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Amphipathic Helices from Aromatic Amino Acid Oligomers

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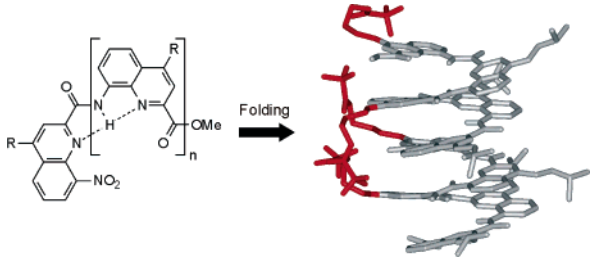

Synthetic helical foldamers are of significant interest for mimicking the conformations of naturally occurring molecules while at the same time introducing new structures and properties. In particular, oligoamides of aromatic amino acids are attractive targets, as their folding is highly predictable and stable. Here the design and synthesis of new amphipathic helical oligoamides based on quinoline-derived amino acids having either hydrophobic or cationic side chains are described. Their structures were characterized in the solid state by single-crystal X-ray diffraction and in solution by NMR. Results of these studies suggest that an oligomer as short as a pentamer folds into a stable helical conformation in protic solvents, including MeOH and H_2O. The introduction of polar proteinogenic side chains to these foldamers, as described here for the first time, promises to provide possibilities for the biological applications of these molecules. In particular, amphipathic helices are versatile targets to explore due to their importance in a variety of biological processes, and the unique structure and properties of the quinoline-derived oligoamides may allow new structure−activity relationships to be developed.

Introduction

Inspired by nature's ability to create a vast array of macromolecular structures and functions from a relatively limited set of monomers arranged in linear sequences, there is significant interest in the development of synthetic oligomers that fold into stable, well-defined conformations. These molecules, commonly referred to as "foldamers" promise to provide new scaffolds for a wide range of biological and materials science applications.[1] While the degree of structural and functional complexity achievable with synthetic systems does not yet approach that of natural systems, some potential advantages of the synthetic oligomers include resistance to enzymatic degradation and access to the vast array of functional groups available to synthetic chemists.

Helices are a key structural motif in natural biopolymers, such as proteins and DNA, and are also the most extensively investigated foldamer architecture. Thus far, a wide variety of synthetic oligomers ranging from β-peptides[2−7] and pep-

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toids[8−12] to aromatic oligoamides[13−19] and poly(*m*-phenylene ethynylene)[20] have been demonstrated to fold into helical structures. While the vast majority of reports on helical foldamers still deal with their design, synthesis, and structural characterization, some biological studies have recently been reported describing the promising therapeutic potential of this class of molecules, particularly β-peptides[2,21−28] and peptoids.[29−32]

In our group, we have been focusing on aromatic oligoamides that fold into helical conformations due to hydrogen bonds between the protons of the amide functionality and the endocyclic nitrogens of the adjacent aromatic rings, repulsive electrostatic interactions between these nitrogen atoms and the amide oxygens, and additional stabilization by aromatic interactions within the helix.[17,18] These structures have advantageous properties such as tunability, predictability, and ease of synthesis, as no chiral building blocks are involved. In addition, their helical conformations are exceptionally stable. Hydroxy-substituted oligopyridine dicarboxamides have been shown to form stable helices in water,[33] and oligomers of a quinoline-derived amino acid remain folded at 120 °C in DMSO.[18,34] Thus far, helices based on aromatic amino acid monomers have not yet been functionalized with polar peptide-like side chains for biological applications, but their unique structures and properties relative to α-peptides and aliphatic synthetic analogues may provide new opportunities for structure−activity relationships in biological systems and for the development of therapeutics. For example, while the helical folding of peptoids[8,9,11,12] and β-peptides[35−38] is often dependent on the side-chain functionality and oligomer length, we expect the helical conformation of the aromatic oligoamides not to vary much with these parameters; helix stability does increase with oligomer length, but the shortest oligomers already possess well-defined and stable conformations similar to those of longer oligomers. Thus, a property of a folded oligomer may be directly related to the presence or absence of a given side chain.

Amphipathic helices are promising initial targets for the exploration of biological activity in synthetic foldamers, as they are implicated in a variety of biological functions of therapeutic relevance. For example, naturally occurring α-peptide antibiotics such as magainins[39] and cecropins[40] are believed to assume amphipathic helical conformations in the presence of bacterial cell membranes, leading to membrane disruption.[41−47] In addition, an amphipathic helix of apolipoprotein A-1 has been shown to be the key structural motif involved in the inhibition of facilitated cholesterol transport across the brush border membrane in the small intestines.[48,49] Furthermore, an amphipathic α-helix or β-sheet structure is a common motif to the binding sites of proteins whose activities are modulated by heparin.[50] Thus far, synthetic foldamers have successfully been designed to mimic the roles of the amphipathic helices in these systems,[21−25,27,51−53] but many questions related to the effect of

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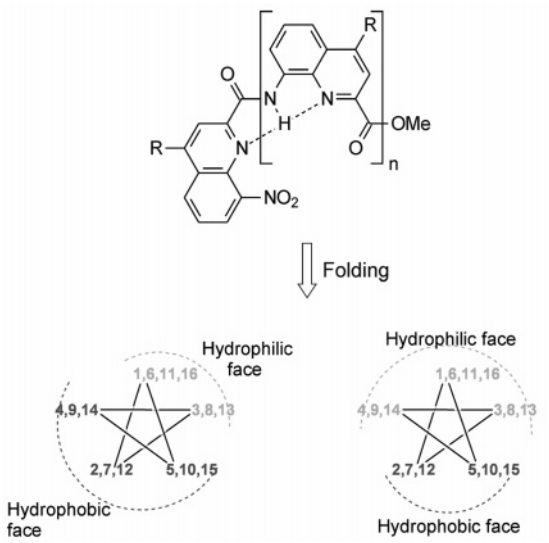

FIGURE 1. Design of a facially amphipathic quinoline-derived helical oligoamide having 2.5 units per turn. Hydrophilic residues are represented in light gray and hydrophobic residues are represented in dark gray.

structure on their efficacy and mechanism of action still exist. Here we report a novel series of amphipathic helices composed of quinoline-derived amino acids. The introduction of peptide-like side chains to these oligomers provides the first possibility for the evaluation of this class of foldamers in biological applications.

Results and Discussion

Design. On the basis of data from X-ray crystallography[18,34] and solution NMR,[54] we have previously determined that as a result of hydrogen bonding between the amide protons and the nitrogens of adjacent aromatic rings, as well as aromatic interactions, quinoline-derived oligoamides fold into helices having close to 2.5 residues per turn, where residue *i* is placed above residue $i + 5$. Therefore, looking end-on down the helix, as illustrated in Figure 1, it was possible to design two simple amphipathic analogues of these helices: one having a larger hydrophobic face and the other having a larger hydrophilic face. The simplest versions of these analogues require only two different quinoline monomers. A quinoline monomer having an isobutoxy side chain was selected as the hydrophobic monomer, a mimic of leucine, while a monomer having an aminopropoxy side chain was chosen as the hydrophilic monomer, a mimic of lysine. The amino group is expected to be protonated and, thus, positively charged at neutral physiological pH. A cationic face is a common feature of biomimetic amphipathic helices exhibiting biological activity.[21−25,27,51−53]

Synthesis. While oligomers of quinoline monomers bearing isobutoxy side chains had previously been prepared in our group, the preparation of the proposed oligomers consisting of two different monomers required a new synthetic approach. Because quinoline oligoamides are currently prepared using solution chemistry,[34] it is desirable to use the most convergent approach possible, using the minimum number of building blocks to

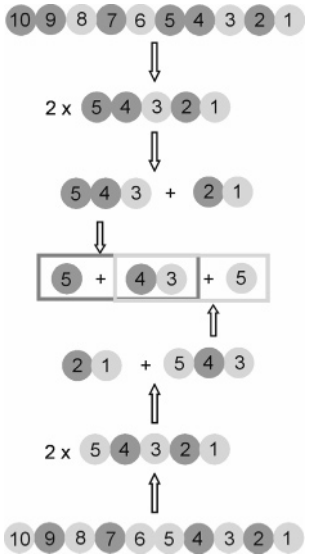

FIGURE 2. Retrosynthetic analysis of two amphipathic quinoline decamers: one having a larger hydrophobic face (above) and another having a larger hydrophilic face (below). Both sequences can be prepared from two monomers and a single dimer. Hydrophilic residues are shaded in light gray while hydrophobic residues are shaded in dark gray.

prepare both the series of helices having the larger hydrophobic face and the series having the larger hydrophilic face. As shown in Figure 2, retrosynthetic analysis of the proposed amphipathic sequences reveals that an amphipathic decamer can be dissected into two identical pentamers, while the pentamer can ultimately be dissected into two identical dimers and a monomer. The constituting dimer is the same in both series of helices, while the monomer completing the pentamer is different in each case. Thus, the first step in the synthesis was to prepare significant quantities of the requisite monomer and dimer building blocks.

A trifluoroacetamide protecting group was chosen for the pendant amine group of the hydrophilic monomer, because experience in our group has shown that the preparation of quinoline oligomers generally requires the activation of the monomer or oligomer acids to acid chlorides. As this has been accomplished in our group by heating the acids in refluxing thionyl chloride, it is desirable to use a protecting group that is very resistant to acid. Thus, the quinolone **1**[55] was converted to the protected hydrophilic monomer **2**, by introduction of the trifluoroacetamide-protected aminopropoxy side chain under Mitsunobu conditions, as shown in Scheme 1. Monomer **2** could then be reduced to the corresponding amine **3** by hydrogenation of the nitro group and subsequently coupled with the previously reported quinoline acid **4**,[34] following the acid's activation with thionyl chloride, to provide the dimer **5** (Scheme 2), the structure of which was confirmed by single-crystal X-ray crystallography (see Supporting Information). The preparation of key intermediate **5** is described in the Experimental Section on a 1.5-g scale, but synthetic procedures could easily be scaled up, all the more easily as none of them involve chromatographic purification.

With the required dimer in hand, one possible approach to the pentamer was to couple two dimers to form a tetramer then add the fifth monomer. One drawback to this approach is that we have found that the activation of quinoline acids is frequently

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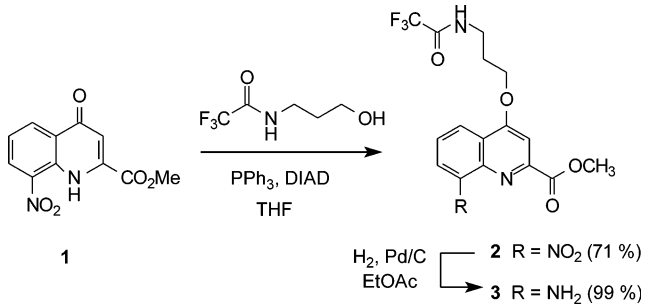
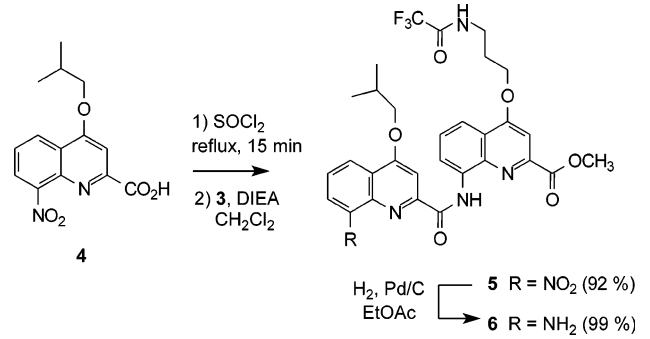
SCHEME 1



SCHEME 2 [a]

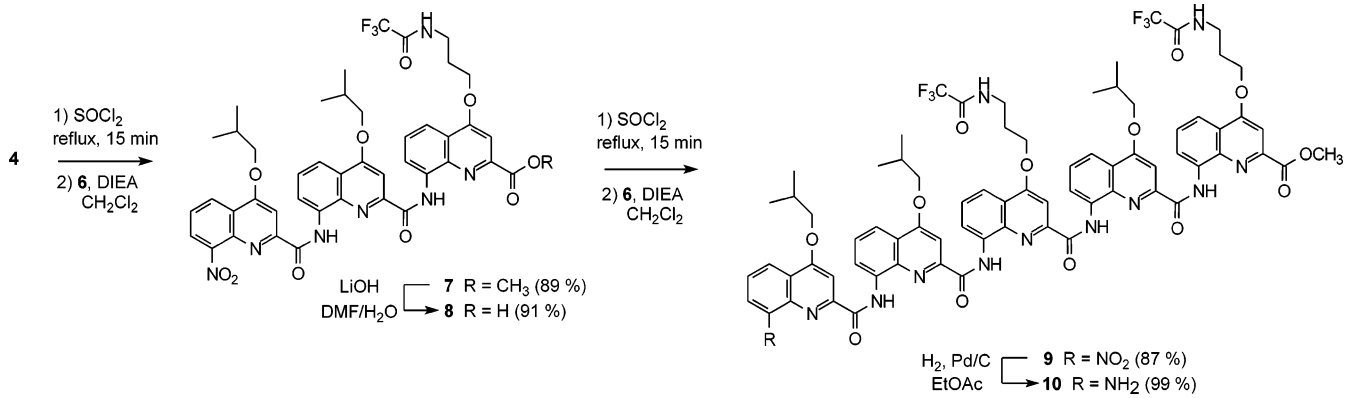


[a] Note that all amide functions are trans in the folded oligomers, but for the purpose of structure clarity, they are shown as cis conformers in the schemes.

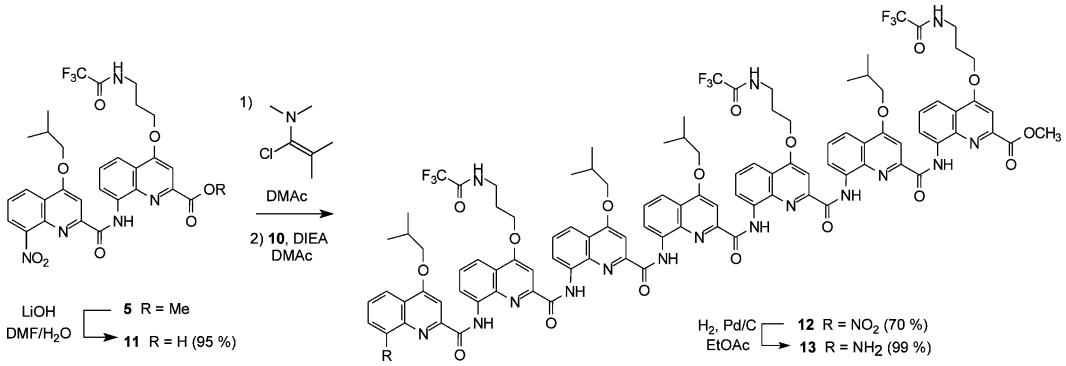
accompanied by the formation of a small amount of the symmetrical anhydride,[56] which is resistant to coupling or hydrolysis due to folding. In the case of coupling two dimers to form the tetramer, both the desired product and the anhydride impurity consist of four residues, making purification difficult by chromatography or cystrallization. Therefore, the 3 + 2 strategy toward the pentamer was explored. The dimer **5** was reduced to the corresponding amine **6** and was coupled with **4** to form the trimer **7**, as illustrated in Scheme 3. The ester group of **7** was selectively saponified using LiOH in 10:1 DMF/H_2O at 0 °C to provide the acid **8**. The base-sensitive trifluoroacetamide protecting group remained intact under these relatively mild conditions. The trimer acid was then activated to the acid chloride in thionyl chloride and coupled with the amine **6** to form the pentamer **9**.

While the most convergent approach to the decamer would involve the coupling of two pentamers, it was not possible to obtain the desired pentamer acid. As the length of the oligomers increases, folding appears to make the saponification of the terminal ester group more difficult. Thus, under the conditions required for the ester hydrolysis, the trifluoroacetamide groups were also cleaved. However, the decamer can be prepared by adding first dimer, then trimer to the pentamer amine **10**. The dimer **5** can be converted to the acid **11** using LiOH in 10:1 DMF/H_2O at 0 °C, but activation to the corresponding acid chloride using thionyl chloride is not possible due to the poor solubility of **11** in thionyl chloride. Prolonged heating of **11** in thionyl chloride leads to eventual dissolution and acid chloride formation, but this is accompanied by the formation of significant quantities of byproducts involving chlorination of the quinoline aromatic ring. Standard peptide coupling agents such as HBTU/HOBT, PyBOP, PyClOP, PyBrOP, and HCTU were surveyed but did not lead to efficient coupling. Fortunately, it was found that the dimer **5** could be efficiently activated to the corresponding acid chloride under mild conditions using the Ghosez reagent (1-chloro-*N*,*N*,2-trimethylpropenylamine).[57] While this reagent has typically been used for activation to acid

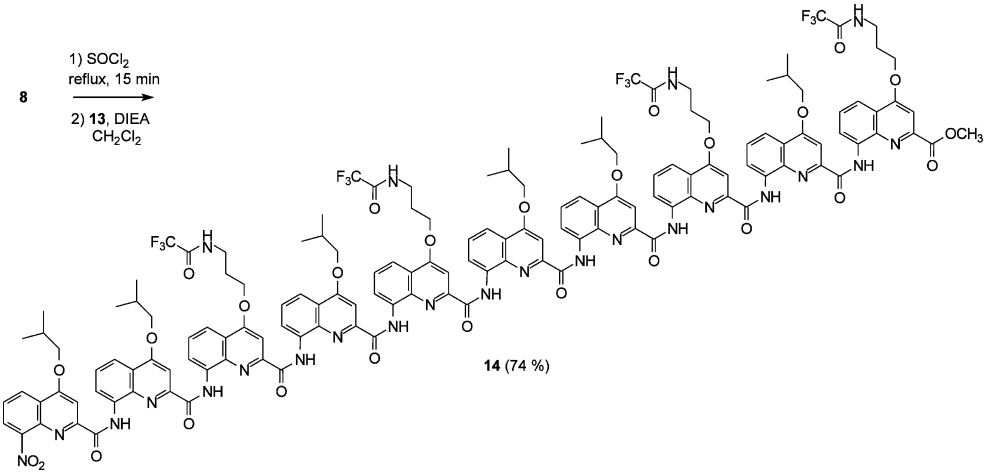
SCHEME 3



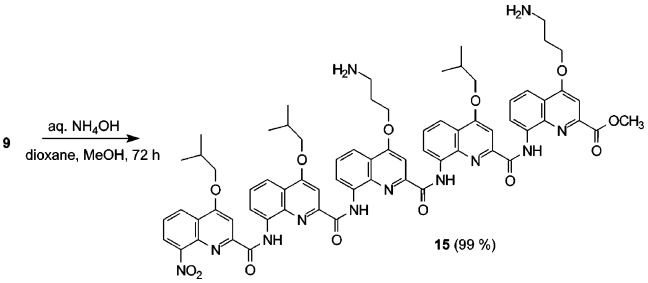
SCHEME 4



SCHEME 5



SCHEME 6



chlorides in nonpolar solvents, such as dichloromethane, in which **11** is not soluble, we found that the activation of **11** can be performed efficiently in *N*,*N*-dimethylacetamide (DMAc). The success of the Ghosez reagent in the activation of quinoline oligomer acids is an important synthetic step as the mild, nonacidic conditions that it requires should allow for the incorporation of a wide range of quinoline amino acids, having functional side chains with a variety of protecting groups, including the widely used BOC group. Thus, coupling of the pentamer amine **10** with **11** provides the heptamer **12**, as shown in Scheme 4, while the subsequent reduction to the amine **13** and coupling with **8** gives the decamer **14** (Scheme 5).

The final step in the preparation of the target amphipathic helices was removal of the trifluoroacetamide protecting groups. In this transformation, it is desirable to either completely saponify the terminal ester group or leave it completely intact. As described above, this ester becomes increasingly resistant to saponification as oligomer length increases. After surveying various conditions, it was found that using aqueous ammonium hydroxide in dioxane/methanol made it possible to selectively hydrolyze the trifluoroacetamides of pentamer **9**, heptamer **12**, and decamer **14**, leaving the esters intact to provide the corresponding amphipathic helical oligomers **15**, **16**, and **17**. An example showing the conversion of pentamer **9** to **15** is given in Scheme 6. These targets belong to the target series having a larger hydrophobic face. The amphipathic helices having a larger hydrophilic than hydrophobic face were prepared by an analogous strategy (see Supporting Information), providing the pentamer **18**, heptamer **19**, and decamer **20**. The general structures of each target amphipathic helix are given in Table 1.

Structure Characterization. The structures of the dimer **5** (see Supporting Information), heptamer **12**, and decamer **14** were characterized in the solid state by single-crystal X-ray diffraction (Table 2). As observed for the previously prepared quinoline dimer having two isobutoxy side chains, **5** assumes a crescent-shaped conformation, where the aromatic, amide, and

TABLE 1. Quinoline Side-Chain Identities in the Amphipathic Helical Targets[a]

	compound number					
residue number[b]	**15**	**16**	**17**	**18**	**19**	**20**
1	*o*	*o*	*o*	*i*	*o*	*i*
2	*o*	*i*	*o*	*o*	*i*	*o*
3	*i*	*o*	*i*	*i*	*i*	*i*
4	*o*	*o*	*o*	*o*	*o*	*o*
5	*i*	*i*	*i*	*i*	*i*	*i*
6		*o*	*o*		*o*	*i*
7		*i*	*o*		*i*	*o*
8			*i*			*i*
9			*o*			*o*
10			*i*			*i*

[a] Methyl ester and nitro end groups are conserved, as shown in Scheme 6. $i = -O(CH_2)_3NH_2$ (hydrophilic side chain), $o = -OCH_2CH(CH_3)_2$ (hydrophobic side chain). [b] Residues are numbered starting from the nitro terminus.

TABLE 2. Crystallographic Parameters for the Structures Determined

	5	**12**	**14**
formula	$C_{30}H_{28}F_3N_5O_8$	$C_{102}H_{94}F_9N_{17}O_{20}$ $(C_3H_7NO)_3$	$C_{145}H_{134}F_{12}N_{24}O_{27}$ $(CH_3OH)_7$ $(H_2O)_2$
FW (g mol^{-1})	643.57	2268.23	3133.09
dimensions (mm)	0.20 × 0.15 × 0.15	0.15 × 0.20 × 25	0.20 × 0.15 × 0.10
color	yellow	yellow	yellow
cryst syst	monoclinic	triclinic	triclinic
space group	$P2_1/c$	P1	P1
a (Å)	8.568(3)	10.6083(4)	17.0458(3)
b (Å)	36.381(7)	21.8311(5)	21.4658(3)
c (Å)	9.457(6)	24.3418(11)	21.6536(5)
α (°)	90	86.317(4)	89.712(2)
β (°)	98.27(2)	89.074(4)	78.770(2)
γ (°)	90	83.529(3)	80.944(2)
volume (Å^3)	2917(2)	5589.6(4)	7671.8(2)
ρ (g cm^{-3})	1.465	1.348	1.356
temp (K)	163(2)	153(2)	153(2)
radiation	Cu Kα	Cu Kα	Cu Kα
λ (Å)	1.541 78	1.541 78	1.541 78
θ measured (°)	4.86 to 72.49	6.38 to 72.75	6.35 to 58.93
refl. measured	33 260	57 436	82 569
refl. unique	5117	19 772	18 982
GOF	1.124	1.063	1.066
R_1 ($I > 2\sigma(I)$)	0.0573	0.1427	0.1136
wR_2 (all data)	0.1926	0.5164	0.4387

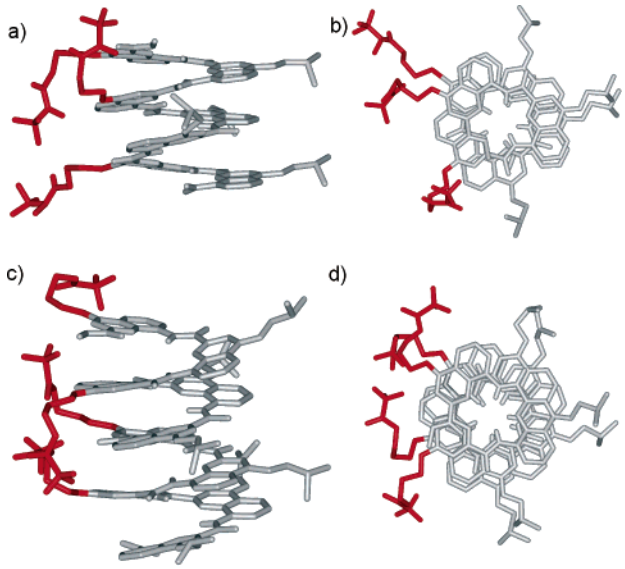


FIGURE 3. Crystal structures of **12** (a and b) and **14** (c and d). Included solvent molecules and hydrogens of the side chains and aromatic rings have been omitted for clarity. In (a) and (c), the views are nearly parallel to the planes of the aromatic rings, while in (b) and (d), the views are nearly parallel to the helix axis.

ester moieties are nearly coplanar. The amide proton is hydrogen bonded to the two nitrogens of the quinoline rings, while the carbonyl of the amide and ester groups are pointing away from the quinoline nitrogens. The crystal structures confirm that **12** and **14** fold into helices in the solid state with close to 2.5 units per turn, as expected. The amido protons are hydrogen bonded to adjacent quinoline nitrogens and they fill the helix hollow, preventing the penetration of solvent molecules. Most importantly, as shown in Figure 3, these solid-state structures verify our design principles by illustrating that the hydrophobic isobutoxy side chains diverge from one face of the helix and the protected aminopropoxy side chains diverge from the other face. Specifically, the top view of the structure of decamer **14** (Figure 3d) clearly shows that the 10 residues protrude from the helix along only five directions. To the best of our knowledge, these are the first examples of X-ray crystal structures of nonalpha peptidic amphipathic helices or their precursors. In alpha peptides, amphipathic helices are often associated with the formation of bundles. However, no well-defined discrete assembly of helices could be identified in the crystal structures of **12** and **14**.

Since our first reports of quinoline oligoamide foldamers, detailed NMR studies have been carried out to verify that the solution structures of these molecules correspond to those observed in the solid state.[54] Key features of the ^{1}H NMR spectra (in $CDCl_3$) of the oligomers reported here correspond well with those of the previously reported oligomers. For example, the signals assignable to the amido protons are spread over a remarkably large range of chemical shifts, suggesting different chemical environments for each unit, and they are shifted relatively far downfield (10.5−12.2 ppm), consistent with the hydrogen-bonded structures. As the lengths of the oligomers increase, signals from the amide, aromatic, and ester C*H*$_3$ protons shift upfield as a result of shielding by nearby aromatic rings. In addition, for oligomers of pentamer length and longer, the signals from the OC*H*$_2$ groups of the side chains appear as diastereotopic motifs, indicative of chiral conformations that undergo inversion slowly on the NMR time scale.

NMR studies were also previously performed to demonstrate the high helical stability of a quinoline oligoamide octamer in DMSO, even at 120 °C. These results suggested that it might be possible to obtain stable helices, even in protic solvents such as MeOH and H_2O. However, solubility limitations due to the hydrophobicity of the side chains did not permit these studies. The introduction of the hydrophilic aminopropoxy side chains in the amphipathic helices reported here provided the possibility for the evaluation of helical stability in protic solvents. Therefore, ^{1}H NMR spectra of the amphipathic pentamer **18** with its sidearms as free bases (unprotonated) were obtained in $CDCl_3$ with increasing percentages of CD_3OD. In pure $CDCl_3$, the peaks are somewhat broad, indicative of nonspecific aggregation arising from their amphipathic structures and possible partial protonation of the amines by residual acid from the chloroform. The addition of only 5% CD_3OD produces sharp peaks, likely a result of the solvation of the hydrophilic side chains. As the percentage of CD_3OD is increased to 90%, no dramatic changes are observed in the spectrum. Diastereotopic motifs are still observed for the OC*H*$_2$ groups of the side chains, indicating that the molecules are still in a chiral conformation. Remarkably, even at high concentrations of CD_3OD, exchange of the amide protons with deuterium is slow, and the rate is different for each proton. For example, after approximately 1 h, one of the amide protons is completely exchanged, while another amide proton is 80% unexchanged. This is indicative of different chemical environments for each amide proton in the folded helices. Poor solubility of the amphipathic quinoline oligomers prohibits their structural evaluation in 100% CD_3OD, but overall, it appears that methanol does not lead to helix destabilization when the sidearms are not protonated.

Experiments were also performed on the fully protonated form of pentamer **18**. While the hydrochloride salts of the amphipathic helices reported here are not soluble in 100% water at the concentrations required for NMR, the hydrochloride salt of pentamer **18** was dissolved in DMSO-d_6, and D_2O was gradually added. As shown in Figure 4, the peaks in pure DMSO-d_6 are somewhat broad and are sharpened upon the addition of D_2O. At higher concentrations of D_2O (≈50%), the peaks again begin to slightly broaden, indicating aggregation in water presumably a result of the hydrophobic side chains. Consistent with this hypothesis, the peaks sharpen again upon diluting the sample while keeping the concentration of D_2O constant. At a D_2O concentration of 80%, the highest concentration investigated, the helical conformation appears to be retained, as indicated by the diastereotopic motifs from the OC*H*$_2$ groups of the side chains. In addition, as the solvent is gradually changed from pure DMSO-d_6 to 80/20 D_2O/DMSO-d_6, signals from the amide protons shift farther upfield by approximately 0.5 ppm, and exchange of all amide protons with deuterium is very slow. Various aromatic protons on the quinoline ring also shift upfield ($\Delta\delta \approx 0.5$), and the signal from the C*H*$_3$ group of the terminal methyl ester gradually shifts from 3.2 to 2.8 ppm.

In contrast, when the amphipathic decamer **20** is dissolved in DMSO-d_6 and D_2O is gradually added up to 80%, no significant upfield shifts of the signals of the analogous protons on this molecule are observed. This suggests that the upfield

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(57) Ghosez, L.; Haveaux, B.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 454−455.

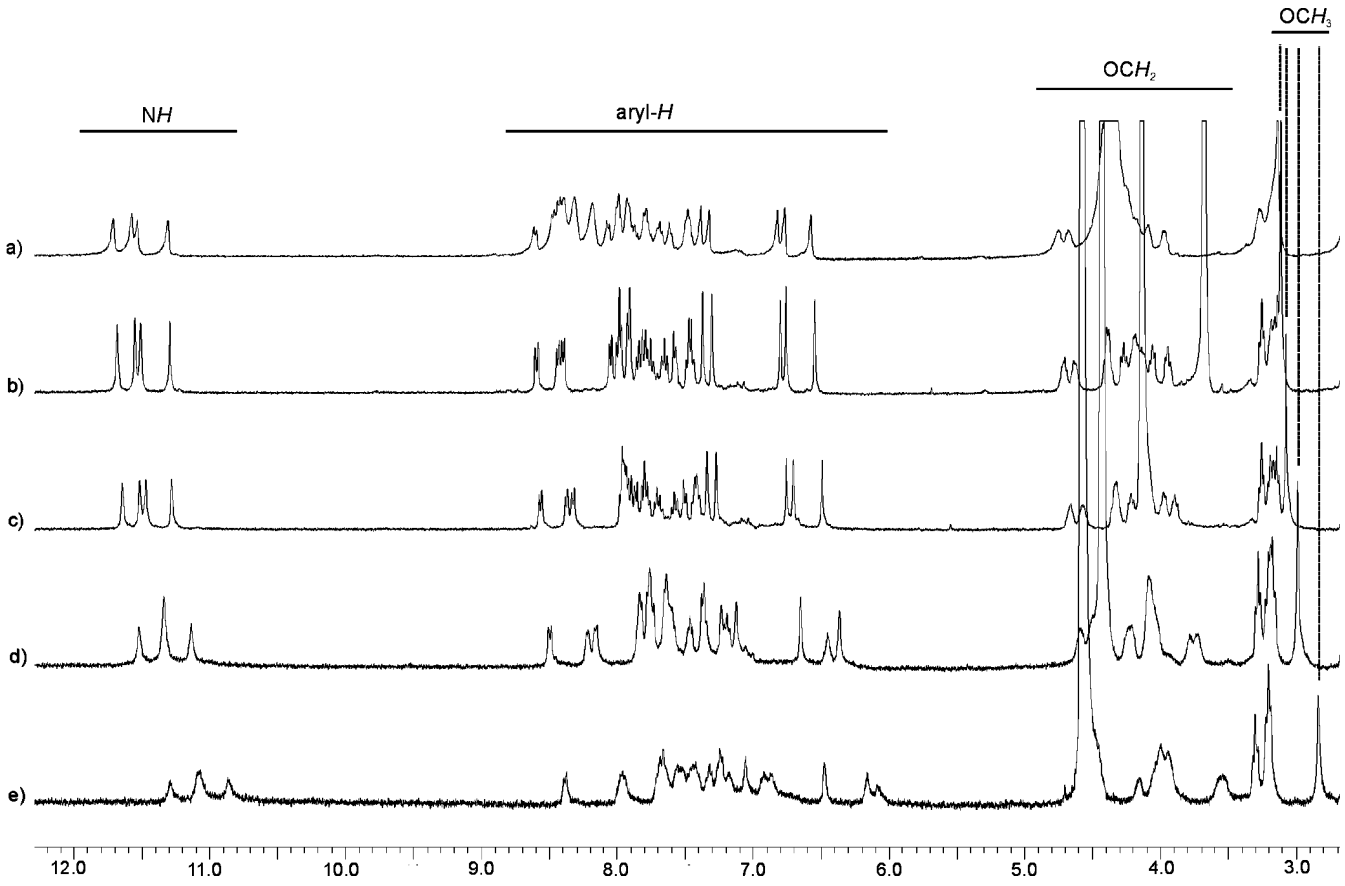

FIGURE 4. Part of the ^{1}H NMR (400 MHz) spectrum of **18** in DMSO-d_6, with increasing amounts of D_2O added: (a) pure DMSO-d_6, (b) 10% D_2O, (c) 30% D_2O, (d) 50% D_2O, and (e) 80% D_2O. Chemical shift values are given in ppm.

shifts observed for the pentamer are due to increased shielding by the aromatic rings as the helical conformation becomes more stable. Changes are not observed for the decamer because this molecule, in contrast to the pentamer, already adopts a highly stable helical conformation in pure DMSO, and the signals for the amide, aromatic, and ester OC*H*$_3$ protons are already at similar chemical shifts to the signals observed for the pentamer **18** at high D_2O concentrations. Thus, it appears that the helices are even more stable in water than in organic solvents! The formation of stable helices in water is noteworthy for oligoamide foldamers, particularly for short oligomers such as the pentamer investigated here. However, it is not unreasonable considering that, in addition to hydrogen bonding, these quinoline oligomers are favored to fold into helices as a result of aromatic interactions between the quinoline rings, which should become stronger in protic solvents as solvophobic terms dominate. Such solvent effects have previously been observed for foldamers based on aromatic units, where aromatic stacking is promoted by solvophobic interactions.[20,58,59] An additional feature of our quinoline oligomers that may contribute to their high stability in a variety of solvents is the fact that the helix hollow is inaccessible to solvent molecules, thus protecting the hydrogen-bonding motif from competing interactions with polar solvent molecules.

Conclusions

Here we reported the synthesis of a new series of amphipathic helices based on quinoline oligoamides having hydrophilic aminopropoxy side chains on one face and hydrophobic isopropoxy groups on the other face. Relative to previously investigated amphipathic helices, we believe that these molecules provide exceptional helical stability and rigidity as a result of their aromatic structures. This helical stability was demonstrated even for an oligomer as short as a pentamer, which spans two helical turns, in 80/20 D_2O/DMSO-d_6. The introduction of peptide-like side chains as described here opens the possibility for the first biological evaluations of aromatic oligoamide foldamers, and it is hoped that their unique structures and properties will provide new structure−activity relationships. As amphipathic helices are implicated in a wide variety of biological processes ranging from cholesterol transport to membrane disruption, these molecules are versatile initial targets. The application of our amphipathic helical quinoline oligoamides in several therapeutic areas is currently being explored. Future work will additionally focus on synthetic methods for the incorporation of a variety of peptide-like side chains and for improving the solubility of the helices in pure water.[60]

Experimental Section

Monomer 2. The quinolone **1**[55] (8.0 g, 32 mmol, 1.0 equiv), triphenylphosphine (PPh_3; 9.3 g, 35 mmol, 1.1 equiv) and hydroxy-

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(59) Sindkhedkar, M. D.; Mulla, H. R.; Worth, M. A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991−2996.
(60) For an example of a short folded oligomer in water, see: Formaggio, F.; Crisma, M.; Rossi, P.; Scrimin, P.; Kaptein, B.; Broxterman, Q. B.; Kamphuis, J.; Toniolo, C. *Chem.—Eur. J.* **2000**, *6*, 4498−4504.

propyltrifluoroacetamide[61] (6.1 g, 35 mmol, 1.1 equiv) were combined under argon and then partially dissolved in dry THF (80 mL). The reaction mixture was cooled to 0 °C, and then diisopropylazodicarboxylate (DIAD; 7.2 mL, 35 mmol, 1.1 equiv) was added. The reaction mixture was stirred at 0 °C for 30 min and then was allowed to come to room temperature and stirred overnight. The reaction progress was monitored by TLC (90/10 toluene/EtOAc) and, when necessary, an additional 0.15 equiv of PPh_3 and DIAD were added. The reaction mixture was stirred for an additional night. The reaction mixture was evaporated, and the product was recrystallized from 150 mL of 3/1 MeOH/$CHCl_3$ to provide 9.2 g (71% yield) of **2** as pale brown crystals: mp 188.8−190.2 °C. IR ($CHCl_3$ solution) ν_{max}: 1732, 1540 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.11−2.19 (m, 2H), 3.47−3.52 (m, 2H), 3.96 (s, 3H), 4.23 (t, 2H, J = 5.4 Hz), 7.64 (s, 1H), 7.83 (t, 1H, J = 7.9 Hz), 8.34 (d, 1H, J = 7.6 Hz), 8.43 (d, 1H, J = 8.6 Hz), 9.53−9.60 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 28.5, 37.1, 55.9, 67.9, 103.4, 116.8 (q, J = 288 Hz), 123.1, 125.3, 126.4, 127.8, 139.6, 149.1, 151.7, 157.2 (q, J = 36 Hz), 163.0, 165.7. MS calcd $[M + H]^+$ ($C_{16}H_{15}N_3O_6F_3$), 402.0913; found (TOF MS ES+), 402.0905.

Monomer Amine 3 and General Procedure for the Nitro Group Reduction. Compound **2** (2.0 g, 5.0 mmol) was dissolved in 400 mL of EtOAc, and 200 mg of 10 wt % Pd/C was added. The reaction was stirred under a hydrogen atmosphere overnight. Progress was monitored by TLC and NMR, and an additional 10 wt % of Pd/C was added if necessary to complete the reaction. Upon completion, the catalyst was removed by filtration over Celite, and the filtrate was evaporated to provide 1.9 g (99% yield) of the amine **3** as a yellow solid. IR ($CHCl_3$ solution) ν_{max}: 3427, 1726, 1645, 1546, 1509 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.08−2.14 (m, 2H), 3.42−3.46 (m, 2H), 3.95 (s, 3H), 4.32 (t, 3H, J = 5.6 Hz), 6.03 (s, 1H), 6.94 (d, 1H, J = 7.3 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.45 (s, 1H), 9.46−9.60 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 28.7, 37.2, 53.4, 66.9, 101.5, 107.9, 110.7, 116.8 (q, J = 288 Hz), 123.1, 129.9, 138.0, 145.9, 146.9, 157.2 (q, J = 36 Hz), 162.5, 166.4. MS calcd $[M + H]^+$ ($C_{16}H_{17}N_3O_4F_3$), 372.1171; found (TOF MS ES+), 372.1176.

Dimer 5 and General Procedure for Coupling Using Thionyl Chloride Activation. The acid **4** (0.86 g, 3.0 mmol, 1.0 equiv) was heated at reflux in $SOCl_2$ (11 mL, 150 mmol, 50 equiv) for 15 min and then cooled in an ice bath, and the excess $SOCl_2$ was removed in vacuo to provide the corresponding acid chloride. To a suspension of amine **3** (0.88 g, 2.4 mmol, 0.8 equiv) in dry CH_2Cl_2 (20 mL) and diisopropylethylamine (DIEA; 1.0 mL, 5.9 mmol, 2.0 equiv) was added the acid chloride in CH_2Cl_2 via cannula. The reaction mixture was stirred at room temperature overnight, resulting in complete dissolution of the amine. The solvent was evaporated, and the product was purified by recrystallization from $CHCl_3$/MeOH to provide 1.4 g (92% yield) of the dimer **5** as pale brown crystals: mp 212.2−213.7 °C. IR ($CHCl_3$ solution) ν_{max}: 3435, 1720, 1639, 1520 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.06 (d, 6H, J = 6.6 Hz), 2.10−2.19 (m, 3H), 3.44−3.52 (m, 2H), 4.09 (s, 3H), 4.13 (d, 2H, J = 6.4 Hz), 4.37 (t, 2H, J = 5.5 Hz), 7.53 (s, 1H), 7.65 (t, 1H, J = 8.0 Hz), 7.74 (s, 1H), 7.79 (t, 1H, J = 7.9 Hz), 7.85 (d, 1H, J = 8.0 Hz), 8.37−8.40 (m, 2H), 8.93 (d, 1H, J = 7.6 Hz), 9.56 (t, 1H, J = 5.1 Hz), 11.51 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.7, 28.4, 28.6, 37.2, 54.0, 67.3, 76.0, 101.0, 102.3, 116.8 (q, J = 288 Hz), 117.0, 118.5, 122.2, 123.2, 126.5, 126.9, 127.5, 128.7, 135.1, 138.9, 139.2, 148.2, 149.1, 153.7, 157.2 (q, J = 36 Hz), 162.4, 162.8, 163.6, 167.0. MS calcd $[M + H]^+$ ($C_{30}H_{29}N_5O_8F_3$), 644.1968; found (TOF MS ES+), 644.1938.

Trimer Acid 8 and General Procedure for Saponification Using LiOH. The trimer **7** (0.65 g, 0.73 mmol, 1.0 equiv.) was dissolved in DMF (14 mL), and the solution was cooled to 0 °C. LiOH·H_2O (62 mg, 1.5 mmol, 2.0 equiv) in H_2O (1.4 mL) was added, and the reaction mixture was stirred at 0 °C overnight. An additional 2.0 equiv of LiOH·H_2O was added, and the reaction mixture was stirred for another 24 h at 0 °C. The reaction mixture was acidified with 1 M HCl and then diluted with H_2O at room temperature. The resulting precipitate was filtered off and then purified by silica gel chromatography using 90/10 CH_2Cl_2/EtOAc to elute a small amount of starting material, followed by 98/2 CH_2Cl_2/MeOH to elute the product, providing 0.59 g (91% yield) of **8** as a yellow solid. IR ($CHCl_3$ solution) ν_{max}: 3310, 1739, 1695, 1670, 1590, 1565, 1527, 1509 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.15 (d, 6H, J = 6.8 Hz), 1.19 (d, 6H, J = 6.8 Hz), 2.10−2.15 (m, 2H), 2.28−2.34 (m, 2H), 3.50−3.55 (m, 2H), 4.14 (t, 2H, J = 5.6 Hz), 4.29 (d, 2H, J = 6.4 Hz), 4.33 (d, 2H, J = 6.4 Hz), 6.69 (s, 1H), 7.55 (t, 1H, J = 7.8 Hz), 7.64 (d, 1H, J = 7.8 Hz), 7.74 (t, 1H, J = 8.0 Hz), 7.80 (s, 1H), 7.83 (s, 1H), 7.86 (d, 1H, J = 8.3 Hz), 8.04 (d, 1H, J = 8.3 Hz), 8.46 (d, 1H, J = 8.3 Hz), 8.88 (d, 1H, J = 7.3 Hz), 8.96 (d, 1H, J = 7.8 Hz), 9.63 (t, 1H, J = 4.4 Hz), 11.94 (s, 1H), 12.12 (s, 1H), 12.48 (br s, 1H). ^{13}C NMR (2/1 $CDCl_3$/CD_3OD, 100 MHz): δ 18.8, 27.95, 27.99, 28.05, 36.7, 66.2, 75.1, 75.5, 98.8, 99.4, 99.8, 116.0, 116.8, 118.1, 121.6, 122.2, 123.4, 124.5, 125.5, 127.3, 127.4, 128.2, 134.0, 134.6, 138.7, 138.8, 139.2, 145.4, 145.6, 150.3, 154.0, 162.1, 162.9, 163.0, 163.6, 164.6. MS calcd $[M + H]^+$ ($C_{43}H_{41}N_7O_{10}F_3$), 872.2867; found (TOF MS ES+), 872.2864.

Heptamer 12 and General Procedure for Coupling Using 1-Chloro-*N*,*N*,2-trimethylpropenylamine. The dimer acid **11** (60 mg, 93 μmol, 1.0 equiv) was dissolved in anhydrous DMAc (2 mL) under an argon atmosphere and 1-chloro-*N*,*N*,2-trimethylpropenylamine (62 mg, 460 μmol, 5.0 equiv) was added. The reaction mixture was stirred at room temperature overnight, and then the DMAc and excess reagent was evaporated in vacuo to provide the corresponding acid chloride. To a solution of the amine **10** (100 mg, 70 μmol, 0.75 equiv) in dry CH_2Cl_2 (3 mL) containing DIEA (160 μL, 930 μmol, 10 equiv) was added the acid chloride in dry CH_2Cl_2 via cannula. The reaction mixture was stirred at room temperature overnight, and then the solvent was evaporated. The product was purified by silica gel chromatography using a gradient from 80/20 to 65/35 toluene/EtOAc to provide 100 mg (70% yield) of **12** as a yellow solid. IR ($CHCl_3$ solution) ν_{max}: 3426, 1720, 1677, 1608, 1539 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.07−1.37 (m, 24H), 2.16−2.36 (m, 10H), 3.07 (s, 3H), 3.74−4.04 (m, 11H), 4.09−4.17 (m, 5H), 4.22−4.30 (m, 1H), 4.34−4.42 (m, 2H), 4.50−4.57 (m, 1H), 6.39 (s, 1H), 6.52 (s, 1H), 6.53 (s, 1H), 6.57 (s, 1H), 7.05 (s, 1H), 7.08−7.13 (m, 2H), 7.17−7.28 (m, 4H), 7.35−7.47 (m, 5H), 7.58−7.65 (m, 3H), 7.72 (d, 1H, J = 8.3 Hz), 7.81 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 8.3 Hz), 7.94−7.98 (m, 1H), 8.00−8.03 (m, 2H), 8.08 (d, 1H, J = 7.8 Hz), 8.13 (d, 1H, J = 7.3 Hz), 8.19 (d, 2H, J = 7.8 Hz), 8.40 (d, 1H, J = 7.8 Hz), 11.05 (s, 1H), 11.21 (s, 1H), 11.24 (s, 1H), 11.35 (s, 1H), 11.39 (s, 1H), 11.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3, 19.36, 19.40, 19.48, 19.54, 19.6, 19.7, 27.9, 28.2, 28.27, 28.31, 28.4, 28.7, 29.8, 37.0, 37.5, 39.3, 52.2, 65.8, 66.4, 68.1, 75.1, 75.47, 75.5, 75.7, 97.6, 97.7, 98.5, 98.6, 99.1, 100.0, 100.1, 115.6, 115.9, 116.0, 116.11 (q, J = 288 Hz), 116.16 (q, J = 288 Hz), 116.23, 116.40 (q, J = 288 Hz), 116.41, 116.7, 117.0, 117.2, 117.2, 121.3, 121.4, 121.7, 122.0, 122.3, 122.6, 123.8, 124.1, 125.9, 126.0, 126.3, 126.9, 127.0, 128.1, 128.2, 132.66, 132.72, 133.2, 133.5, 133.86, 133.94, 137.56, 137.62, 137.8, 138.1, 138.4, 138.7, 138.9, 144.7, 144.8, 148.7, 148.9, 149.2, 150.0, 153.1, 157.7 (q, J = 36 Hz), 157.9 (q, J = 37 Hz), 158.0 (q, J = 36 Hz), 159.7, 160.1, 160.2, 160.7, 160.8, 161.0, 162.45, 162.53, 162.9, 163.0, 163.1, 163.2, 164.4. MS calcd $[M + H]^+$ ($C_{102}H_{95}N_{17}O_{20}F_9$), 2048.6796; found (TOF MS ES+), 2048.6523.

Pentamer 15 and General Procedure for the Removal of the Trifluoroacetamide Protecting Groups. The pentamer **9** (50 mg, 34 μmol) was dissolved in 5.0 mL of dioxane, and 7.5 mL of methanol was added, followed by 2.5 mL of 28% w/w aqueous NH_3. The reaction mixture was stirred at room temperature for 72 h, adding an additional 2.5 mL of aqueous NH_3 after the first 24 h

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and an additional 2 mL of dioxane after 48 h to ensure that everything was soluble. The reaction mixture was then diluted with CH_2Cl_2, extracted with water, dried with $MgSO_4$, and evaporated to give 43 mg (99% yield) of **15** as a yellow solid. IR (solution) ν_{max}: 3313, 1683, 1530 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.21−1.31 (m, 18H), 2.10−2.17 (m, 4H), 2.32−2.37 (m, 1H), 2.47−2.53 (m, 2H), 3.07−3.17 (m, 4H), 3.20 (s, 3H), 3.92−3.95 (m, 2H), 4.13−4.21 (m, 4H), 4.24−4.31 (m, 2H), 4.37−4.39 (m, 2H), 6.60 (s, 1H), 6.28 (s, 1H), 6.87 (s, 1H), 7.31−7.41 (m, 3H), 7.47−7.50 (m, 3H), 7.60 (d, 1H, J = 8.6 Hz), 7.64 (d, 1H, J = 8.1 Hz), 7.82 (d, 1H, J = 8.6 Hz), 7.94 (d, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 8.3 Hz), 8.10 (d, 1H, J = 8.6 Hz), 8.17−8.21 (m, 2H), 8.44−8.47 (m, 2H), 8.55 (d, 1H, J = 6.8 Hz), 11.5 (s, 1H), 11.7 (s, 1H), 11.8 (s, 1H), 11.9 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.48, 19.54, 19.58, 19.64, 28.4, 28.5, 29.9, 32.6, 32.7, 39.16, 39.24, 52.2, 66.9, 67.1, 75.4, 75.6, 75.9, 97.4, 98.2, 99.8, 100.5, 115.5, 116.5, 116.6, 116.8, 117.1, 117.3, 117.4, 121.8, 121.9, 122.2, 122.6, 124.1, 124.5, 126.1, 126.7, 126.9, 127.5, 127.9, 128.1, 133.75, 133.85, 134.2, 134.4, 138.2, 138.5, 138.6, 139.2, 139.2, 145.32, 145.34, 149.29, 149.39, 150.6, 153.7, 160.7, 161.0, 161.4, 162.1, 162.3, 163.1, 163.1, 163.3, 163.5, 164.1. MS calcd $[M + H]^+$ ($C_{69}H_{71}N_{12}O_{13}$), 1275.5265; found (TOF MS ES+), 1275.5242.

X-ray Crystallography. Single crystals of dimer **5**, heptamer **12**, and decamer **14** were mounted on a Rigaku R-Axis Rapid diffractometer equipped with a MM007 micro focus rotating anode generator with monochromatized Cu Kα radiation (1.541 78 Å). The data collection, unit cell refinement, and data reduction were performed using the CrystalClear software package. The positions of non-H atoms were determined by the program SHELXS 87, and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined.

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Supporting Information Available: Complete synthesis details, characterization data and NMR spectra of all products, crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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