purification, the glycoside was used as the starting material for the next reaction.

***β*-*O*-Methyl-*N*-(9-fluorenylmethoxycarbonyl)neuraminic Acid.** *β*-*O*-Methylneuraminic acid (190 mg, 0.67 mmol) was dissolved in a mixture of 10% $NaHCO_3$ (20 mL) and dioxane (15 mL). The mixture was cooled to 0 °C, and 9-fluorenylmethyl chloroformate (190 mg, 0.737 mmol, 1.1 equiv) in dioxane (5 mL) was added dropwise over 30 min. The reaction mixture was kept at 0 °C for 4 h and at room



	Chain Length	Peak Max	Peak Min	Peak - Trough	Concentration (mg/mL)
■	Monomer	-5.160	-2.256	-2.904	0.4412
●	Dimer	5.623	-1.838	7.461	0.2986
▲	Trimer	7.051	-1.961	9.012	0.5902
✚	Tetramer	9.102	-1.810	10.912	0.3115
□	Pentamer	8.882	-2.024	10.906	0.4437
○	Hexamer	8.852	-2.081	10.933	0.4675
△	Heptamer	9.489	-1.974	11.463	0.3374
✳	Octamer	9.936	-1.994	11.930	0.3672

Figure 4. CD Spectra of amide-linked sialooligomers in H_2O. Analyses of peak and trough ellipticities indicate stable secondary structure in higher order constructs (4−8mers).

temperature for 16 h. The mixture was diluted with water (200 mL) and was extracted with diethyl ether (3 × 20 mL). The inorganic phase pH was set to 3 with 10% HCl solution. The acidic solution was evaporated to 25 mL, and the residue was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with distilled water (3 × 5 mL) and evaporated to give 244 mg (71.7%) yellow amorphous solid.

***β*-*O*-Methyl-4,7,8,9-tetra-*O*-acetyl-*N*-(9-fluorenylmethoxycarbonyl)neuraminic Acid.** *β*-*O*-Methyl-*N*-(9-fluorenylmethoxycarbonyl)neuraminic acid (530 mg) was dissolved in pyridine (2 mL) and cooled to 0 °C, and acetic anhydride was added dropwise. The yellowish solution was kept at room temparature 1 day. After the TLC plate showed only the peracetylated analogue, methanol (2 mL) was added. After 2 h the mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate (30 mL) and washed 3× with 0.1 M HCl solution and with water, and the pH was kept at 4. The organic layer was dried, evaporated, and reevaporated with benzene in vacuo to give 640 mg as yellow amorphous solid: yield 90.5%; $[\alpha]^{20}_D = +20.0°$ (*c* 1.4); ^{1}H NMR (in $CDCl_3$) δ 7.76−7.30 (m, 8H, ArH), 5.43 (dd, $J_{7\text{-H}-8\text{-H}} = 1.2$ Hz, $J_{6\text{-H}-7\text{-H}} = 4.6$ Hz, 7-H), 5.23 (m, 1H, 8-H), 5.19 (ddd, $J_{3\text{eqH}-4-\text{H}} = 4.7$ Hz, $J_{3\text{axH}-4-\text{H}} = 11.3$ Hz, $J_{4\text{-H}-5\text{-H}} = 11.3$ Hz, 1H, 4-H), 4.92 (d, $J_{\text{NH}-5-\text{H}} = 10.2$ Hz, 1H, NH), 4.57 (dd, $J_{9\text{-H}-9'\text{-H}} = 11.0$ Hz, $J_{9\text{-H}-8\text{-H}} = 0.8$ Hz, 1H, 9-H), 4.24 (dd, $J_{\text{FmocCH}-\text{FmocCH}_2} = 4.1$ Hz, $J_{\text{FmocCH}-\text{FmocCH}_2} = 9.0$ Hz, 1H, Fmoc CH), 4.11 (m, 2H, Fmoc CH_2), 4.02 (dd, $J_{6\text{-H}-5\text{-H}} = 12.4$ Hz, $J_{6\text{-H}-7\text{-H}} = 7.2$ Hz, 1H, 6-H), 3.96 (dd, 1H, 9′−H), 3,74 (dd, 1H, 5-H), 3.22 (s, 3H, OCH_3), 2.46 (dd, $J_{3\text{eq-H}-3\text{ax-H}} = 13.1$ Hz, 2.16, 2.07, 2.05, 1.94 (4s, 12H, CH_3COO) 1.92 (dd, 1H, 3axH); ^{13}C NMR (in $CDCl_3$) δ 171.05, 171.04, 171.01, 170.5 168.53 (COO), 155.98 (CONH), 144.14, 143.40, 141.23, 141.11 (quat Ar C), 128.24, 128.24, 127.82, 127.66, 126.99, 125.24, 124.89, 119.91 (Ar C), 98.75 (C-2), 71.69, 71.17, 68.63 and 68.15 (C-4, C-6, C-7 and C-8), 67.41 (Fmoc CH_2), 62.51 (C-9), 51.61, 51.16 (C-5 and OCH_3), 46.87 (Fmoc CH), 36.32 (C-3), 20.95, 20.77, 20.69, 20.68 (CH_3COO). FAB HRMS [M + H$^+$] 672.2307, calcd $C_{33}H_{37}NO_{14}$ 672.2292.

(1→5) Amide-Linked Neuraminic Acid Oligomers Conjugated to ϵ-Amino Caproamide. (1→5) Amide linked sialooligomer assembly via Fmoc chemistry was performed manually (0.07 mmol scale, 1.5 mL wash volumes), starting with 4-(2′,4′-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxy resin (Rink Resin−Advanced ChemTech) (0.52 mmol/g, 135 mg). Fmoc removal from the original resin and from the coupled ϵ-aminocaproic acid was accomplished with piperidine/NMP (3:7, 2 × 10 min), followed by washing with NMP (6 × 1 min). The caproic acid (5 equiv) was coupled with BOP reagent (5 equiv) and ^{i}Pr$_2$NEt (5 equiv) in 1.5 mL of NMP. Couplings of the Fmoc *β*-*O*-Me-neuraminic acid was achieved by adding the reagents sequentially to the resin in order: 1.4

equiv of Fmoc amino acid, 1.4 equiv of BOP reagent, and 4 equiv of $^{i}Pr_2NEt$ in 1.5 mL of NMP. The mixture was agitated by bubbling argon through the reaction mixture (frit) for 4 h. If the Kaiser test was positive, the coupling was repeated with 0.5 equiv of Fmoc amino acid, 0.5 equiv of BOP reagent, and 4 equiv of $^{i}Pr_2NEt$ for 2−4 h (negative ninhydrin test obtained). After coupling the monomer unit, the Fmoc and acetyl protecting groups were removed with $H_2NNH_2 \cdot H_2O$/MeOH (4:1, 2 h) while the 1→5 amide-linked sialooligomers remained anchored to the resin. The excess H_2NNH_2 was washed with MeOH (4 × 1 min), and NMP (4 × 1 min), and CH_2Cl_2 (6 × 1 min). The resin was split. On one part of the resin the coupling was continued as above. The other part of the resin was cleaved which was carried out with CF_3COOH/CH_2Cl_2 (3:7, 10 mL). The filtrate was vacuum distilled at 25 °C, dissolved in H_2O (2 mL), and filtered, and the filtrate was freeze-dried. The white-yellowish residues were purified on Bio-Gel (the di, tri, tetra, penta, and hexamer on P-2 gel, the heptamer and octamer on P-10 gel) column to give the pure oligomers. Characterization data is listed in Table 2 (Supporting Information).

NMR Amide NH/ND Exchange Experiments. ^1H NMR spectra were collected on a Bruker AM-500 spectrometer at 295 K using the standard Bruker kinetics program. Samples were prepared at 0.002 M concentration in 0.5 mL of DMSO-d_6 (99.96%) under an inert atmosphere. Initial spectra were collected, followed by the addition of 10% D_2O by volume. A total of 50 FIDs were obtained, 64 scans each, at increasing time intervals for a period of 20 h. Data were transferred to a Silicon Graphics Indy workstation and processed using Felix-95 NMR processing software by BioSym/Molecular Simulations. Data analysis and graphics generation were carried out using CA-Cricket Graph III by Computer Associates. NMR plots of NH/ND exchange for each oligomer are given in the Supporting Information (Figures 5 and 6). Resolution of the internal amides for the trimer and tetramer are also given in the Supporting Information (Figure 7). Pseudo-first-order rate plots are shown in Figures 8 and 9 of the Supporting Information.

Circular Dichroism. Samples of each oligomer were weighed out to the tenth of a microgram utilizing a Cahn 29 Automatic Electrobalance. The oligomers were then diluted using deionized water and stored at −20 °C between CD analyses. Dilutions were as follows (mg mL^{-1}): monomer 0.4412; dimer 0.2986; trimer 0.5902; tetramer 0.3115; pentamer 0.4437; hexamer 0.4675; heptamer 0.3374; octamer 0.3672. The CD spectra were acquired on an Aviv CD Spectropolarimeter Model 62A DS. Each sample was run at room temperature in a 2 mm path length quartz cuvette at a total volume 600 μL. Three scans for each sample were obtained from 320 to 190 nm with data points taken every 1.0 nm. The data were manually baseline-corrected by averaging the mdeg readings from 260 to 320 nm, where the curve was a flat line. This average value was then subtracted over the entire data series. These corrected mdeg values were used to calculate the molar ellipticity values $[\theta]$, using the equation $[\theta] = (\theta M)/(cl)$, where θ is the corrected mdeg value, M is the molecular weight, c is the concentration in mg/mL, and l is the path length in mm. These values were plotted against wavelength (nm), and the peak maximum and trough minumum values were found for each oligomer and subtracted to determine trends in molar ellipticity values over the series.

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Supporting Information Available: ^1H NMR spectra of oligomers, a table of characterization data (Table 2), amide NH/ND exchange data and pseudo-first order rate plots (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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