Communication

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Folding of a Linear Array of α-Amino Acids within a Helical Aromatic Oligoamide Frame

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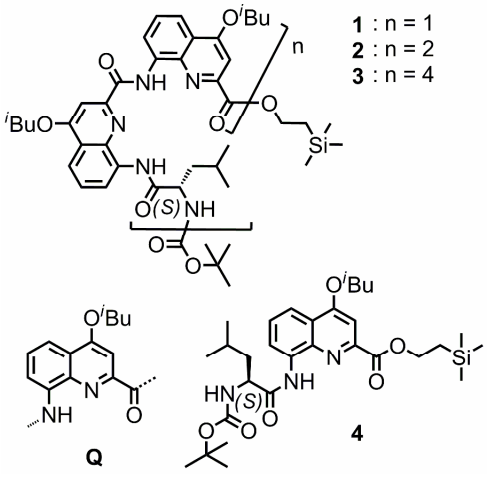
Supporting Information Placeholder

ABSTRACT: Controlling the spatial organization of proteinogenic side chains is critical to develop protein mimics with selective recognition properties toward target protein surfaces. We present a novel methodology to produce a linear array of proteinogenic residues based on the incorporation of α-amino acids into sequences of rigid, helically folded, oligoamides of 8-amino-2-quinolinecarboxylic acid (**Q**). When L-leucine (**L**) was alternated with dimer $\mathbf{Q_2}$, the resulting sequence adopted a right-handed helical conformation, as deduced in solution from the CD spectra of L-$(\mathbf{LQ_2})_n$ (n = 2, 4), and in the solid from X-ray crystallographic analysis of (±)-$(\mathbf{LQ_2})_4$. Each $\mathbf{LQ_2}$ segment spanned just one helix turn (pitch of 3.5 Å) and, consequently, the four leucine side chains of $(\mathbf{LQ_2})_4$ formed a linear array. In solution, NMR showed that L-$(\mathbf{LQ_2})_2$ and L-$(\mathbf{LQ_2})_4$ both exist as a mixture of two, slowly equilibrating, folded conformers, the proportion of which strongly vary with the solvent.

Protein tertiary structures and protein-protein recognition largely rest on intramolecular and intermolecular interactions between α-amino-acid side chains projected at well-defined positions in space from β-strands, turns and helical subunits. Controlling the spatial organization of proteinogenic side chains has thus been a prime objective in peptide and protein mimetics in order to fine tune their ability to self-assemble or to interact with protein targets. For example, β- and γ-peptides may adopt several types of helical conformations from which side chains are projected in a variety of arrays distinct from those of α-helical α-peptides.[1] The possibility to combine α-, β-, and γ-amino acids in the same helically folded sequences further increases the number of spatial arrays of side chains that can be created.[2] Based on these helix designs, artificial tertiary or quaternary structures[3] and important steps towards protein surface recognition by non natural sequences have been reported.[4] The appendage of proteinogenic side chains to rigid scaffolds such as linear aryl oligomers (for example terphenyl groups and linear aryl oligoamides)[5] or macrocycles[6] in order to mimic protein epitopes has also been thoroughly investigated. In particular, strong emphasis was given in recent years to linear arrays of side chains at defined intervals that can mimic the projection of *i*, *i*+4 and *i*+7 residues from one face of an α-helix.[7] Here, we present a novel approach towards linear arrays of side chains *via* the incorporation of α-amino acids into rigid helical aromatic oligoamide frames. The new folded motifs we have discovered possess a facial polarity and provide a valuable alternative to currently known examples of peptide/protein mimics for protein surface recognition or as amphipathic structures to interact with bilayer membranes.

Chart 1. Structures of Q, LQ and $(\mathbf{LQ_2})_n$ oligomers



Aromatic oligoamide foldamers have emerged as an important class of folding oligomers characterized by a high conformational stability and a high predictability of their

folded conformations.[8] Oligoamides derived from 8-amino-2-quinolinecarboxylic acid **Q** (Chart 1) fold into helices having 2.5 units per turn and a pitch of 3.5 Å, as demonstrated both in the solid state and in solution.[9] These helices are extremely stable in essentially any solvent.[10,9] For example, they show no denaturation at 120°C in DMSO. Their robustness is such that they can accommodate a number of more flexible aliphatic units a priori not prone to folding to which they dictate a folding behavior compatible with the aromatic oligoamide $\mathbf{Q_n}$ helix.[11] This contrasts with other examples of hybrid aromatic-aliphatic sequences which often display novel unexpected folding behaviors.[12]

α-Amino acids have no apparent feature that would make them compatible with helically folded $\mathbf{Q_n}$ oligoamides. Nevertheless, we were interested in exploring the folding behavior of combinations thereof that would allow to exploit the robustness of $\mathbf{Q_n}$ conformations and the wide range of α-amino acid residues readily available from commercial sources. Given that a dimer $\mathbf{Q_2}$ spans 0.8 helix turn, we speculated that an additional α-amino acid, e.g. leucine **L**, would allow an $\mathbf{LQ_2}$ segment[13] to span just about one turn, and that repeating this segment in the same sequence would potentially bring the leucine residues in close proximity. In the following, we report on the synthesis and structural characterization of $(\mathbf{LQ_2})_n$ oligomers and the discovery that they adopt helically folded conformations from which the leucine residues are projected in a linear array from one face of the helix. The aromatic amide helix provides a rigid frame in which a certain number of α-amino acids may be inserted and from which linear arrays of side chains may be projected for molecular recognition purposes or to build amphipathic structures.

The synthesis of $(\mathbf{LQ_2})_n$ oligomers[13] is presented in detail in the supporting information. It makes use of optimized monomer and oligomer synthetic procedures.[14] In short, the main chain terminal aliphatic amine was protected by a Boc group. The main chain terminal acid was protected as a 2-trimethylsilyl-ethyl ester which can be removed in the presence of fluoride and thus avoid basic conditions that might racemize leucine α-carbons. The direct coupling of Boc-L-leucine to the free amine of a quinoline dimer to give **1** (Chart 1) failed in our hands. Even with an acid fluoride activation of leucine, it required long heating times in the presence of diisopropyl-ethyl-amine that eventually led to racemization of the leucine α-carbon (see supporting information) On the other hand, the acid fluoride of Boc-L-leucine could be coupled to an 8-aminoquinoline monomer to give **4** in 93 % yield without any racemization (Chart 1). Cleavage of the ester of **4**, activation of the resulting acid as an acid chloride under neutral conditions, and coupling to another 8-aminoquinoline gave **1**. Iterative deprotections of the N- and C-termini, activation of the terminal acid with HBTU and coupling to the terminal aliphatic amine then allowed to prepare **2** and **3** in a convergent fashion. For the purpose of racemic crystallographic investigations (see below), the synthesis was carried out twice, in the L and in the D series.

Preliminary data concerning the conformation behavior of these new aliphatic-aromatic hybrids in solution was collected using circular dichroism (Figure 1). Similar behaviors were observed in $CHCl_3$, acetonitrile and acetone. While L-**LQ** (**4**) showed no CD signal in the 200-400 nm range, L-$\mathbf{LQ_2}$ (**1**) showed distinct negative bands at 252.9 nm ($\Delta\varepsilon$ = −48.3 cm^2mmol^{-1}) and 370.0 nm ($\Delta\varepsilon$ = −19.2 cm^2mmol^{-1}) in $CHCl_3$. According to previous assignments, the negative band at 370 nm is suggestive of a left-handed helix twist.[15a] L-$(\mathbf{LQ_2})_2$ and L-$(\mathbf{LQ_2})_4$ featured intense CD bands characteristic of a folded structure but their signs were reversed from that of L-$\mathbf{LQ_2}$ indicating a reversed (right-handed) handedness. The CD band intensity per $\mathbf{LQ_2}$ repeat units were similar for L-$(\mathbf{LQ_2})_2$ and L-$(\mathbf{LQ_2})_4$ which suggests that the extent of folding is similar for these two species.

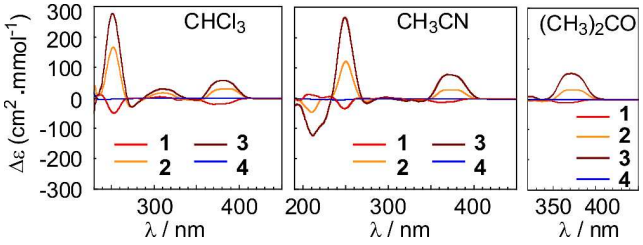


Figure 1. Circular dichroism spectra of **1**-**4** in $CHCl_3$, CH_3CN and acetone at 25°C. The horizontal scales have been set to regions above the absorption range of the solvent.

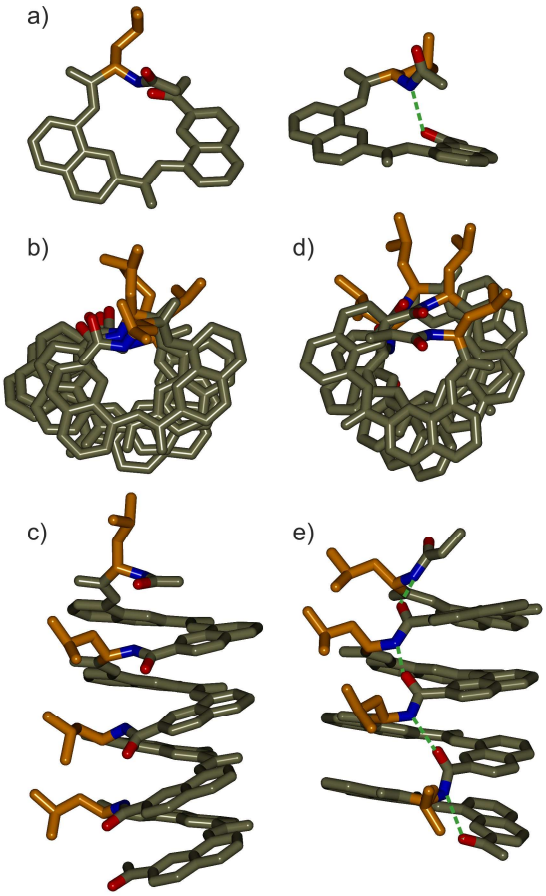


Figure 2. Crystal structures of the left handed helix of **1** (a), and the right-handed helix of **3** (b,c) and molecular model of an alternate structure of **3** (d,e). Leucine nitrogen atoms and side chains are shown in blue and gold, respectively. Some quinoline or carbamate carbonyl oxygen atoms are shown in red. Some key hydrogen bonds are shown as dashed green lines. Included solvent molecules, isobutoxy chains, TMSE groups, *tert*-butyl groups, and hydrogen atoms have been omitted for clarity.

Attempts to grow crystals of **1**-**3** (single L-enantiomers) that would be suitable for x-ray crystallographic analysis all failed. Our experience with helical aromatic oligomamides is that racemic or quasi-racemic crystals grow much more readily,[15] as is the case for other peptides and small proteins.[16] This proved to be valid also in $(\mathbf{LQ_2})_n$ oligomers and the structures of *rac*-$\mathbf{LQ_2}$ and *rac*-$(\mathbf{LQ_2})_4$ in the solid state could both be solved in the *P*-1 centrosymmetrical space group (Fig. 2). The structure of $\mathbf{LQ_2}$ revealed that the *L* enantiomer adopts a left-handed helical conformation, consistent with the sign of the CD band observed in solution (Fig. 1). The helix is stabilized by a hydrogen bond ($d_{(N\text{-}O)}$ = 2.9 Å) between the N-terminal NH proton and the C-terminal carbonyl oxygen atom which are located almost exactly above each other down the helix axis, confirming the initial assumption that the $\mathbf{LQ_2}$ motif would span one helix turn. This hydrogen bond sets the L-leucine ϕ = −117° and ψ = −5°, resulting in an almost perfect *anti* conformation of the $C^{\alpha}H$ and NH bonds (179°). The N-terminal carbamate CONH plane is parallel to the helix axis.

In contrast *L*-$(\mathbf{LQ_2})_4$ adopts a right-handed helical conformation, also in agreement with the sign of its CD band. The leucine amide NHs (not the carbamate NH) all point toward the helix axis and hydrogen bond to the endocyclic nitrogen atom of the neighbor (*i*–1) quinoline unit. The four $\mathbf{LQ_2}$ segments each account for about one helix turn (pitch of 3.5 Å) resulting in a linear array of the leucine side chains (see top view in Fig. 2b) which protrude in an almost perpendicular fashion from the helix axis. C^{α}–C^{α} distances between consecutive leucines are 4.8, 4.7 and 4.2 Å starting from the N-terminus, which is smaller than between *i*, *i*+4, and *i*+7 residues of α-helices (on average 6.3 Å). Starting from the N terminus, L-leucines in *L*-$(\mathbf{LQ_2})_4$ have ϕ values of −133, −143, −140 and −155° and ψ values of −5, 26, 40 and 35°, respectively. Such high negative ϕ values are common in peptides as they can be found both in β-sheets and α-helices; the small positive ψ values fall in an allowed (though not favored) area of the Ramachandran plot.

NMR studies were carried out to investigate conformations in solution (Figure 3, see also supporting information). When going from **1** to **3**, ^{1}H NMR spectra show upfield shifts of most signals, including of terminal groups which indicate increasing and additive effects of ring current effects associated with π-π stacking. For example, signals of the terminal TMS group are found at 0.04 , −0.16 and −0.30 ppm for **1**, **2** and **3**, respectively, in $CDCl_3$ at 25°C. Such chain-length dependence is typical of folding phenomena.[17] While the spectrum of **1** in $CDCl_3$ is sharp at 25°C, the spectra of **2** and **3** show some broad signals which sharpen upon heating to 45°C. Upon cooling, signals of **2** and **3** first broaden further then split into two sets of sharp signals near 5°C. This behavior indicate the coexistence of two well-defined species that equilibrate slowly on the NMR time scale. A possible aggregated state was ruled out as the proportions between these two species do not depend upon concentration. The proportions, however, show strong solvent dependence. In the case of **2**, proportions of 53:47, 88:12 and 85:15 were measured at 5°C in $CDCl_3$, CD_3CN and acetone-d_8, respectively. Spectra in solvent mixtures confirm that the major species is the same in all three cases. This large variation of proportions contrast with CD bands which have the same intensity in all three solvents, indicating that the two species observed by NMR cannot be assigned to two diastereomeric *P* and *M* helices, and that induction of handedness is probably quantitative in the case of **2** and **3**.[15]

The data above point to the existence of two well defined non aggregated states having the same handedness. Direct full NMR assignment and structure elucidation was hampered by broadness and the fact that exchange phenomena may be difficult to distinguish from NOE correlations. The sharp spectrum of **2** at 5°C allowed to record COSY spectra from which the NHs of the central leucine unit were assigned to two signals at 8.98 and 8.69 ppm for the major and minor species, respectively. Coupling constants were measured to be $^3J_{(NH\ C\alpha H)}$ = 6.9 and 10.5 Hz, for the signals at 8.98 and 8.69 ppm, respectively. These values indicate quite different conformations of the leucine unit. The large coupling constant above 10 Hz is the most likely to match with the conformation observed in the crystal structure of **3**. Indeed the Karplus equation applied to $^3J_{(NH\ C\alpha H)}$ couplings indicate ϕ values close to −120° and a $C^{\alpha}H$-NH dihedral angle close to 180° (see supporting information). In contrast, the coupling constant at 6.9 Hz may correspond to various ϕ values near −160°, −80° or near +60°.

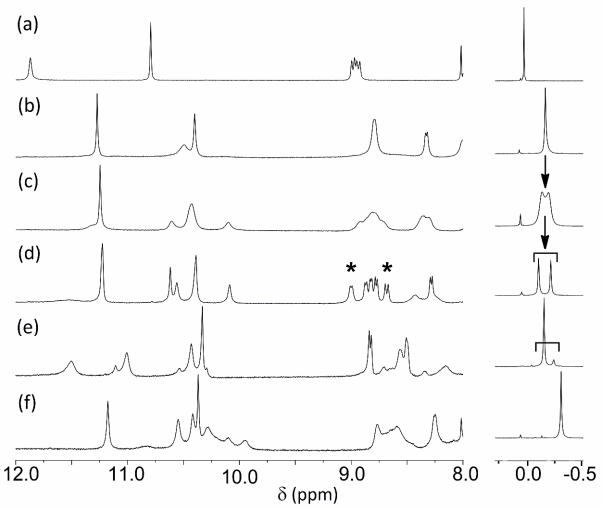


Figure 3. Part of the 300 MHz ^{1}H NMR spectra of **1**, and 400 MHz ^{1}H NMR spectra of **2** and **3** showing aromatic amide resonances (10-12 ppm), some aliphatic amide and aromatic proton resonances (8-9 pmm), and TMS resonances (−0.5-0 ppm). (a) **1** in $CDCl_3$ at 25°C; (b,c,d) **2** 45, 25 and 5°C in $CDCl_3$; (e) **2** at 5° in CD_3CN; (f) **3** at 25°C in $CDCl_3$. The stars indicate two leucine NH protons having very different $^3J_{(NH\ C\alpha H)}$ coupling constants.

The examination of molecular models led to the proposal of a alternate structure of **3** different from its structure in the solid state. This model is inspired by the structure of **1** in the solid state (Figure 2) as it also involves intramolecular hydrogen bonds between leucine NH protons of unit *i* and the amide carbonyl group of quinoline unit *i*+2, instead of the quinoline endocyclic nitrogen atom of unit *i*–1. When this pattern is repeated along the four leucines of **3**, the corresponding amide functions tilt to planes parallel to the helix axis and form a linear array of hydrogen bonds reminiscent of alpha helices. This is accommodated without a change of the helix pitch (3.5 Å) by a slight increase of the helix diameter and a tilt of the array of leucines with respect to the helix

axis. This conformation is very stable in molecular dynamic simulations (see supporting information) making it a plausible hypothetical candidate for one of the species observed in solution. Indeed, in this conformation, leucine C^{α}-H and N-H are eclipsed, leading to ϕ values of +60°, consistent with the NMR observations mentioned above.

In summary, sequences combining α-amino acids and quinoline units Q in the particular $(\mathbf{LQQ})_n$ arrangement gives rise to folded conformation in which linear arrays of proteinogenic side chains are produced. The next step consist in bringing such sequences into water where aromatic oligoamide helical folding is dramatically enhanced[tob,18] and where stable patterns might be expected to form. Research in this direction is in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new compounds, crystallographic data, detailed NMR and CD investigations. "This material is available free of charge via the Internet at http://pubs.acs.org."

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(Word Style "Section_Content"). †If an author's address is different than the one given in the affiliation line, this information may be included here.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.*, **1996**, *118*, 13071. (b) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta*, **1996**, *79*, 913. (c) Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, I. A.; Parker B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018.

(2) (a) Vasudev, P. G.; Chatterjee, S.; Shamala N.; Balaram, P. *Chem. Rev.* **2011**, *111*, 657. (b) Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.*, **2004**, *43*, 505. (c) Sharma, G. V.; Reddy, K. R.; Krishna, P. R.; Sankar, A. R.; Narsimulu, K.; Kumar, S. K.; Jayaprakash, P.; Jagannadh; B.; Kunwar, A. C. *J. Am. Chem. Soc.* **2003**, *125*, 13670. (d) Mándity, I. M.; Wéber, E.;. Martinek, T. A.; Olajos, G.; Tóth, G. K.; Vass E.; Fülöp, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2171. (e) Hetényi, A.; Tóth, G. K.; Somlai, C.; Vass, E.; Martinek T. A.; Fülöp, F. *Chem.–Eur. J.* **2009**, *15*, 10736. (f) Claudon, P.; Violette, A.; Lamour, K.; Decossas, M.; Fournel, S.; Heurtault, B.; Godet, J.; Mély, Y.; Jamart-Grégoire, B.; Averlant-Petit, M.-C.; Briand, J.-P.; Duportail, G.; Monteil H.; Guichard, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 333. (g) Guo, L.; Almeida, A. M.; Zhang, W.; Reidenbach, A. G.; Choi, S. H.; Guzei, I. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2010**, *132*, 7868.

(3) (a) Daniels, D. S.; Petersson, E. J.; Qiu, J. X.; Schepartz, A. *J. Am. Chem. Soc.* **2007**, *129*, 1532. (b) Horne, W. S.; Price, J. L.; Keck, J. L.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 4178.

(4) (a) Michel, J.; Harker, E. A.; Tirado-Rives, J.; Jorgensen, W. L.; Schepartz, A. *J. Am. Chem. Soc.* **2009**, *131*, 6356. (b) Sadowsky, J. D.; Schmitt, M. A.; Lee, H.-S.; Umezawa, N.; Wang, S.; Tomita Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11966. (c) Boersma, M. D.; Haase, H. S.; Peterson-Kaufman, K. J. Lee, E. F.; Clarke, O. B.; Colman, P. M.; Smith, B. J.; Horne, W. S.; Fairlie, W. D.; Gellman, S. H. *J. Am. Chem. Soc.* **2012**, *134*, 315. (d) Robinson, J. A. *ChemBioChem*. **2009**, *10*, 971. (e) Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479. (f) Kritzer, J. A.; Lear, J. A.; Hodsdon, M. E.; Schepartz, A. *J. Am. Chem. Soc.* **2004**, *126*, 9468.

(5) (a) Kutzki, O.; Park, H. S.; Ernst, J. T.; Orner, B. P.; Yin, H.; Hamilton, A. D. *J. Am. Chem. Soc.* **2002**, *124*, 11838. (b) Cummings, C. G.; Hamilton, A. D. *Curr. Opin. Chem. Biol.* **2010**, *14*, 341. (c) Plante, J. P.; Burnley, T.; Malkova, B.; Webb, M. E.; Warriner, S. L.; Edwards, T. A.; Wilson, A. J. *Chem. Commun.* **2009**, 5091. (d) Yin, H.; Lee, G.–i.; Sedey, K. A.; Rodriguez, J. M.; Wang, H.–G.; Sebti, S. M.; Hamilton, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 5463.

(6) (a) Park, H. S.; Lin, Q.; Hamilton, A. D. *J. Am. Chem. Soc.* **1999**, *121*, 8. (b) Fasan, R.; Dias, R. L. A.; Moehle, K.; Zerbe, O.; Obrecht, D.; Mittl, P. R. E.; Grütter, M. G.; Robinson, J. A. *ChemBioChem* **2006**, *7*, 515.

(7) Wilson, A. J. *Chem. Soc. Rev.* **2009**, *38*, 3289

(8) Huc, I. *Eur. J. Org. Chem.* **2004**, 17; Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. *Chem. Rev.* **2012**, *112*, 5271.

(9) (a) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448. (b) Jiang, H.; Léger, J.-M.; Dolain, C.; Guionneau, P.; Huc, I. *Tetrahedron* **2003**, *59*, 8365. (c) Dolain, C.; Grélard, A.; Laguerre, M.; Jiang, H.; Maurizot, V.; Huc, I. *Chem.—Eur. J.* **2005**, *11*, 6135.

(10) (a) Delsuc, N.; Kawanami, T.; Lefeuvre, J.; Shundo, A.; Ihara, H.; Takafuji, M.; Huc, I. *ChemPhysChem* **2008**, *9*, 1882. (b) Qi, T.; Maurizot, V. Noguchi, H.; Charoenraks, T.; Kauffmann, B.; Takafuji, M.; Ihara, H.; Huc, I. *Chem. Commun.* **2012**, *48*, 6337

(11) (a) Sánchez-García, D.; Kauffmann, B.; Kawanami, T.; Ihara, H.; Takafuji, M.; Delville, M.-H.; Huc, I. *J. Am. Chem. Soc.* **2009**, *131*, 8642. (b) Baptiste, B.; Douat-Casassus, C.; Laxmi-Reddy, K.; Godde, F.; Huc, I. *J. Org. Chem.* **2010**, *75*, 7175. (c) Delsuc, N.; Poniman, L.; Léger, J.-M.; Huc, I. *Tetrahedron* **2012**, *68*, 4464.

(12) (a) Prabhakaran, P.; Kale, S. S.; Puranik, V. G.; Rajamohanan, P. R.; Chetina, O.; Howard, J. A.; Hofmann H. J.; Sanjayan, G. J. *J. Am. Chem. Soc.* **2008**, *130*, 17743. (b) Srinivas, D.; Gonnade, R.; Ravindranathan, S.; Sanjayan, G. J. *J. Org. Chem.* **2007**, *72*, 7022. (c) Roy, A.; Prabhakaran, P.; Baruah, P. K.; Sanjayan G. J. *Chem. Commun.* **2011**, *47*, 11593.

(13) Throughout the manuscript sequences abbreviated $(\mathbf{LQ_2})_n$ possess a Boc group at the *N* terminus and a 2-trimethylsilyl-ester at the *C* terminus.

(14) Qi, T.; Deschrijver, T.; Huc, I. *Nat. Protoc.* **2013**, *8*, 693.

(15) (a) Dolain, C.; Jiang, H.; Léger, J.-M.; Guionneau, P.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 12943. (b) Maurizot, V.; Dolain, C.; Leydet, Y.; Leger, J.-M.; Guionneau, P.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 10049. (c) Delsuc, N.; Massip, S.; Léger, J.-M.; Kauffmann, B.; Huc; I. *J. Am. Chem. Soc.* **2011**, *133*, 3165. (d) Ferrand, Y.; Kendhale, A. M.; Kauffmann, B.; Grélard, A.; Marie, C.; Blot, V.; Pipelier, M.; Dubreuil, D.; Huc, I. *J. Am. Chem. Soc.* **2010**, *132*, 7858.

(16) (a) Toniolo, C.; Peggion, C.; Crisma, M.; Formaggio, F.; Shui, X.; Eggleston, D. S. *Nat. Struct. Biol.* **1994**, *1*, 908; (b) Pentelute, B. L.; Gates, Z. P.; Tereshko, V.; Dashnau, J. L.; Vanderkooi, J. M.; Kossiakoff, A.; Kent, S. B. H. *J. Am. Chem. Soc.* **2008**, *130*, 9695.

(17) Stone, M. T.; Heemstra, J. M.; Moore, J. S. *Acc. Chem. Res.* **2006**, *39*, 11.

(18) Baptiste, B.; Douat-Casassus, C.; Laxmi-Reddy, K.; Godde, F.; Huc, I. *J. Org. Chem.* **2010**, *75*, 7175.

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