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Hybrid Foldamers

Synthesis and Conformational Analysis of Quinoline–Oxazole Peptides

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Abstract: The incorporation of flexible aliphatic units into otherwise rigid aromatic foldamer sequences may result in different outcomes. The flexible units may have conformational preferences of their own that can be expressed orthogonally to those of the aromatic units. Alternatively, the latter may dictate their folding behavior onto the former. Hybrid aliphatic–aromatic peptidic oligomers combining oxazole-based (O) and quinoline-based (Q) amino acids have been synthesized, and their folding behavior has been investigated in solution by NMR spectroscopy and CD spectroscopy, and in the solid state by X-ray crystallography. Sequences based on the OQQ repeat motif were shown to fold into a canonical aromatic helix motif dominated by the preferences of the quinoline, whereas sequences based on OQ repetitions preferred to fold into a herringbone helix in which the conformational preference of the oxazole units is also expressed.

Introduction

Foldamers are artificial folded molecular architectures inspired by the structures of biopolymers.[1] They have been the object of much attention because they open the long-term prospect of mimicking and even going beyond the structures and functions of biopolymers. Like their natural peptidic or nucleotidic counterparts, early generations of foldamers were based on the repetition of a common building block decorated with diverse side-chains. Chemists have shown their creativity, providing a broad palette of monomers with a wide range of shapes, conformational preferences, and chemical compositions, thus making a variety of folded structures synthetically accessible. Foldamers have been divided into two categories. Biotic structures are closely related to natural backbones, mostly aliphatic, and include peptidic and nucleotidic structures.[2] Abiotic foldamers do not relate closely to biopolymers, and often have aromatic groups in their main chains.[3] Interestingly, despite the diverse chemical nature of foldamer backbones, the folded secondary structures that have been observed experimentally are less diverse: most of them belong to the canonical folds found for biopolymers: helices, turns, and linear strands. Nevertheless, some unusual and original folding motifs have also been found, such as pillars,[4] knots,[5] or "tail biters".[6] These usually arise when different monomers are combined in the main chain that have distinct, and not necessarily compatible, folding propensities, for example when aromatic and aliphatic building blocks are combined together.[7] The outcome of such combinations may be the prevalence of one folding tendency over the other,[8] or an unconventional conformation that combines the features of both folding tendencies.[9] More often than not, conflicting folding propensities may remain unresolved, resulting in structures that retain a certain degree of disorder.[10]

Oligoamides of 8-amino-2-quinolinecarboxylic acid (Q, see Figure 1) fold into exceptionally robust helices.[11] This folding propensity is so strong that the helix backbone tolerates the presence of a number of aliphatic building blocks, and forces them into the canonical aromatic helical fold.[8] In a recent paper, helical Q_n oligomers were challenged by the incorporation of α-amino acids (X), which have a priori no compatibility with aromatic helices. In the case of $(XQQ)_n$ oligomers, α-amino acids were forced into the aromatic helix motif,[8b,8c] giving rise to a linear array of side-chains at the helix surface. However, in $(XQ)_n$ oligomers, the folding propensities of both types of monomer were combined to give zig-zag tapes.[10a] Similarly, in sequences combining Q and 6-aminomethyl-2-pyridinecarboxylic acid (P), canonical aromatic helices prevail if the Q units are present in sufficient number,[8a] but in $(PQ)_n$ sequences, an unusual "herringbone motif" was characterized in which the benzylic CH_2 of the P units gives rise to 90° angles between adjacent aromatic PQ segments.[9a]

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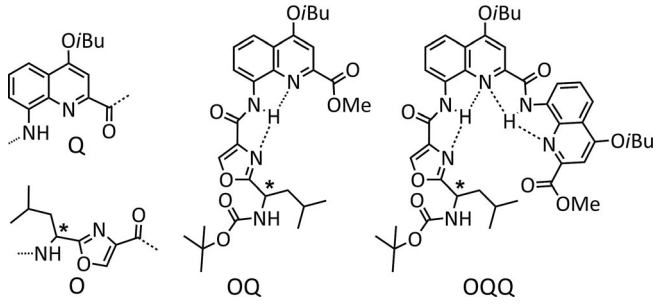


Figure 1. Structures of Q and O monomers and OQ and OQQ oligomers. Unless otherwise noted, oligomers have Boc-amine and methyl ester termini.

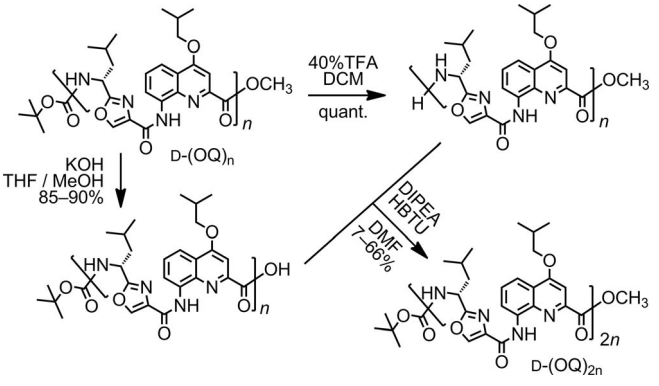
Several reasons can provide motivation for combining different monomer types. One such reason is the curiosity-driven search for unusual folds and the understanding of the principles that govern them. A second reason lies in the fact that the introduction of aliphatic amines greatly facilitates coupling reactions between long aromatic segments.[8a] A third reason is that building blocks such as α-amino acids are commercially available; they allow the easy introduction of a variety of proteinogenic side-chains, thus avoiding the labor-intensive preparation of many aromatic monomers, each bearing a different functionality. This last point is important given the demonstrated potential of aromatic oligoamide sequences bearing particular side-chains to recognize the surface of proteins or nucleic acids.[12]

As a continuation of these efforts, we considered oxazole monomer O (see Figure 1) as an interesting building block to challenge the folding motif of Q_n oligomers. This monomer is no stranger to peptides, being itself derived from a leucine-serine dipeptide,[13] and is a common component of marine natural products.[14] Structurally, O is moderately rigid. Its oxazole ring will not make a significant contribution to aromatic stacking compared to a quinoline, but it does share with the quinoline the presence of an endocyclic nitrogen atom capable of forming hydrogen bonds with amide NH protons, as can be seen in macrocycles composed of several O units.[13] This similarity prompted us to extend the research done with α-amino acids and P units, to prepare $(OQ)_n$ and $(OQQ)_n$ oligomers to study their folding behavior both in solution and in the solid state. As presented below, we found that Q units dominate the folding behavior of $(OQQ)_n$ into aromatic helices, but that $(OQ)_n$ oligomers form "herringbone" motifs in which the O units introduce 90° kinks between adjacent aromatic planes.

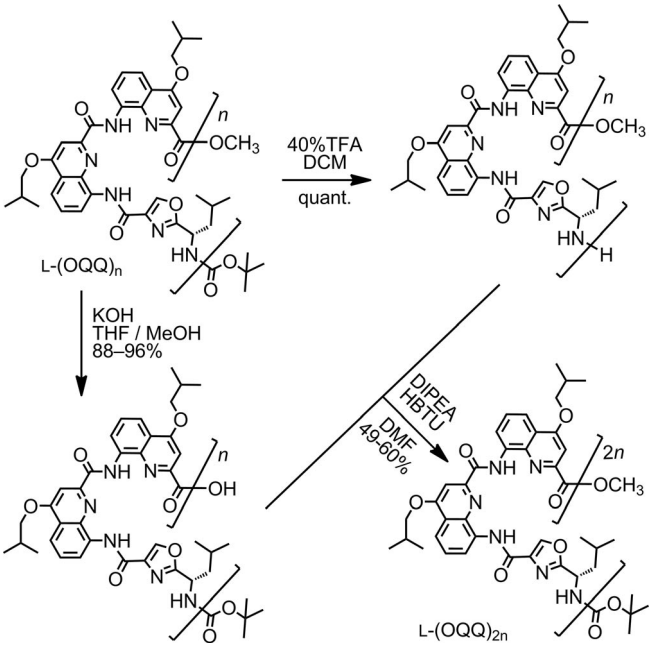
Results and Discussion

Synthesis of $(OQ)_n$ (n = 1, 2, 4, 8) and $(OQQ)_n$ (n = 1, 2, 4)

Monomers Q and O and dimer Q_2 were prepared according to previously described procedures.[15,13a] The main building blocks, OQ and OQQ segments (Figure 1), were obtained by coupling acid chloride BocNH-O-Cl to H_2N-Q or to H_2N-QQ, respectively. As shown in Schemes 1 and 2, oligomer assembly then made use of a segment doubling approach as reported for Q_n oligomers.[15] Each Boc-amine- and methyl-ester-terminated segment was divided in two batches. One was treated with TFA (trifluoroacetic acid) to deprotect the terminal amine. The other was saponified to generate a terminal carboxylic acid. The condensation of these two after HBTU [*N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate] activation yielded a segment twice as long as the original one. Repetition of these deprotection and coupling steps convergently yielded oligomers with up to 16 units in the $(OQ)_n$ series, and 12 units in the $(OQQ)_n$ series. To allow racemic crystallographic investigations,[16] (see below) all syntheses were carried out both in the L and D series. Full characterization is reported in the Supporting Information.



Scheme 1. Synthesis of D-OQ oligomers; DIPEA = diisopropylethylamine, DCM = dichloromethane.



Scheme 2. Syntheses of L-OQQ oligomers.

^{1}H NMR Spectra of $(OQ)_n$ and $(OQQ)_n$

Folding was first investigated in solution by ^{1}H NMR spectroscopy. A typical test that reveals a folding behavior is the oligomer-length-dependence of spectral features.[17] Typical indications of helicity in the canonical helix of $(Q)_n$ include anisochronicity of the signals of diastereotopic isobutoxy CH_2 protons; spreading of aromatic protons over a wide chemical shift range; deshielding of aromatic amide NH protons due to their involvement in intramolecular hydrogen-bonds resulting in signals above δ = 11 ppm; and increasing upfield shifts of the terminal methyl group and amide NH signals as oligomer length increases due to ring-current effects associated with intramolecular π–π stacking.[11]

The NMR spectra of D-$(OQ)_n$ (n = 1, 2, 4, 8) oligomers are shown in Figure 2. The amide resonances from the aromatic amines are found in a narrow region around δ = 10.8 ppm, while those of the aliphatic amines are around δ = 8.6 ppm, similar to the signals found previously[8b] in leucine-QQ oligomers (LQQ). These chemical shift values indicate that both aromatic and aliphatic amides are involved in intramolecular hydrogen bonding. However, upon increasing the oligomer length, the spectra grew in complexity, but no specific trend (in particular no upfield shift of the signals) was observed. In addition, no significant anisochronicity of the diastereotopic isobutoxy CH_2 signals was observed (see Figure S25). All these features are consistent with an absence of canonical aromatic helices in the conformations of D-$(OQ)_n$. Nevertheless, the spectra remained sharp, suggesting either the prevalence of a single conformational state or the fast equilibrium between different states.

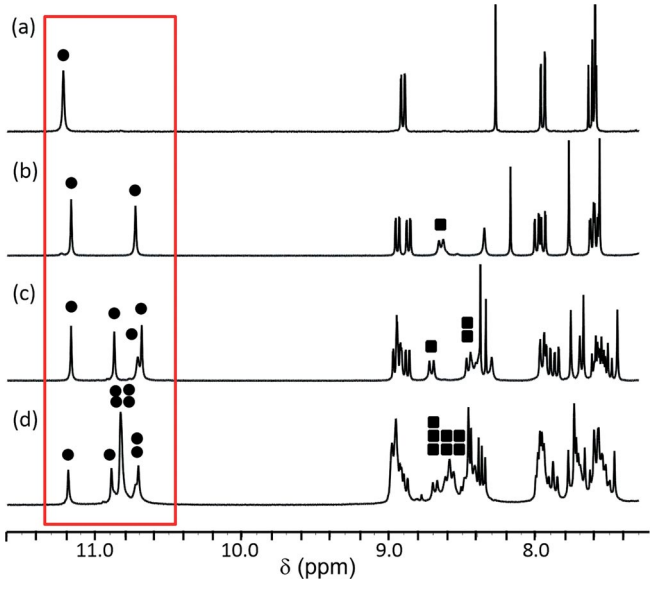


Figure 2. Part of the 300 MHz ^{1}H NMR spectra of D-$(OQ)_n$ (n = 1, 2, 4, 8) in $CDCl_3$ at 25 °C. (a) D-OQ; (b) D-$(OQ)_2$; (c) D-$(OQ)_4$; (d) D-$(OQ)_8$. Circles and squares indicate aromatic and aliphatic NH resonances, respectively.

The NMR spectra of L-$(OQQ)_n$ oligomers contrasted with those of D-$(OQ)_n$ (Figure 3). The aromatic amides were found in two clusters between δ = 9.5 and 12.5 ppm, corresponding to quinoline–quinoline linkages at the lower field, and oxazole–quinoline linkages at the higher field. These signals all underwent an upfield shift of at least 1 ppm when n was increased from 1 to 4. The same change occurred for the amide signals from the aliphatic amines, which can be spotted as slightly broader bands overlapping with aromatic signals. Overall, the signals were well spread out. Additionally, the isobutoxy CH_2 signals are clearly anisochronous (see Figure S39). It became clear then, that the folding behavior of the two oligomer series in solution was different, and that the spectral features of the OQQ oligomers were consistent with a canonical aromatic helix.

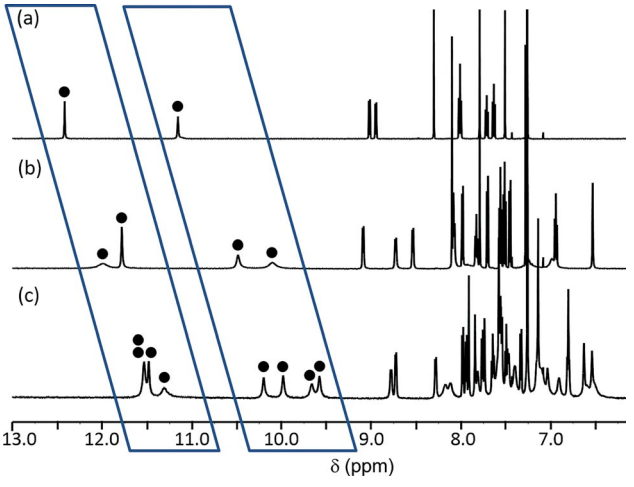


Figure 3. Part of the 600 MHz ^{1}H NMR spectra of L-$(OQQ)_n$ (n = 1, 2, 4) in $CDCl_3$ at 25 °C. (a) L-OQQ; (b) L-$(OQQ)_2$; (c) L-$(OQQ)_4$. Circles indicate aromatic NH resonances.

Circular Dichroism (CD) Spectra of $(OQ)_n$ and $(OQQ)_n$

The conformational behavior of these oligomers was then studied by CD spectroscopy. While D-OQ showed no signal in the 200–400 nm range (Figure 4), D-$(OQ)_n$ (n > 1) showed negative bands over the whole 240–380 nm region, indicating the existence of some chirally biased conformations. The CD patterns differ from those of $(Q)_n$ canonical helices, which feature an intense and distinct band around 380 nm.[18] When the sample

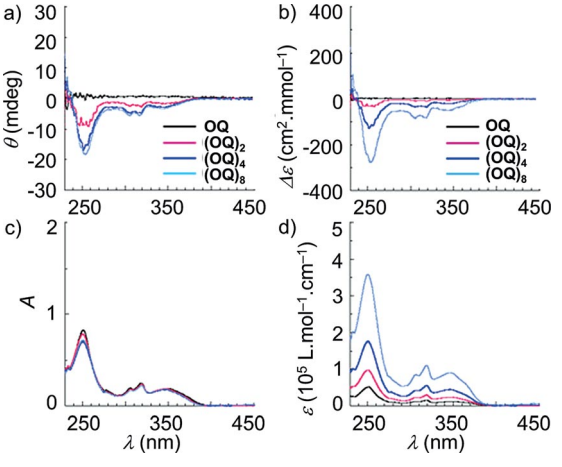


Figure 4. CD (a, b) and UV (c, d) spectra of D-$(OQ)_n$ (n = 1, 2, 4, 8) in $CHCl_3$ at 25 °C. [Concentrations: D-OQ: 8.0×10^{-5} M; D-$(OQ)_2$: 4.0×10^{-5} M; D-$(OQ)_4$: 2.0×10^{-5} M; D-$(OQ)_8$: 1.0×10^{-5} M].

concentration was adjusted such that the concentration per OQ unit was the same for each oligomer, a certain degree of cooperativity was observed: the CD intensity per OQ unit was larger for D-$(OQ)_4$ than for D-$(OQ)_2$. This effect levels off, and the CD intensity does not increase further for D-$(OQ)_8$. Meanwhile, the UV spectra per OQ unit showed a slight hypochromic shift of the absorption band at 250 nm, which could be indicative of π–π stacking. The CD intensity increased slightly when the temperature was decreased from 45 °C to −5 °C, suggesting a better-structured conformation at lower temperatures (Figure S1). Altogether, these results hint at the existence of structured conformations for $(OQ)_n$, and confirm the results suggested by the NMR spectroscopic analysis that these conformations differ from canonical aromatic helices.

The CD spectra of $(OQQ)_n$ (Figure 5) corroborated the trend seen in the NMR spectra: the data are consistent with canonical aromatic helices, and differ markedly from those of $(OQ)_n$. As for D-OQ, L-OQQ showed no Cotton effects in the UV region in $CHCl_3$. Yet a distinct CD spectrum was recorded in acetonitrile (Figure S2). Even though this suggests some kind of conformational order that does not exist in $CHCl_3$, the bands were weak in intensity, and are unlikely to correspond to a well-defined helical conformation. This was not investigated further. Furthermore, the spectra of all longer oligomers were identical in acetonitrile and $CHCl_3$. These spectra showed both negative and positive bands, suggesting exciton coupling typical of helical conformations,[18] including a negative band centered at around 380 nm. This pattern is similar to that observed in the LQQ series,[8b] for which a canonical aromatic helix was demonstrated. As for $(OQ)_n$, some cooperativity in the conformational behavior was observed, as the CD signal intensity per OQQ unit increased with oligomer length. The CD intensity also increased upon lowering the temperature, and this effect was more pronounced for shorter sequences (Figures S3 and S4). These results thus support the idea that the longer oligomers stack better than the shorter ones, and adopt more stable chirally biased, possibly helical, conformations.

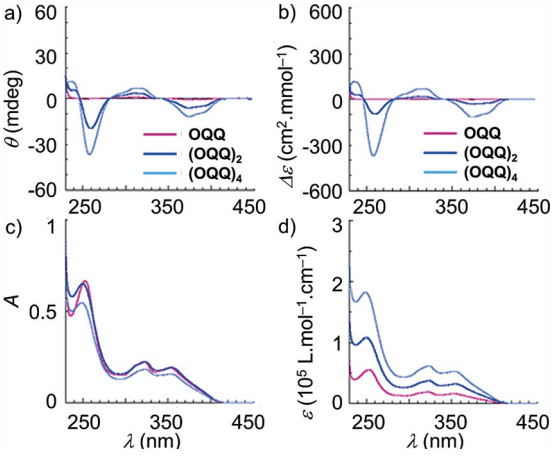


Figure 5. CD (a, b) and UV (c, d) spectra of L-$(OQQ)_n$ (n = 1, 2, 4) in $CHCl_3$ at 25 °C. [concentrations: L-OQQ: 6.0×10^{-5} M; L-$(OQQ)_2$: 3.0×10^{-5} M; L-$(OQQ)_4$: 1.5×10^{-5} M].

X-ray Crystallography of $(OQ)_n$ and $(OQQ)_n$

Crystallographic investigations were undertaken to assess the conformations in the solid state. Except for D-OQ and D-$(OQ)_2$, which crystallized in space groups $P2_12_12_1$ and $P4_32_12$, respectively, in other oligomer crystallized in its pure enantiomeric D or L form. To overcome this difficulty, we resorted to racemic crystallography. This method requires that all syntheses have to be carried out twice to produce both enantiomers, which can then be mixed to form a racemate. But this additional effort is often well rewarded by the high propensity of racemates to form crystals suitable for X-ray diffraction analysis.[16] In this way, the structures of $(OQ)_4$, OQQ, and $(OQQ)_2$ were obtained in centrosymmetrical space groups $P\bar{1}$, $P\bar{1}$, and $P2_1/c$, respectively. Figure 6 shows tube representations of the D enantiomer of these five molecules.

The crystal structure of D-OQ (Figure 6, a) confirmed the expected coplanarity of the aromatic rings of consecutive oxazole and quinoline units. This pattern is constant throughout all of

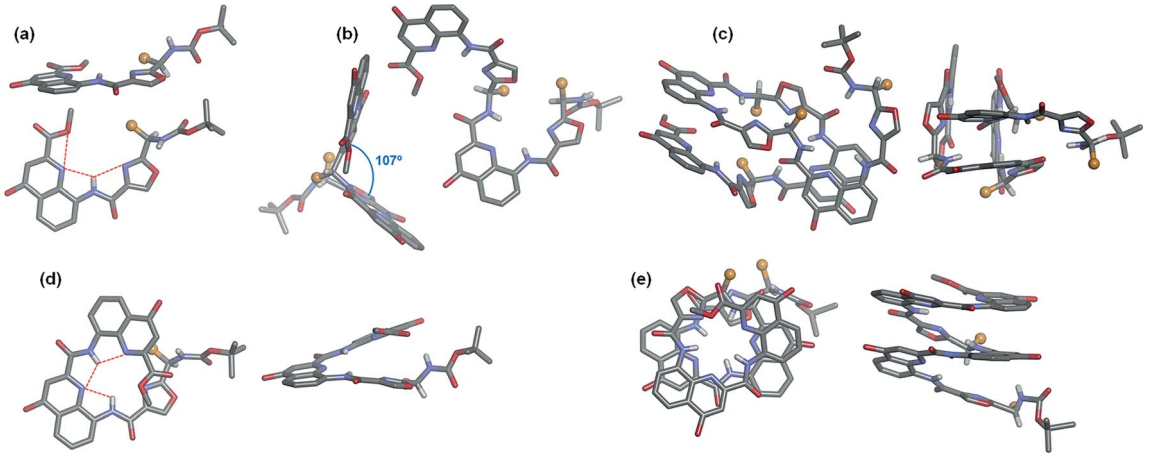


Figure 6. Views of the solid-state structure of D-OQ (a) and D-$(OQ)_2$ (b) from enantiomerically pure crystals. The two OQ units in D-$(OQ)_2$ are at an angle of 107° imparted by the central aliphatic CH. Views of the solid-state structures of D-$(OQ)_4$ (c), D-OQQ (d), and D-$(OQQ)_2$ (e) from racemic crystals. The structure of D-$(OQ)_4$ shows that consecutive OQ units are almost perpendicular to each other. The structure of D-OQQ is left-handed. Crystals of $(OQQ)_2$ are disordered as D-$(OQQ)_2$ and L-$(OQQ)_2$ occupy P helix positions with almost identical occupancy factors (or M helix positions due to the inversion center of the structure). Only the right-handed canonical helically folded D-$(OQQ)_2$ is shown in (e). Leucine side-chains have been replaced by a golden ball for clarity. Included solvent molecules, isobutyl groups, and hydrogen atoms (except NH and CαH) have been removed for clarity.

the structures, and is stabilized by (i) conjugation between amide and adjacent aryl groups; (ii) electrostatic repulsions between the aromatic amide carbonyl group and adjacent endocyclic nitrogen atoms; and (iii) bifurcated intramolecular hydrogen bonds between the aromatic amide NH and the quinoline nitrogen atom [$d_{(N–N)}$ = 2.6 Å] and the oxazole nitrogen atom [$d_{(N–N)}$ = 2.8 Å]. In contrast, the terminal Boc-NH group lies out of the oxazole–quinoline plane, and does not form a hydrogen bond with the neighboring oxazole endocyclic nitrogen atom, in contrast with cyclic $(O)_3$ oligomers.[13h] This reflects a preference of the benzylic CH_2 group, when not constrained in a macrocycle, to generate an angle between the two sp^2-conjugated systems to which it is connected. This prevails in all $(OQ)_n$ oligomers (see below), and also in a number of oligomers reported in the literature.[9] Indeed, the structure of D-$(OQ)_2$ showed two distinct OQ planes at an angle of 107° (Figure 6, b). This arrangement at an angle was maintained upon elongating the sequence to D-$(OQ)_4$, in which consecutive OQ segments are found at an angle close to 90°, allowing segment *i* and segment *i* + 2 to stack on top of each other (Figure 6, c). This structure thus demonstrates the possibility of intramolecular π–π interactions for $(OQ)_4$ and $(OQ)_8$. Nevertheless, the π–π overlap observed in the solid state is not extensive. In addition, it is possible that several comparable arrangements can be built, which could equilibrate rapidly in solution, and that the solid-state structure is just one of these. This, together with a certain degree of flexibility in the structure might explain the absence of NMR signals with upfield shifts, even for the longer oligomers (Figure 2). The way handedness bias operates in such structures, giving rise to CD bands (Figure 4), is not obvious. Such an organization of successive OQ segments in a close-to-perpendicular fashion is reminiscent of earlier aromatic–aliphatic structures that were termed "herringbone motifs". For example, $(PQ)_n$ oligomers, where P stands for 6-aminomethyl-2-pyridinecarboxylic acid, were shown to fold in such a herringbone helix,[9a] as too were oligoamides of 2-(2-aminophenoxy)acetic acid.[9b] There is indeed a certain degree of similarity between O and P units that results in these similar folding modes. These multiple occurrences tend to confirm this pattern as a true class of folds that does not occur in biopolymers, in contrast with canonical helices, linear strands, and turns, which are common both in natural and synthetic folded secondary structures.

The crystal structures of D-OQQ and D-$(OQQ)_2$ (Figure 6, d and e) showed canonical aromatic helical conformations consistent with the NMR and CD spectroscopic data. The helix of D-(OQQ) is left-handed with no disorder, despite the apparent absence of handedness bias in solution, as judged from the flat CD spectrum (Figure 5). In contrast, crystals of $(OQQ)_2$ are disordered, as D-$(OQQ)_2$ and L-$(OQQ)_2$ both occupy *P* helix positions with almost identical occupancy factors: for the two independent molecules found in the asymmetric unit, the occupancy factors of the two enantiomers are 0.582/0.418 and 0.546/0.454, respectively. Thus, although there is some helix sense bias in solution, the D-*P* and L-*P* diastereomeric structures are not well discriminated upon crystallization, and cocrystallize in almost equal proportions. It should be pointed out that helix sense bias in solution is only partial in $(OQQ)_2$, as judged by the higher CD intensity per residue of $(OQQ)_4$ (Figure 5).

The folding behavior of $(OQQ)_n$ thus differs from that of $(OQ)_n$ in all respects. In the former, the folded structure reflects an original combination of somewhat antagonistic tendencies, of OQ linkages, which impart coplanarity, and QO linkages, which prefer a close-to-perpendicular angle. In the latter, the folding behavior of the Q units prevails, and dictates a folding mode to the QO linkages distinct from what it normally prefers. This precedence of Q units over another monomer when mixed in a 2:1 ratio was also observed in $(LQQ)_n$ oligomers.[8b]

Conclusions

In summary, we have synthesized two series of oligomers containing different proportions of O and Q monomers. Their folded structures have been investigated in solution and in the solid state. The prevalence of the canonical aromatic helical structure for $(OQQ)_n$ has been demonstrated, and this corroborates earlier results showing the ability of Q units to dictate their folding behavior to other monomers. The existence of close-to-90° kinks between aromatic segments imparted by O units in the structures of $(OQ)_n$ is comparable to patterns previously reported in $(PQ)_n$ oligomers and in oligoamides of 2-(2-aminophenoxy)acetic acid.[9] The recurrence of that pattern contributes to making it an established mode of folding of aromatic–aliphatic hybrid sequences that is not found in all-aromatic or all-aliphatic backbones. Although the oxazole building block considered here was derived from leucine only, other side-chains may be considered and incorporated into aromatic–aliphatic sequences having specific and predictable folded conformations.

Experimental Section

General Methods and Materials: Unless otherwise noted, all reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, Kanto Kagaku Co., Inc., Novabiochem (Switzerland), and Alfa Aesar. Column chromatography was carried out on Silica gel 60N (spherical, neutral, particle size 100–210 μm; Kanto) or Silica gel (40–60 μm; Merck). Circular chromatography purifications were carried out with a Chromatotron® on Silica gel (Merck grade 7749, TLC grade with binder and fluorescent indicator). ^1H and ^{13}C NMR spectra were recorded with Bruker 300 Avance II, Bruker Avance II 600, and Bruker Avance III 600 spectrometers. Chemical shifts for ^1H NMR spectra are reported in parts per million (ppm), and were calibrated using the singlet at δ = 7.26 ppm for $CHCl_3$ in $CDCl_3$, or the center line of a quintet at δ = 3.31 ppm for CD_2HOD in [D_4]methanol. Coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. s = broad singlet. Chemical shifts for ^{13}C NMR spectra are reported in ppm, and were calibrated using the center line of a triplet at δ = 77.16 ppm for $CDCl_3$, and the center line of a septet at δ = 49.00 ppm for [D_4]methanol. Mass spectra were recorded with a Bruker Daltonics microTOF-2focus spectrometer, or a Bruker Daltonics UltrafleXtreme in the positive-ion detection mode. UV/Vis and CD spectra were recorded in a 0.2 mm quartz

cell with a JASCO V-650 spectrometer and JASCO J-820, or JASCO J-815 spectrometer.

CCDC 1013712 (for D-OQ), 1013711 [for D-$(OQ)_2$], 1013713 [for *rac*-$(OQ)_4$], 1451767 (for *rac*-OQQ) and 1451768 [for *rac*-$(OQQ)_2$] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Synthesis: Compounds O-COOH,[13a] H_2N-Q,[15] and H_2N-QQ[15] were synthesized according to the reported procedures.

General Procedure A for Boc Deprotection: The carbamate was dissolved in dichloromethane/TFA (2:3), and the solution was stirred at 25 °C until the starting material disappeared. The reaction mixture was evaporated to give the corresponding amine trifluoroacetate.

General Procedure B for Ester Saponification: The ester was dissolved in THF/methanol, and potassium hydroxide (4–8 equiv.) was added. The mixture was stirred at room temp. until the starting material disappeared. The reaction was quenched with citric acid solution (5 % aq.), and the mixture was extracted with dichloromethane. The organic layer was washed with water and brine, dried with magnesium sulfate, and filtered. The solvent was removed in vacuo to give the corresponding carboxylic acid.

General Procedure C for Coupling the Amine Trifluoroacetate and Carboxylic Acid: The acid and HBTU (2 equiv.) were dissolved in dry DMF. Dry *N*,*N*-diisopropylethylamine (5 equiv.) was added under Ar, and the mixture was stirred for 15 min at room temp. Then, a solution of the amine trifluoroacetate (1–1.5 equiv.) in dry DMF was added to the reaction mixture under Ar, and the mixture was stirred at room temp. until the starting material disappeared. The reaction mixture was quenched with citric acid solution (5 % aq.), and extracted with dichloromethane. The organic layer was washed with saturated sodium hydrogencarbonate solution, water, and brine, dried with magnesium sulfate, and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography to give the corresponding amide.

Synthesis of D-O-COCl: 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (1.8 mL, 13.6 mmol) was added to a solution of D-O-COOH (2.001 g, 6.71 mmol) in dry chloroform (60 mL) under Ar, and the mixture was stirred for 2.5 h at room temp. The reaction mixture was concentrated to give D-O-COCl (quant.) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 5.07–4.93 (m, 2 H), 1.76–1.61 (m, 3 H), 1.43 (s, 9 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 6.3 Hz, 3 H) ppm.

Synthesis of D-OQ: A solution of compound D-O-COCl in dry chloroform (20 mL) was added to a solution of H_2N-Q (1.783 g, 6.50 mmol) and dry *N*,*N*-diisopropylethylamine (5.5 mL, 32.3 mmol) in dry chloroform (40 mL) at 0 °C under Ar, and the mixture was stirred for 16 h at room temp. The reaction was quenched with saturated ammonium chloride solution, and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried with magnesium sulfate, and filtered. The solvent was removed in vacuo, and the residue was purified by open column chromatography (silica gel, ethyl acetate/cyclohexane, 1:8 → 1:5) to give D-OQ (2.217 g, 4.00 mmol, 60 % over two steps from D-**O-COCl**) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.21 (br. s, 1 H), 8.91 (dd, *J* = 7.7, 1.1 Hz, 1 H), 8.28 (s, 1 H), 7.95 (dd, *J* = 8.5, 1.3 Hz, 1 H), 7.62 (t, *J* = 8.1 Hz, 1 H), 7.60 (s, 1 H), 5.12 (br. s, 2 H), 4.12 (s, 3 H), 4.06 (d, *J* = 6.5 Hz, 2 H), 2.37–2.24 (m, 1 H), 1.94–1.65 (m, 3 H), 1.46 (s, 9 H), 1.15 (d, *J* = 6.7 Hz, 6 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.1, 164.9, 163.2, 158.9, 155.2, 147.2, 141.7, 139.1, 137.0, 134.9, 128.4, 122.3, 117.9, 116.3, 101.4, 80.4, 75.4, 53.2, 47.5, 43.7, 28.5, 28.3, 24.9, 22.8, 22.3, 19.4 ppm. HRMS (ESI): calcd. for $C_{29}H_{39}N_4O_7$ $[M + H]^+$ 555.2819; found 555.2818.

Synthesis of D-H_2N-OQ: Compound D-H_2N-OQ was synthesized as described in general procedure A. Boc deprotection of D-OQ (297 mg, 0.535 mmol) gave D-H_2N-OQ (467 mg, 0.821 mmol, quant.) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.78 (br. s, 1 H), 8.54 (dd, *J* = 7.8, 1.0 Hz, 1 H), 8.46 (s, 1 H), 8.18 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.80 (t, *J* = 8.0 Hz, 1 H), 7.62 (s, 1 H), 4.80 (t, *J* = 7.1 Hz, 1 H), 4.23 (d, *J* = 6.5 Hz, 2 H), 4.10 (s, 3 H), 2.45–2.32 (m, 1 H), 2.12–1.94 (m, 2 H), 1.82–1.63 (m, 1 H), 1.20 (d, *J* = 6.7 Hz, 6 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 167.0, 164.4, 161.7, 159.8, 148.8, 145.1, 140.2, 138.2, 135.6, 129.1, 123.3, 118.9, 117.6, 102.7, 76.5, 53.6, 48.5, 41.8, 29.4, 25.8, 22.7, 22.3, 19.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{31}N_4O_5$ $[M + H]^+$ 455.2289; found 455.2294.

Synthesis of D-OQ-COOH: Compound D-OQ-COOH was synthesized as described in general procedure B. Saponification of D-OQ (304 mg, 0.548 mmol) gave D-OQ-COOH (293 mg, 0.542 mmol, 99 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.96 (br. s, 1 H), 8.86 (d, *J* = 7.5 Hz, 1 H), 8.28 (s, 1 H), 7.99 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.67 (s, 1 H), 7.66 (t, *J* = 7.9 Hz, 1 H), 5.02 (br. s, 2 H), 4.10 (d, *J* = 6.5 Hz, 2 H), 2.38–2.25 (m, 1 H), 1.90–1.65 (m, 3 H), 1.46 (s, 9 H), 1.15 (d, *J* = 6.7 Hz, 6 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.6, 164.6, 164.4, 158.5, 155.5, 146.1, 141.8, 137.7, 136.6, 133.8, 128.9, 122.7, 118.4, 116.7, 99.9, 80.6, 75.9, 47.5, 42.9, 28.5, 28.4, 25.0, 22.9, 22.2, 19.4, 19.4 ppm. HRMS (ESI): calcd. for $C_{28}H_{36}N_4NaO_7$ $[M + Na]^+$ 563.2476; found 563.2466.

Synthesis of D-$(OQ)_2$: Compound D-$(OQ)_2$ was synthesized as described in general procedure C. Compounds D-H_2N-OQ (467 mg, 0.821 mmol) and D-OQ-COOH (293 mg, 0.542 mmol) were coupled, and the product was purified by open column chromatography (silica gel, ethyl acetate/cyclohexane, 1:3) to give D-$(OQ)_2$ (351 mg, 0.359 mmol, 66 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.17 (br. s, 1 H), 10.72 (br. s, 1 H), 8.94 (d, *J* = 7.7 Hz, 1 H), 8.87 (d, *J* = 7.6 Hz, 1 H), 8.64 (br. d, *J* = 8.4 Hz, 1 H), 8.35 (s, 1 H), 8.17 (s, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 8.6 Hz, 1 H), 7.77 (s, 1 H), 7.60 (t, *J* = 8.1 Hz, 2 H), 7.57 (s, 1 H), 5.81–5.74 (m, 1 H), 5.06–4.94 (m, 2 H), 4.08 (d, *J* = 6.6 Hz, 2 H), 4.06 (d, *J* = 6.6 Hz, 2 H), 3.90 (s, 3 H), 2.31–2.21 (m, 4 H), 1.93–1.80 (m, 1 H), 1.71 (t, *J* = 7.0 Hz, 2 H), 1.60–1.49 (m, 1 H), 1.39 (s, 9 H), 1.16–1.09 (m, 18 H), 0.87 (d, *J* = 6.4 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 164.8, 164.4, 164.2, 163.6, 163.1, 158.9, 158.8, 154.9, 149.2, 147.3, 142.2, 142.0, 139.1, 138.4, 137.1, 137.0, 134.8, 134.1, 128.3, 127.8, 122.4, 122.3, 118.6, 117.9, 116.7, 116.3, 101.4, 99.7, 80.5, 75.5, 75.4, 52.9, 47.9, 46.7, 43.2, 42.8, 28.4, 28.3, 28.3, 25.3, 24.9, 22.9, 22.6, 22.3, 22.2, 19.4, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{52}H_{65}N_8O_{11}$ $[M + H]^+$ 977.4773; found 977.4756.

Synthesis of D-H_2N-$(OQ)_2$: Compound D-H_2N-$(OQ)_2$ was synthesized as described in general procedure A. Boc deprotection of D-$(OQ)_2$ (149 mg, 0.152 mmol) gave D-H_2N-$(OQ)_2$ (207 mg, 0.209 mmol, quant.) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.74 (br. s, 1 H), 10.72 (br. s, 1 H), 8.95 (d, *J* = 9.4 Hz, 1 H), 8.78 (dd, *J* = 7.7, 0.8 Hz, 1 H), 8.51 (s, 1 H), 8.42 (s, 1 H), 8.19 (dd, *J* = 8.5, 1.0 Hz, 1 H), 8.09 (dd, *J* = 8.4, 1.0 Hz, 1 H), 7.83 (s, 1 H), 7.77 (t, *J* = 8.0 Hz, 1 H), 7.66 (t, *J* = 8.1 Hz, 1 H), 7.62 (s, 1 H), 5.82–5.74 (m, 1 H), 4.86–4.81 (m, 1 H), 4.20 (d, *J* = 6.5 Hz, 2 H), 4.15 (d, *J* = 6.5 Hz, 2 H), 4.05 (s, 3 H), 2.43–2.25 (m, 2 H), 2.16–2.06 (m, 3 H), 2.00–1.89 (m, 1 H), 1.85–1.72 (m, 1 H), 1.68–1.54 (m, 1 H), 1.18 (d, *J* = 6.9 Hz, 6 H), 1.15 (d, *J* = 6.8 Hz, 6 H), 1.04 (d, *J* = 6.5 Hz, 6 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz,

$CDCl_3$): δ = 166.0, 165.9, 165.0, 163.8, 163.6, 160.0, 158.9, 158.1, 149.3, 147.0, 143.3, 141.8, 138.7, 138.4, 137.2, 136.4, 133.7, 133.6, 128.5, 127.7, 122.4, 118.8, 118.7, 117.3, 117.2, 101.8, 99.9, 75.6, 75.6, 53.3, 48.4, 45.7, 42.2, 40.9, 38.9, 28.3, 28.3, 25.1, 24.8, 22.6, 22.4, 22.1, 21.5, 19.3 ppm. HRMS (ESI): calcd. for $C_{47}H_{57}N_8O_9$ $[M + H]^+$ 877.4243; found 877.4223.

Synthesis of D-$(OQ)_2$-COOH: Compound D-$(OQ)_2$-COOH was synthesized as described in general procedure B. Saponification of D-$(OQ)_2$ (157 mg, 0.161 mmol) gave D-$(OQ)_2$-COOH (132 mg, 0.137 mmol, 85 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.98 (br. s, 1 H), 10.77 (br. s, 1 H), 8.95 (dd, *J* = 7.7, 1.1 Hz, 1 H), 8.86 (dd, *J* = 7.7, 1.0 Hz, 1 H), 8.56 (br. d, *J* = 7.7 Hz, 1 H), 8.33 (s, 1 H), 8.26 (s, 1 H), 8.02–7.97 (m, 2 H), 7.79 (s, 1 H), 7.64 (t, *J* = 8.2 Hz, 1 H), 7.65 (s, 1 H), 7.61 (t, *J* = 8.2 Hz, 1 H), 5.70–5.62 (m, 1 H), 4.96 (br. s, 2 H), 4.10 (d, *J* = 6.5 Hz, 2 H), 4.08 (d, *J* = 6.5 Hz, 2 H), 2.35–2.25 (m, 4 H), 1.91–1.61 (m, 4 H), 1.39 (s, 9 H), 1.15–1.10 (m, 18 H), 0.86 (d, *J* = 5.5 Hz, 3 H), 0.77 (d, *J* = 5.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 164.6, 164.3, 164.1, 163.7, 158.8, 158.5, 154.9, 148.9, 146.4, 142.3, 142.2, 138.4, 137.9, 136.9, 136.7, 133.9, 133.8, 128.7, 127.8, 122.6, 122.5, 118.7, 118.5, 116.9, 116.7, 100.1, 99.7, 80.7, 75.7, 75.5, 48.0, 46.9, 43.2, 41.9, 38.8, 28.3, 28.2, 25.4, 24.9, 22.8, 22.3, 22.3, 22.2, 19.3, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{51}H_{62}N_8NaO_{11}$ $[M + Na]^+$ 985.4430; found 985.4404.

Synthesis of D-$(OQ)_4$: Compound D-$(OQ)_4$ was synthesized as described in general procedure C. Compounds D-H_2N-$(OQ)_2$ (134 mg, 0.152 mmol) and D-$(OQ)_2$-COOH (132 mg, 0.137 mmol) were coupled, the product was and purified by open column chromatography (silica gel, ethyl acetate/cyclohexane, 1:3) to give D-$(OQ)_4$ (138 mg, 0.0757 mmol, 55 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.17 (br. s, 1 H), 10.87 (br. s, 1 H), 10.71 (br. s, 1 H), 10.68 (br. s, 1 H), 8.97–8.91 (m, 3 H), 8.88 (dd, *J* = 7.7, 1.0 Hz, 1 H), 8.71 (d, *J* = 8.8 Hz, 1 H), 8.47–8.40 (m, 2 H), 8.38 (s, 1 H), 8.34 (s, 1 H), 8.30 (br. s, 1 H), 7.96 (dd, *J* = 8.4, 1.1 Hz, 2 H), 7.92 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.86 (dd, *J* = 8.4, 1.1 Hz, 2 H), 7.76 (s, 1 H), 7.70 (s, 1 H), 7.68 (s, 1 H), 7.62–7.48 (m, 4 H), 7.45 (s, 1 H), 5.85–5.77 (m, 1 H), 5.66–5.55 (m, 2 H), 5.04 (br. s, 2 H), 4.07 (d, *J* = 6.4 Hz, 2 H), 4.02–3.98 (m, 6 H), 3.98 (s, 3 H), 2.55–2.08 (m, 10 H), 1.95–1.55 (m, 6 H), 1.43 (s, 9 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.16–1.04 (m, 33 H), 0.99 (d, *J* = 6.2 Hz, 3 H), 0.97 (d, *J* = 6.2 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 164.7, 164.4, 164.1, 164.0, 163.9, 163.7, 163.6, 163.5, 163.4, 162.9, 158.8, 158.7, 158.7, 158.6, 154.7, 149.3, 149.1, 148.9, 147.0, 142.6, 142.4, 142.2, 142.1, 138.9, 138.3, 138.2, 138.2, 137.1, 137.0, 136.9, 134.7, 134.0, 133.9, 133.9, 128.2, 127.8, 127.7, 127.6, 122.3, 122.2, 122.1, 118.5, 118.4, 117.9, 116.7, 116.6, 116.1, 101.1, 99.7, 99.5, 80.6, 75.4, 75.4, 75.3, 75.2, 52.9, 48.0, 47.4, 47.3, 46.9, 43.5, 42.4, 42.1, 41.8, 28.4, 28.3, 28.2, 28.2, 28.2, 25.5, 25.4, 25.3, 25.0, 23.1, 22.8, 22.7, 22.6, 22.4, 22.3, 22.3, 22.3, 19.3, 19.3, 19.3, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{98}H_{117}N_{16}O_{19}$ $[M + H]^+$ 1821.8681; found 1821.8661.

Synthesis of D-H_2N-$(OQ)_4$: Compound D-H_2N-$(OQ)_4$ was synthesized as described in general procedure A. Boc deprotection of D-$(OQ)_4$ (51 mg, 0.0279 mmol) gave D-H_2N-$(OQ)_4$ (86 mg, 0.0468 mmol, quant.) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.60 (br. s, 1 H), 10.55 (br. s, 1 H), 10.43 (br. s, 2 H), 9.36–9.24 (m, 1 H), 9.02 (br. d, *J* = 8.3 Hz, 1 H), 8.86–8.66 (m, 2 H), 8.61 (s, 1 H), 8.49–8.44 (m, 5 H), 8.33 (d, *J* = 7.7 Hz, 1 H), 8.19–8.05 (m, 5 H), 7.93 (br. s, 1 H), 7.84 (br. s, 1 H), 7.76–7.57 (m, 4 H), 7.50 (br. s, 1 H), 5.70–5.49 (m, 3 H), 5.03–4.98 (m, 1 H), 4.23–4.13 (m, 8 H), 3.95–3.94 (m, 3 H), 2.41–2.23 (m, 4 H), 2.17–1.84 (m, 8 H), 1.82–1.60 (m, 4 H), 1.18–1.11 (m, 24 H), 1.04–0.92 (m, 24 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.2, 165.3, 165.1, 164.9, 164.5, 163.4, 163.4, 163.3, 162.7, 160.9, 159.1, 159.1, 158.8, 158.4, 149.5, 149.0, 146.1, 143.5, 142.8, 142.6, 140.2, 138.9, 138.7, 138.4, 137.5, 137.1, 136.6, 136.4, 134.1, 133.6, 133.5, 132.9, 127.9, 127.6, 127.5, 127.4, 122.4, 122.2, 121.9, 121.8, 119.9, 119.1, 118.1, 117.5, 117.2, 117.0, 116.5, 116.4, 114.5, 101.0, 99.8, 99.7, 99.6, 75.6, 75.4, 75.4, 75.1, 52.8, 48.5, 47.1, 46.9, 46.1, 42.5, 42.1, 41.8, 41.2, 29.8, 28.3, 28.3, 28.2, 25.4, 25.3, 25.0, 24.7, 22.8, 22.7, 22.5, 22.4, 22.0, 21.9, 19.4, 19.3, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{93}H_{109}N_{16}O_{17}$ $[M + H]^+$ 1721.8151; found 1721.8117.

Synthesis of D-$(OQ)_4$-COOH: Compound D-$(OQ)_4$-COOH was synthesized as described in general procedure B. Saponification of D-$(OQ)_4$ (58 mg, 0.0318 mmol) gave D-$(OQ)_4$-COOH (52 mg, 0.0288 mmol, 90 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.95 (br. s, 1 H), 10.86 (br. s, 1 H), 10.74 (br. s, 1 H), 10.29 (br. s, 1 H), 8.98–8.90 (m, 3 H), 8.84 (d, *J* = 7.4 Hz, 1 H), 8.38 (d, *J* = 8.9 Hz, 1 H), 8.44–8.41 (m, 2 H), 8.35 (s, 3 H), 8.28 (br. s, 1 H), 8.21 (d, *J* = 7.0 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.84–7.80 (m, 2 H), 7.71 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.62–7.55 (m, 3 H), 7.47 (t, *J* = 8.1 Hz, 1 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.12 (s, 1 H), 5.81–5.73 (m, 1 H), 5.63–5.56 (m, 1 H), 5.39–5.32 (m, 1 H), 5.11–5.04 (m, 2 H), 4.14–3.79 (m, 8 H), 2.69–2.12 (m, 12 H), 1.99–1.56 (m, 4 H), 1.42 (s, 9 H), 1.25–0.87 (m, 48 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 164.6, 164.2, 164.1, 164.0, 163.7, 163.6, 163.4, 163.3, 158.8, 158.7, 158.6, 158.2, 154.8, 149.2, 149.1, 148.9, 145.7, 142.5, 142.2, 142.0, 138.4, 138.3, 137.9, 137.4, 137.1, 136.9, 136.8, 136.7, 134.0, 133.9, 133.7, 133.5, 128.7, 127.8, 127.4, 122.4, 122.4, 122.2, 122.0, 118.8, 118.6, 118.2, 116.8, 116.6, 116.4, 99.8, 99.7, 99.4, 99.0, 80.6, 75.5, 75.5, 75.4, 75.4, 48.1, 47.8, 47.4, 46.5, 43.6, 42.5, 41.5, 41.0, 28.4, 28.3, 28.2, 28.2, 28.1, 25.5, 25.1, 25.0, 23.2, 22.8, 22.6, 22.6, 22.6, 22.4, 22.1, 22.1, 19.3, 19.3, 19.3, 19.3, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{97}H_{114}N_{16}NaO_{19}$ $[M + Na]^+$ 1829.8338; found 1829.8299.

Synthesis of D-$(OQ)_8$: Compound D-$(OQ)_8$ was synthesized as described in general procedure C. Compounds D-H_2N-$(OQ)_4$ (48 mg, 0.0279 mmol) and D-$(OQ)_4$ COOH (52 mg, 0.0288 mmol) were coupled, and the product was purified by open column chromatography (silica gel, dichloromethane/ethyl acetate, 20:3, and ethyl acetate/cyclohexane, 1:3) and chromatotron (silica gel, dichloromethane/ethyl acetate, 10:1) to give D-$(OQ)_8$ (7 mg, 0.00199 mmol, 7 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.18 (br. s, 1 H), 10.89 (br. s, 1 H), 10.83 (br. s, 4 H), 10.71 (br. s, 2 H), 8.98–8.87 (m, 8 H), 8.69 (d, *J* = 8.8 Hz, 1 H), 8.62–8.56 (m, 4 H), 8.51–8.35 (m, 9 H), 8.00–7.95 (m, 6 H), 7.88 (t, *J* = 8.8 Hz, 2 H), 7.78–7.50 (m, 16 H), 7.47 (s, 1 H), 5.87–5.57 (m, 7 H), 5.04 (br. s, 2 H), 4.11–3.98 (m, 19 H), 2.57–2.10 (m, 24 H), 1.97–1.58 (m, 8 H), 1.43 (s, 9 H), 1.28–0.92 (m, 96 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 164.7, 164.4, 164.2, 164.1, 164.1, 164.1, 164.0, 163.9, 163.9, 163.7, 163.6, 163.6, 163.6, 163.4, 162.9, 158.9, 158.7, 158.7, 158.7, 158.7, 154.8, 149.2, 149.0, 149.0, 148.9, 147.0, 142.8, 142.8, 142.7, 142.5, 142.2, 142.1, 139.0, 138.3, 138.3, 138.3, 138.2, 137.1, 137.1, 137.0, 137.0, 134.8, 134.0, 134.0, 134.0, 133.9, 128.3, 127.9, 127.8, 127.8, 127.7, 122.4, 122.4, 122.4, 122.4, 122.2, 122.1, 118.6, 118.5, 118.4, 117.9, 116.8, 116.7, 116.7, 116.6, 116.2, 101.2, 99.7, 99.5, 99.5, 99.4, 80.7, 75.5, 75.4, 75.3, 75.2, 65.7, 53.0, 48.0, 47.4, 47.3, 46.9, 43.6, 42.5, 42.4, 42.3, 42.3, 42.1, 42.0, 29.8, 28.7, 28.4, 28.3, 28.2, 28.2, 25.9, 25.5, 25.5, 25.4, 25.3, 25.0, 23.1, 22.9, 22.9, 22.9, 22.8, 22.7, 22.6, 22.4, 22.4, 22.4, 22.3, 19.4, 19.4, 19.3, 19.3 ppm. HRMS (MALDI-TOF): calcd. for $C_{190}H_{220}N_{32}NaO_{35}$ $[M + Na]^+$ 3532.6317; found 3532.635.

Synthesis of L-O-COCl: Compound L-O-COCl was synthesized by the same procedure as D-O-COCl.

Synthesis of L-OQQ: A solution of compound L-O-COCl (1.0230 g, 3.23 mmol) in dry chloroform (10 mL) was added to a solution of H_2N-QQ (1.5124 g, 2.93 mmol) and dry *N*,*N*-diisopropyl-ethylamine (2.5 mL, 14.7 mmol) in dry chloroform (20 mL) at 0 °C under Ar, and

the mixture was stirred for 18.5 h at room temp. The reaction was then quenched with saturated ammonium chloride solution, and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried with magnesium sulfate, and filtered. The solvent was removed in vacuo, and the residue was purified by open column chromatography (silica gel, dichloromethane → ethyl acetate/*n*-hexane, 1:3) to give L-OQQ (1.9704 g, 2.47 mmol, 84 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.42 (s, 1 H), 11.16 (s, 1 H), 9.02 (dd, *J* = 7.7, 1.2 Hz, 1 H), 8.95 (dd, *J* = 7.6, 1.1 Hz, 1 H), 8.30 (s, 1 H), 8.02 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.00 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.79 (s, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 7.51 (s, 1 H), 4.52–4.48 (m, 1 H), 4.36–4.34 (m, 1 H), 4.14 (d, *J* = 6.5 Hz, 2 H), 4.09–4.05 (m, 2 H), 3.70 (s, 3 H), 2.36–2.28 (m, 2 H), 1.38 (s, 9 H), 1.23–1.18 (m, 1 H), 1.16 (d, *J* = 6.7 Hz, 6 H), 1.16 (d, *J* = 6.6 Hz, 6 H), 0.91–0.86 (m, 1 H), 0.68–0.63 (m, 1 H), 0.48 (d, *J* = 6.4 Hz, 3 H), 0.38 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.2, 164.6, 163.9, 163.3, 163.2, 159.4, 155.2, 150.7, 147.4, 142.1, 139.7, 138.6, 137.1, 135.1, 134.6, 128.7, 127.9, 122.4, 118.4, 118.1, 116.7, 116.4, 101.4, 99.3, 80.0, 75.6, 75.4, 53.1, 46.6, 41.0, 28.4, 28.3, 28.3, 24.2, 22.3, 21.2, 19.4, 19.4 ppm. HRMS (ESI): calcd. for $C_{43}H_{53}N_6O_9$ $[M + H]^+$ 797.3869; found 797.3884.

Synthesis of L-H_2N-OQQ: Compound L-H_2N-OQQ was synthesized as described in general procedure A. Boc deprotection of L-OQQ (0.9192 g, 1.15 mmol) gave L-H_2N-OQQ (1.1795 g, 1.45 mmol, quant.) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.99 (s, 1 H), 10.85 (s, 1 H), 8.90 (dd, *J* = 7.7, 1.2 Hz, 1 H), 8.85 (dd, *J* = 7.5, 0.8 Hz, 1 H), 8.41 (s, 1 H), 8.06 (dd, *J* = 8.4, 1.1 Hz, 1 H), 7.97 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.71 (s, 1 H), 7.71 (t, *J* = 7.9 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.44 (s, 1 H), 4.17–4.06 (m, 5 H), 3.72 (s, 3 H), 2.35–2.28 (m, 2 H), 1.64–1.55 (m, 2 H), 1.50–1.43 (m, 1 H), 1.17 (d, *J* = 6.7 Hz, 6 H), 1.15 (d, *J* = 6.8 Hz, 6 H), 0.67 (d, *J* = 6.6 Hz, 3 H), 0.63 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 166.9, 164.8, 164.3, 164.0, 161.0, 160.0, 151.6, 148.5, 144.9, 140.3, 139.2, 138.6, 135.7, 135.0, 129.2, 128.6, 123.2, 123.2, 119.0, 118.5, 118.0, 117.2, 116.1, 102.4, 100.0, 76.4, 53.3, 47.8, 40.6, 29.4, 29.4, 24.7, 22.4, 21.4, 19.5, 19.5, 19.5 ppm. HRMS (ESI): calcd. for $C_{38}H_{45}N_6O_7$ $[M + H]^+$ 697.3344; found 697.3345.

Synthesis of L-OQQ-COOH: Compound L-OQQ-COOH was synthesized as described in general procedure B. Saponification of L-OQQ (0.9218 g, 1.16 mmol) gave L-OQQ-COOH (0.8717 g, 1.11 mmol, 96 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.95 (s, 1 H), 10.95 (s, 1 H), 8.96 (d, *J* = 7.6 Hz, 1 H), 8.94 (d, *J* = 7.4 Hz, 1 H), 8.33 (s, 1 H), 8.05 (d, *J* = 8.7 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.79 (s, 1 H), 7.74 (t, *J* = 8.2 Hz, 1 H), 7.61 (t, *J* = 7.7 Hz, 1 H), 7.61 (s, 1 H), 4.45–4.38 (m, 1 H), 4.34–4.28 (m, 1 H), 4.13 (d, *J* = 6.3 Hz, 2 H), 4.11–4.09 (m, 2 H), 2.36–2.29 (m, 2 H), 1.35 (br. s, 9 H), 1.28–1.19 (m, 1 H), 1.17 (d, *J* = 6.7 Hz, 6 H), 1.16 (d, *J* = 6.7 Hz, 6 H), 0.98–0.92 (m, 1 H), 0.86–0.79 (m, 1 H), 0.45 (d, *J* = 6.5 Hz, 3 H), 0.41 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.4, 164.4, 163.8, 163.7, 163.0, 159.3, 155.2, 150.3, 147.0, 142.8, 138.8, 138.3, 136.6, 134.4, 134.1, 128.6, 127.8, 122.6, 122.2, 118.8, 118.4, 116.7, 116.6, 100.5, 99.1, 80.0, 75.6, 75.4, 46.7, 41.2, 28.4, 28.3, 24.1, 22.4, 21.2, 19.4, 19.3, 19.3 ppm. HRMS (ESI): calcd. for $C_{42}H_{50}N_6NaO_9$ $[M + Na]^+$ 805.3531; found 805.3551.

Synthesis of L-$(OQQ)_2$: Compound L-$(OQQ)_2$ was synthesized as described in general procedure C. Compounds L-H_2N-OQQ (1.1264 g, 1.39 mmol) and L-OQQ-COOH (0.8198 g, 1.05 mmol) were coupled, and the product was purified by open column chromatography (silica gel, ethyl acetate/*n*-hexane, 1:5 → 1:4 → 1:2, and dichloromethane/ethyl acetate, 10:1 → 5:1) to give L-$(OQQ)_2$ (0.9190 g, 0.629 mmol, 60 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.00 (br. s, 1 H), 11.78 (br. s, 1 H), 10.49 (br. s, 1 H), 10.10 (br. s, 1 H), 9.09 (d, *J* = 7.4 Hz, 1 H), 8.73 (d, *J* = 7.5 Hz, 1 H), 8.54 (d, *J* = 7.6 Hz, 1 H), 8.10 (s, 1 H), 8.09–8.06 (m, 2 H), 7.98 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.83 (t, *J* = 7.9 Hz, 1 H), 7.79 (s, 1 H), 7.71 (dd, *J* = 8.3, 1.2 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 7.46 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.28 (s, 1 H), 6.99 (br. s, 1 H), 6.94 (t, *J* = 8.0 Hz, 1 H), 6.53 (s, 1 H), 4.56–4.51 (m, 1 H), 4.33–4.21 (m, 2 H), 4.21–4.15 (m, 1 H), 4.08 (br. d, *J* = 6.9 Hz, 1 H), 3.99–3.76 (m, 4 H), 3.46–3.40 (m, 2 H), 3.38 (s, 3 H), 2.44–2.33 (m, 2 H), 2.30–2.24 (m, 1 H), 2.19–2.13 (m, 1 H), 1.80–1.71 (m, 1 H), 1.34–1.23 (m, 18 H), 1.22 (d, *J* = 6.7 Hz, 3 H), 1.21 (d, *J* = 6.7 Hz, 3 H), 1.16–1.10 (m, 9 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 0.98–0.85 (m, 7 H), 0.79–0.67 (m, 1 H), 0.41 (br. s, 3 H), 0.37 (br. s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 164.8, 163.9, 163.4, 163.0, 163.0, 162.6, 162.3, 162.0, 158.4, 157.8, 155.1, 150.7, 149.9, 146.9, 142.6, 141.7, 139.0, 138.7, 138.1, 137.7, 136.5, 136.4, 134.7, 134.1, 133.9, 133.6, 128.3, 127.8, 127.4, 122.5, 122.0, 121.8, 121.4, 118.7, 117.6, 116.8, 116.3, 116.0, 114.9, 101.6, 99.8, 99.0, 97.9, 79.9, 75.6, 75.4, 75.2, 74.7, 52.7, 47.4, 46.6, 42.5, 40.4, 28.4, 28.3, 28.2, 25.3, 24.2, 23.2, 22.5, 21.4, 21.0, 19.5, 19.4, 19.4, 19.4, 19.3 ppm. HRMS (ESI): calcd. for $C_{80}H_{93}N_{12}O_{15}$ $[M + H]^+$ 1461.6878; found 1461.6896.

Synthesis of L-H_2N-$(OQQ)_2$: Compound L-H_2N-$(OQQ)_2$ was synthesized as described in general procedure A. Boc deprotection of L-$(OQQ)_2$ (150.1 mg, 0.103 mmol) gave L-H_2N-$(OQQ)_2$ (182.8 mg, 0.124 mmol, quant.) as a yellow solid. ^{1}H NMR (600 MHz, CD_3OD): δ = 11.95 (br. s, 1 H), 11.82 (br. s, 1 H), 10.40 (br. s, 1 H), 10.08 (br. s, 1 H), 9.12 (d, *J* = 7.7 Hz, 1 H), 8.65 (s, 1 H), 8.58 (br. d, *J* = 6.3 Hz, 1 H), 8.52 (dd, *J* = 7.6, 0.9 Hz, 1 H), 8.41 (s, 1 H), 8.16 (d, *J* = 8.1 Hz, 1 H), 8.05 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.90 (t, *J* = 7.9 Hz, 1 H), 7.75 (s, 1 H), 7.69 (br. s, 1 H), 7.65 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.63 (t, *J* = 8.1 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.33 (s, 1 H), 7.01 (br. s, 1 H), 6.93 (t, *J* = 8.0 Hz, 1 H), 6.82 (br. s, 1 H), 6.49 (s, 1 H), 4.46–4.40 (m, 1 H), 4.38–4.33 (m, 1 H), 4.27–4.24 (m, 1 H), 4.18–4.16 (m, 1 H), 4.07–4.03 (m, 2 H), 3.96–3.94 (m, 1 H), 3.57–3.52 (m, 2 H), 3.44–3.41 (m, 1 H), 3.36 (s, 3 H), 2.49–2.40 (m, 2 H), 2.28–2.18 (m, 2 H), 1.87–1.79 (m, 1 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.33 (d, *J* = 6.8 Hz, 3 H), 1.30 (d, *J* = 6.7 Hz, 3 H), 1.29 (d, *J* = 6.7 Hz, 3 H), 1.26–0.97 (m, 5 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.14–1.12 (m, 6 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.39 (d, *J* = 6.5 Hz, 3 H), 0.18 (br. s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 165.7, 164.3, 163.4, 162.9, 162.8, 162.7, 162.4, 162.1, 159.1, 157.4, 157.3, 150.6, 149.8, 149.3, 147.1, 143.5, 143.4, 138.9, 138.9, 138.0, 137.6, 136.8, 136.4, 134.7, 133.7, 133.5, 133.3, 128.9, 127.9, 127.8, 127.7, 122.7, 121.9, 121.8, 121.4, 119.4, 118.3, 117.8, 117.4, 117.1, 116.8, 116.2, 114.9, 101.6, 99.9, 98.1, 97.8, 75.8, 75.7, 75.4, 74.6, 52.8, 48.1, 47.7, 43.3, 39.9, 28.4, 28.3, 28.2, 28.2, 25.1, 24.1, 23.2, 21.9, 21.0, 20.4, 19.5, 19.4, 19.4, 19.4, 19.4, 19.3, 19.2, 19.1 ppm. HRMS (ESI): calcd. for $C_{75}H_{85}N_{12}O_{13}$ $[M + H]^+$1361.6354; found 1361.6319.

Synthesis of L-$(OQQ)_2$-COOH: Compound L-$(OQQ)_2$-COOH was synthesized as described in general procedure B. Saponification of L-$(OQQ)_2$ (151.6 mg, 0.104 mmol) gave L-$(OQQ)_2$-COOH (131.9 mg, 0.0911 mmol, 88 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.94 (br. s, 1 H), 11.37 (br. s, 1 H), 10.49 (br. s, 1 H), 9.82 (br. s, 1 H), 9.05 (d, *J* = 7.4 Hz, 1 H), 8.62 (br. s, 1 H), 8.53 (d, *J* = 7.5 Hz, 1 H), 8.16 (s, 1 H), 8.12–8.04 (m, 3 H), 7.96 (d, *J* = 8.1 Hz, 1 H), 7.82 (t, *J* = 7.8 Hz, 1 H), 7.79 (s, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.54 (d, *J* = 8.3 Hz, 1 H), 7.50–7.43 (m, 2 H), 7.41 (s, 1 H), 7.34 (br. s, 1 H), 7.01 (t, *J* = 7.9 Hz, 1 H), 6.98 (br. s, 1 H), 6.48 (s, 1 H), 4.59–4.51 (m, 1 H), 4.30–3.94 (m, 8 H), 3.88–3.74 (m, 1 H), 3.42–3.32 (m, 2 H), 2.44–2.27 (m, 4 H), 2.16–2.09 (m, 2 H), 1.80–1.69 (m, 2 H), 1.27–1.07 (m, 30 H), 0.90 (br. s, 9 H), 0.74–0.65 (m, 2 H), 0.37 (br. s, 3 H), 0.34 (br. s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.8, 164.7, 163.8, 163.6, 163.4, 163.1, 163.0, 162.2, 161.7, 158.4, 157.8, 155.0, 150.5, 149.7,

146.4, 143.6, 141.8, 138.7, 138.0, 137.7, 136.5, 135.8, 134.6, 133.7, 133.5, 133.2, 128.3, 127.9, 127.8, 127.6, 122.5, 121.9, 121.8, 121.8, 118.8, 118.2, 117.7, 117.6, 116.8, 116.3, 115.9, 115.3, 100.4, 99.8, 98.9, 97.8, 79.9, 75.7, 75.6, 75.4, 74.6, 47.4, 46.5, 42.8, 40.4, 28.4, 28.3, 28.1, 25.4, 24.2, 23.1, 22.4, 21.5, 21.0, 19.5, 19.5, 19.4, 19.4, 19.3 ppm. HRMS (ESI): calcd. for $C_{79}H_{90}N_{12}NaO_{15}$ $[M + Na]^+$ 1469.6541; found 1469.6505.

Synthesis of L-(OQQ)$_4$: Compound L-(OQQ)$_4$ was synthesized as described in general procedure C. Compounds L-H_2N-(OQQ)$_2$ (90.9 mg, 0.0616 mmol) and L-(OQQ)$_2$-COOH (88.9 mg, 0.0614 mmol) were coupled, and the product was purified by open column chromatography (silica gel, ethyl acetate/*n*-hexane, 1:2 → 2:3 → 1:1) and gel permeation chromatography (chloroform) to give L-(OQQ)$_4$ (31.7 mg, 0.0114 mmol, 18 %) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.53 (br. s, 2 H), 11.48 (br. s, 1 H), 11.31 (br. s, 1 H), 10.20 (br. s, 1 H), 9.98 (br. s, 1 H), 9.66 (br. s, 1 H), 9.58 (br. s, 1 H), 8.78 (br. d, *J* = 6.9 Hz, 1 H), 8.73 (d, *J* = 7.2 Hz, 1 H), 8.28 (d, *J* = 7.5 Hz, 1 H), 8.17 (br. s, 1 H), 8.12 (br. s, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.91 (s, 1 H), 7.84 (s, 1 H), 7.81 (br. s, 1 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.74 (s, 1 H), 7.65 (t, *J* = 7.8 Hz, 1 H), 7.61–7.54 (m, 7 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.47 (br. s, 2 H), 7.40 (br. s, 2 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.19–7.06 (m, 5 H), 7.03 (br. s, 1 H), 6.91 (br. s, 1 H), 6.82–6.79 (m, 2 H), 6.67–6.46 (m, 4 H), 4.33 (br. s, 1 H), 4.24 (br. s, 1 H), 4.17 (br. s, 1 H), 4.11 (br. s, 2 H), 4.05–3.98 (m, 3 H), 3.93–3.64 (m, 9 H), 3.59 (br. s, 1 H), 3.53–3.43 (m, 2 H), 3.38–3.32 (m, 1 H), 3.28 (s, 3 H), 2.39–2.20 (m, 6 H), 2.17–2.12 (m, 1 H), 2.11–2.04 (m, 1 H), 1.50–0.22 (m, 93 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.7, 164.7, 164.5, 164.3, 163.8, 163.7, 163.6, 163.3, 163.1, 162.9, 162.7, 162.7, 162.6, 162.4, 162.4, 162.2, 161.8, 161.0, 161.0, 158.1, 157.8, 157.3, 157.0, 154.8, 150.6, 149.8, 149.8, 149.7, 146.9, 142.2, 142.1, 142.1, 141.5, 139.0, 138.7, 138.2, 138.1, 137.5, 137.3, 136.3, 135.6, 134.4, 134.3, 133.9, 133.7, 133.5, 133.5, 133.4, 133.3, 127.9, 127.7, 127.6, 127.6, 127.6, 127.3, 127.3, 127.0, 122.5, 122.0, 121.7, 121.6, 121.6, 121.5, 121.3, 118.7, 117.5, 117.4, 117.3, 117.1, 117.0, 116.4, 116.3, 116.0, 115.9, 115.2, 114.9, 114.8, 101.4, 99.7, 99.5, 99.5, 99.3, 98.5, 98.3, 97.8, 79.8, 75.6, 75.4, 75.2, 75.2, 75.1, 74.9, 74.8, 74.6, 70.8, 52.6, 47.3, 47.2, 46.9, 41.8, 41.1, 40.2, 29.8, 28.4, 28.4, 28.3, 28.3, 28.3, 28.2, 28.1, 25.1, 25.0, 24.9, 24.2, 23.0, 22.4, 21.3, 21.2, 21.1, 21.0, 19.6, 19.5, 19.5, 19.5, 19.4, 19.4, 19.4, 19.4, 19.3, 19.3, 19.3, 19.3, 19.2 ppm. HRMS (ESI): calcd. for $C_{154}H_{173}N_{24}O_{27}$ $[M + H]^+$ 2790.2875; found 2790.2897.

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Keywords: Peptidomimetics · Amides · Foldamers · Helical structures · Secondary structure · Solid-state structures

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