Foldamers

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α-Peptide–Oligourea Chimeras: Stabilization of Short α-Helices by Non-Peptide Helical Foldamers**

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Abstract: *Short α-peptides with less than 10 residues generally display a low propensity to nucleate stable helical conformations. While various strategies to stabilize peptide helices have been previously reported, the ability of non-peptide helical foldamers to stabilize α-helices when fused to short α-peptide segments has not been investigated. Towards this end, structural investigations into a series of chimeric oligomers obtained by joining aliphatic oligoureas to the C- or N-termini of α-peptides are described. All chimeras were found to be fully helical, with as few as 2 (or 3) urea units sufficient to propagate an α-helical conformation in the fused peptide segment. The remarkable compatibility of α-peptides with oligoureas described here, along with the simplicity of the approach, highlights the potential of interfacing natural and non-peptide backbones as a means to further control the behavior of α-peptides.*

Chemical approaches aimed at reinforcing or mimicking protein secondary/tertiary structure elements are currently of general interest as a means to develop useful pharmacological tools and innovative medium-size therapeutics complementary to small molecules and biologics.[1] Much progress has been made concerning the development of methods to increase the helical content of natural peptides. Potent peptide-based inhibitors of α-helix-mediated protein–protein interactions (PPIs) and analogues of peptide hormones for which the bioactive conformation is α-helical have been designed using established methods, such as the introduction of constrained α,α-disubstituted amino acids,[2] and side-chain to side-chain macrocyclization.[3] The introduction of helix-nucleation templates at one end of a peptide sequence (mostly N-terminus) is another promising approach to increase α-helicity of short peptides.[4,5]

Concurrently, folded structures formed by non-natural backbones (that is, foldamers) have gained interest as mimics of protein secondary structure elements.[6] Significant achievements include α-helix mimicry for inhibition of protein–protein interactions with β-peptide homooligomers[7] and α/β peptide hybrids.[8,9] However, the possibility for a foldamer backbone to exert a dual effect by also nucleating an α-helical structure in a contiguous α-peptide segment has not been documented except chimeric (α/β + α) peptides designed by Gellman to recapitulate the binding surface of peptide inhibitors of Bcl-X_L proteins.[10] It was suggested in that study that the 14/15-helical α/β-segment at the N-terminus could nucleate an α-helical structure in the C-terminal α-peptide segment. Combining α-peptide and non-natural foldamer backbones in a single chain is also a promising approach to redesign large peptides and proteins (protein prosthesis) and replicate or modulate their tertiary structures and functions.[11] We sought to further explore the concept of chimeric peptide backbones with other types of helical foldamers, and now report on α-peptide–oligourea chimeras (Figure 1).

Aliphatic oligoureas are peptidomimetic foldamers in which the helical conformation is stabilized by a regular pattern of three-centered H-bonds and share features with natural peptide helices, such as helix polarity and pitch.[12] In this work, we have investigated the ability of aliphatic oligoureas fused to short peptide segments to nucleate α-helical structures in both polar organic solvent and crystal state. All oligomers were prepared in a stepwise manner using either solution or solid-phase synthesis.[13,14] A first series of chimeras (**1**–**4**, Figure 1b) was designed by varying the number of amino acid residues (from one to four) and the oligourea attachment position (that is, at the C- (**1**–**3**) or N-terminus (**4**) of the peptide segment). Chimeras **1**–**4** share

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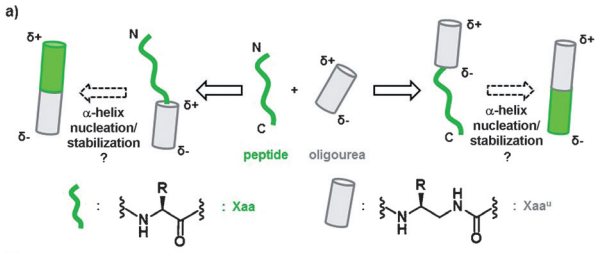

b)

1: Boc-Leu-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe
2: Boc-Ala-Leu-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe
3: Boc-Ala-Leu-Ala-Leu-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-NHMe
4: Boc-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-Ala-Leu-Ala-Leu-NH_2
5: Boc-Leu-Ala-Leu-Ala-Leu-Ala-Leu-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-NH_2
6: Boc-Val^{u}-Ala^{u}-Leu^{u}-Val^{u}-Ala^{u}-Leu^{u}-Ala-Leu-Ala-Leu-Ala-Leu-Ala-NH_2
7: Boc-Leu-Ala-Leu-Ala-Leu-Ala-Leu-Val^{u}-Ala^{u}-NH_2
8: Boc-Leu-Ala-Leu-Ala-Leu-Ala-Leu-Val^{u}-Ala^{u}-Leu^{u}-NH_2
9: Boc-Val^{u}-Ala^{u}-Leu-Ala-Leu-Ala-Leu-Ala-Leu-NH_2
10: Boc-Val^{u}-Ala^{u}-Leu^{u}-Leu-Ala-Leu-Ala-Leu-Ala-Leu-NH_2
11a: Boc-Leu-Ala-Leu-Ala-Leu-Ala-Leu-NH_2
11b: Boc-Leu-Ala-Leu-Ala-Leu-Ala-Leu-Ala-Leu-NH_2

Figure 1. Peptide–oligourea chimeras. a) Representation of peptide helix nucleation/stabilization depending on the oligourea attachment position. b) Chimera sequences prepared and investigated in this work. Residues are numbered consecutively starting from the Boc-protected unit.

a common oligourea sequence of six residues to ensure formation of well-folded canonical 2.5-helical structure.[12d] The peptide sequence was made of alternating Ala and Leu residues known to have helical propensity.[15] Single crystals were obtained for all four sequences and the structures were solved by X-ray diffraction (XRD).[16] The oligourea segment adopts a well-defined 2.5-helical conformation in all structures, irrespective of the length and position of the peptide chain.

The geometry of the α-peptide chain in these structures was examined in more detail. In oligomer **1**, which contains a single Boc-protected amino acid terminus, helix propagation only partially extends to the peptide chain.[14] The situation is different in the case of a dipeptidyl segment as in chimera **2** (Figure 2a). The two amino acid residues appear to be correctly oriented for intramolecular hydrogen bonding, thus allowing the helix to propagate from the oligourea segment to the peptide chain. Although the average Φ,Ψ torsion angles of both amino acids (−74.4°, −29.5° for Ala and −94.1°, −54.6° for Leu) deviate somehow from the canonical torsion angles in the α-helix (−63°, −42°),[17] all three carbonyl groups along the peptide chain are within H-bond distance to urea NHs and are engaged in $i,i+3$ hydrogen bonds. This trend is confirmed upon further increasing the length of the peptide chain as in the structure of oligomer **3** (terminal tetrapeptide). The crystal structure reveals a regular helical conformation spanning the entire chimeric sequence (Figure 2a). It is notable that the peptide chain adopts a helical conformation with mean backbone torsion angles Φ, Ψ (−64°,−32°) lying between those of a canonical α-helix and a 3_{10} helix (−57°, −30°).[17,18]

Chimera **4**, an analogue of **3** in which the hexaurea sequence is linked at the *N*-terminus of the Ala-Leu-Ala-Leu tetrapeptide, was prepared to investigate further the ability of the oligourea segment to promote helix formation in a short peptide chain. Chimera **4** was found to adopt four different (albeit quite similar) conformations in the crystal.[14] Nucleation of a peptide helix is supported in all four conformations by the presence of $i,i+3$ C=O···H–N hydrogen bonds between terminal urea carbonyls and amide NHs of Ala7 and Leu8 (Figure 2a).

However, the propagation of the helical structure in **4** does not extend to Ala9 and Leu10, suggesting helix fraying at the peptide C-terminus. Additional information about the folding behavior of chimeras **3** and **4** was gained from solution studies by ^{1}H NMR in CD_3OH.[14] Amide and urea NH resonances are well dispersed with signals of amide NHs downfield to urea NHs. Qualitative inspection of ^{1}H NMR spectra showed features typical of helically folded oligoureas including dispersion of the urea NH signals, large vicinal coupling constants between NH and CH(R) protons ($^{3}J \approx 10$ Hz) and a high degree of anisochronicity ($\Delta\delta$) of main chain methylene protons ($0.76 < \Delta\delta < 1.35$ ppm).[19] In contrast, the vicinal ^{3}J (NH, $^{\alpha}$CH) coupling constants in the peptide segment, in the range 5.9–7.6 Hz, are above the value generally observed for helical peptides (< 6 Hz),[20] suggesting only partial helical folding and some conformational fluctuations of the peptide backbone. These results confirm the potential of oligoureas to nucleate peptide

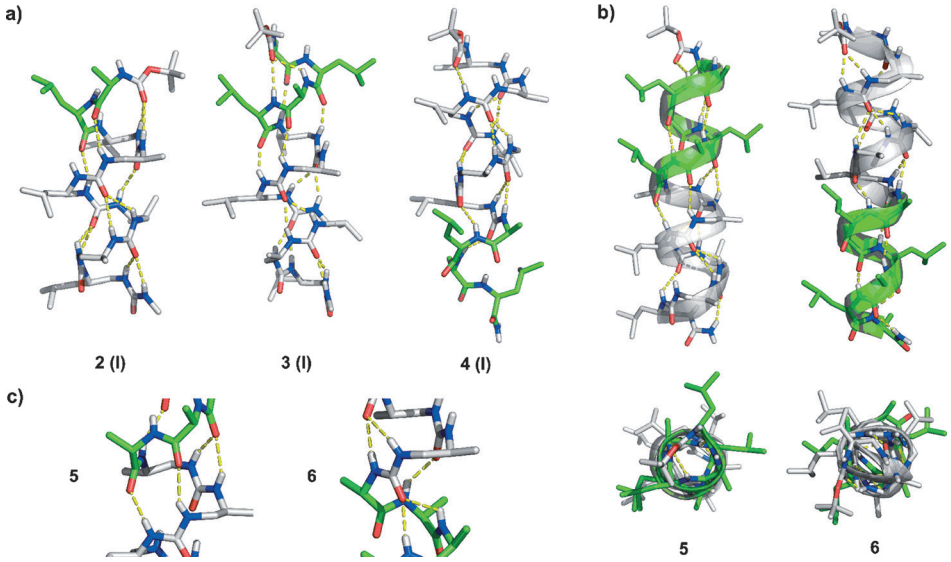

Figure 2. X-ray crystal structure representations of a) **2**–**4** (only one conformation is shown for **3** and **4**); b) **5** and **6** (side views and top views); c) details of the specific H-bonding networks at the junction between oligourea segment (C light gray) and α-peptide segments (C light green). N blue, O red, hydrogen bonding shown by yellow dashed lines.

helical folding but also point to the difficulty to observe propagation of a stable helical conformation in very short (tetra)peptide sequences. To overcome this limitation, we prepared two analogues of **3** and **4** containing a longer heptapeptide sequence, namely **5** and **6**. Again, the structures of the two molecules were solved by XRD (Figure 2b).[16]

In the crystal state, the chimeras adopt a continuous and well-defined helical structure spanning the entire sequence. In both cases, the peptide and oligourea helices are connected by a unique $i,i+3$ and $i,i+4$ C=O···H–N H-bonding network (Figure 2c) : the three terminal amide carbonyl groups in **5** are hydrogen bonded to urea NHs and the α-amino groups of the first three amino acid residues in **6** are hydrogen bonded to the last two carbonyl of the oligourea segment.

Examination of the intramolecular H-bonding interactions within the peptide chain as well as backbone torsion angles for the seven α-amino acid residues (Table 1) in **5** and **6** reveal subtle differences between the two peptide helices. Helix parameters in the peptide segment of **5** and **6** are reported in Table 1 and compared to those reported for the canonical 3_{10}- and α-helices. Whereas the peptide helical conformation in **5** display the hallmarks of an ideal α-helix, the peptide conformation in **6** shares some features with the 3_{10} helix (that is, the $i,i+3$ C=O···H–N H-bonding pattern and Φ values close to −30°). To further characterize the propensity of the peptide chain to adopt a helical conformation, we recorded 1D and 2D ^{1}H NMR spectra of **5** and **6** in CD_3OH.[14] The vicinal ^3J (NH, $^\alpha$CH) coupling constants along the peptide backbone lie in the range of values typical for helical peptide conformations (3.0–6.4 Hz for **5** and 3.2–6.9 Hz for **6**). The observation of all possible non-sequential medium-range αN($i,i+4$), αN($i,i+3$) nuclear Overhauser effects (NOEs) in NOESY spectra of **5** and **6** is fully consistent with both peptide segments adopting a well-defined helical structure. Characteristic αN(4,8) and βN(6,8) NOEs between urea and peptide segments in **5** and **6**, respectively are in good agreement with the short distances measured in the crystal structures and fully support the propagation of a continuous helical conformation.[14]

To better understand the cross-talk between the two folded backbones and define the minimum length required for an oligourea to promote peptide helical folding, a second series of chimeric sequences was designed by shortening the length of the oligourea segment. Chimeras **7**–**10** thus consist of a peptide sequence of seven amino acid residues (as in **5** and **6**) and a short urea oligomer of two or three residues attached either at the N- or the C-terminus of the peptide chain. To determine the influence of the oligourea segment in the process of peptide helix stabilization, we prepared the cognate 7-mer peptide **11a** having the same number of amino acid residues than in corresponding chimeras and a longer 9-mer peptide **11b** to take into account the increased chain length of chimeras. Although NMR analysis of peptides **11** in CD_3OH was hampered by their limited solubility in the millimolar concentration range,[22] the circular dichroism (CD) spectra of peptides **11** recorded in MeOH at 50 μM were indicative of partial helical population with an estimated helix content[23] of 30–35 %.[14]

The effect of capping the peptide N-terminus was found to depend on the length of the urea segment. The attachment of a diurea at the N-terminal end of the heptapeptide had a mixed outcome: the oligomer was more soluble in MeOH but its ^{1}H NMR spectrum showed several species in slow exchange. In contrast, a single set of resonances was observed in the NMR spectrum of chimera **10** with a triurea cap. The amide NH resonances are well dispersed with several ^3J(NH, $^\alpha$CH) values around or below 6 Hz (Figure 3a), thus suggesting a propensity of the peptide segment to adopt a helical conformation. Sequential and medium-range NOEs along the chain are consistent with **10** adopting a helical conformation.[14]

Table 1: Average peptide backbone torsion angles and peptide helix parameters in the crystal structures of chimeras **5** and **6**[a] and comparison with canonical α- and 3_{10}-helices.

	5	**6**	α-helix[17]	3_{10}-helix[17,18]
(Φ, Ψ) [°]	(−66, −40)	(−69, −29)	(−63, −42)	(−57, −30)
residues per turn	3.6	3.6	3.63	3.24
radius [Å]	2.3	2.2	2.3	
unit height [Å]	1.5	1.6	1.56	1.94
rise per turn [Å]	5.4	5.8	5.67	6.29

[a] Parameters calculated with the Helanal progam using $^\alpha$C carbons of amino acid residues only.[21]

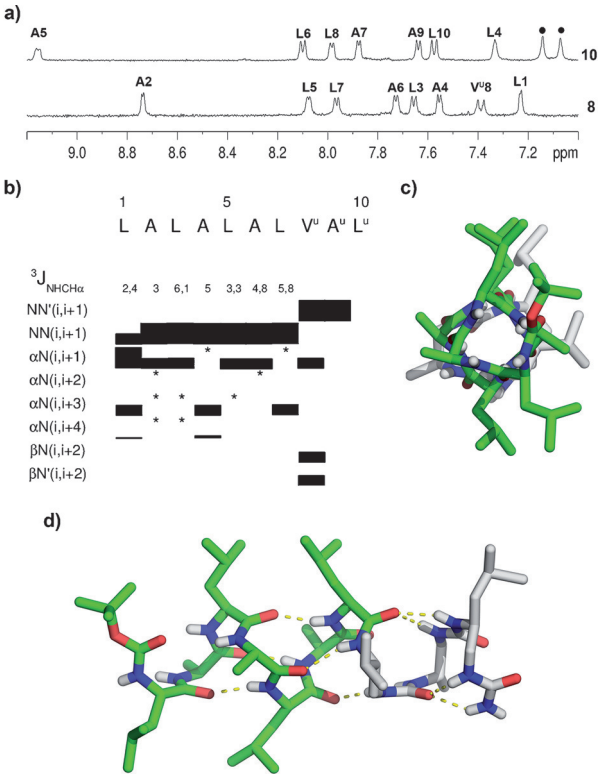

Figure 3. a) Superimposition of amide NH resonances in the ^{1}H NMR spectra of chimeras **8** and **10** (400 MHz, CD_3OH). Resonances of carboxamide NHs in **10** are indicated by ●. b) Sequential and medium-range ^{1}H–^{1}H NOEs and ^3J(NH, $^\alpha$CH) in **8** measured in CD_3OH at 700 MHz and 400 MHz, respectively. c) and d) X-ray crystal structure representations of **8**. The color code is the same as in Figure 2.

Covalent attachment of either di- or tri-urea segments at the C-terminus of the peptide sequence produced similar changes in the ^{1}H NMR spectra recorded in CD_3OH, the corresponding chimeras (**7** and **8**) exhibiting well-defined and well-dispersed amide NH resonances. Remarkably, most amino acid residues in the sequence of **7** and **8** show small ^3J(NH, $^{\alpha}$CH) coupling constants (between 2.6–6.5 Hz), again indicative of a helically folded peptide segment (Figure 3a). These coupling constants compare favorably with those measured for nonapeptide **11b** in [D_2]TFE, a solvent in which the α-helix content of **11b** increases to about 80–87% as estimated by CD.[14,23] The conclusion that a short urea segment at the C-terminal end of a peptide is sufficient to drive stable peptide α-helix formation in MeOH was further supported by the observation of characteristic medium range NOEs along the peptide chain (including a full set of N,N(i,i+1) NOE cross-peaks) and between the oligourea and oligoamide segments in the NMR spectra of **7** and **8** (Figure 3b), and by XRD.[16] The crystal structure of **8** (Figure 3c,d) is fully helical with geometrical features very similar to those of chimera **6**.

Overall our results indicate that short oligourea/peptide chimeras can adopt well-defined helical structures with a continuous intramolecular H-bond network spanning the entire sequence and connecting two geometrically distinct helices, that is, an α- (or 3_{10}) helix in the peptide segment and a canonical 2.5-helix in the oligourea segment. Our results also point to the capacity of short tri-urea segments to stabilize the formation of an α-helical conformation in the fused peptide segment. The high-resolution structural data reported herein may suggest a general approach for the mimicry of peptide and protein helices for various applications. From this perspective, helix propagation in an aqueous environment is another important aspect that we plan to address in continuation of this work using water-soluble chimeras.[24]

Keywords: foldamers · helices · oligourea · peptides · X-ray crystallography

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[1] a) V. Azzarito, K. Long, N. S. Murphy, A. J. Wilson, *Nat. Chem.* **2013**, *5*, 161–173; b) K. Estieu-Gionnet, G. Guichard, *Expert Opin. Drug Discovery* **2011**, *6*, 937–963; c) R. M. J. Liskamp, D. T. S. Rijkers, J. A. W. Kruijtzer, J. Kemmink, *ChemBioChem* **2011**, *12*, 1626–1653; d) J. M. Davis, L. K. Tsou, A. D. Hamilton, *Chem. Soc. Rev.* **2007**, *36*, 326–334.

[2] a) I. L. Karle, P. Balaram, *Biochemistry* **1990**, *29*, 6747–6756; b) C. Toniolo, M. Crisma, F. Formaggio, C. Peggion, *Biopolymers* **2001**, *60*, 396–419; c) J. F. Hernandez, W. Kornreich, C. Rivier, A. Miranda, G. Yamamoto, J. Andrews, Y. Tache, W. Vale, J. Rivier, *J. Med. Chem.* **1993**, *36*, 2860–2867; d) C. García-Echeverría, P. Chène, M. J. Blommers, P. Furet, *J. Med. Chem.* **2000**, *43*, 3205–3208.

[3] a) C. E. Schafmeister, J. Po, G. L. Verdine, *J. Am. Chem. Soc.* **2000**, *122*, 5891–5892; b) E. N. Murage, G. Gao, A. Bisello, J.-M. Ahn, *J. Med. Chem.* **2010**, *53*, 6412–6420; c) H. Jo, N. Meinhardt, Y. Wu, S. Kulkarni, X. Hu, K. E. Low, P. L. Davies, W. F. DeGrado, D. C. Greenbaum, *J. Am. Chem. Soc.* **2012**, *134*, 17704–17713; d) A. M. Spokoyny, Y. Zou, J. J. Ling, H. Yu, Y.-S. Lin, B. L. Pentelute, *J. Am. Chem. Soc.* **2013**, *135*, 5946–5949; e) A. D. de Araujo, H. N. Hoang, W. M. Kok, F. Diness, P. Gupta, T. A. Hill, R. W. Driver, D. A. Price, S. Liras, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2014**, *53*, 6965–6969; *Angew. Chem.* **2014**, *126*, 7085–7089.

[4] a) D. S. Kemp, *Trends Biotechnol.* **1990**, *8*, 249–255; b) W. Maison, E. Arce, P. Renold, R. J. Kennedy, D. S. Kemp, *J. Am. Chem. Soc.* **2001**, *123*, 10245–10254; c) S. Hanessian, G. Papeo, K. Fettis, E. Therrien, M. T. P. Viet, *J. Org. Chem.* **2004**, *69*, 4891–4899.

[5] a) E. Cabezas, A. C. Satterthwait, *J. Am. Chem. Soc.* **1999**, *121*, 3862–3875; b) A. Patgiri, A. L. Jochim, P. S. Arora, *Acc. Chem. Res.* **2008**, *41*, 1289–1300; c) D. Wang, W. Liao, P. S. Arora, *Angew. Chem. Int. Ed.* **2005**, *44*, 6525–6529; *Angew. Chem.* **2005**, *117*, 6683–6687.

[6] G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933–5941.

[7] a) A. D. Bautista, J. S. Appelbaum, C. J. Craig, J. Michel, A. Schepartz, *J. Am. Chem. Soc.* **2010**, *132*, 2904–2906; b) J. Michel, E. A. Harker, J. Tirado-Rives, W. L. Jorgensen, A. Schepartz, *J. Am. Chem. Soc.* **2009**, *131*, 6356–6357; c) M. Hintersteiner, T. Kimmerlin, G. Garavel, T. Schindler, R. Bauer, N.-C. Meisner, J.-M. Seifert, V. Uhl, M. Auer, *ChemBioChem* **2009**, *10*, 994–998.

[8] a) L. M. Johnson, S. H. Gellman, in *Methods Enzymol.*, *Vol. 523* (Ed.: E. K. Amy), Academic Press, San Diego, **2013**, pp. 407–429; b) L. Pilsl, O. Reiser, *Amino Acids* **2011**, *41*, 709–718; c) E. F. Lee, B. J. Smith, W. S. Horne, K. N. Mayer, M. Evangelista, P. M. Colman, S. H. Gellman, W. D. Fairlie, *ChemBioChem* **2011**, *12*, 2025–2032; d) W. S. Horne, L. M. Johnson, T. J. Ketas, P. J. Klasse, M. Lu, J. P. Moore, S. H. Gellman, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 14751–14756; e) W. S. Horne, M. D. Boersma, M. A. Windsor, S. H. Gellman, *Angew. Chem. Int. Ed.* **2008**, *47*, 2853–2856; *Angew. Chem.* **2008**, *120*, 2895–2898.

[9] a) M. Kudo, V. Maurizot, B. Kauffmann, A. Tanatani, I. Huc, *J. Am. Chem. Soc.* **2013**, *135*, 9628–9631; b) P. Prabhakaran, S. S. Kale, V. G. Puranik, P. R. Rajamohanan, O. Chetina, J. A. K. Howard, H.-J. r. Hofmann, G. J. Sanjayan, *J. Am. Chem. Soc.* **2008**, *130*, 17743–17754.

[10] J. D. Sadowsky, M. A. Schmitt, H.-S. Lee, N. Umezawa, S. Wang, Y. Tomita, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11966–11968.

[11] a) U. Arnold, M. P. Hinderaker, B. L. Nilsson, B. R. Huck, S. H. Gellman, R. T. Raines, *J. Am. Chem. Soc.* **2002**, *124*, 8522–8523; b) R. David, R. Günther, L. Baumann, T. Lühmann, D. Seebach, H.-J. Hofmann, A. G. Beck-Sickinger, *J. Am. Chem. Soc.* **2008**, *130*, 15311–15317; c) Z. E. Reinert, G. A. Lengyel, W. S. Horne, *J. Am. Chem. Soc.* **2013**, *135*, 12528–12531; d) C. Mayer, M. M. Müller, S. H. Gellman, D. Hilvert, *Angew. Chem. Int. Ed.* **2014**, *53*, 6978–6981; *Angew. Chem.* **2014**, *126*, 7098–7101.

[12] a) N. Pendem, C. Douat, P. Claudon, M. Laguerre, S. Castano, B. Desbat, D. Cavagnat, E. Ennifar, B. Kauffmann, G. Guichard, *J. Am. Chem. Soc.* **2013**, *135*, 4884–4892; b) J. Fremaux, C. Dolain, B. Kauffmann, J. Clayden, G. Guichard, *Chem. Commun.* **2013**, *49*, 7415–7417; c) J. Fremaux, L. Fischer, T. Arbogast, B. Kauffmann, G. Guichard, *Angew. Chem. Int. Ed.* **2011**, *50*, 11382–11385; *Angew. Chem.* **2011**, *123*, 11584–11587; d) L. Fischer, P. Claudon, N. Pendem, E. Miclet, C. Didierjean, E. Ennifar, G. Guichard, *Angew. Chem. Int. Ed.* **2010**, *49*, 1067–1070; *Angew. Chem.* **2010**, *122*, 1085–1088.

[13] C. Douat-Casassus, K. Pulka, P. Claudon, G. Guichard, *Org. Lett.* **2012**, *14*, 3130–3133.

[14] See the Supporting Information.

[15] a) C. A. Rohl, A. Chakrabartty, R. L. Baldwin, *Protein Sci.* **1996**, *5*, 2623–2637; b) S. E. Miller, A. M. Watkins, N. R. Kallenbach, P. S. Arora, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 6636–6641.

[16] CCDC 1040576 (**1**), CCDC 1040459 (**2**), CCDC 1040750 (**3**), CCDC 1040829 (**4**), CCDC 1040765 (**5**), CCDC 1040761 (**6**), and CCDC 1058821 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[17] M. Crisma, F. Formaggio, A. Moretto, C. Toniolo, *Biopolymers* **2006**, *84*, 3 – 12.
[18] C. Toniolo, E. Benedetti, *Trends Biochem. Sci.* **1991**, *16*, 350 – 353.
[19] a) C. Hemmerlin, M. Marraud, D. Rognan, R. Graff, V. Semetey, J.-P. Briand, G. Guichard, *Helv. Chim. Acta* **2002**, *85*, 3692 – 3711; b) A. Violette, N. Lancelot, A. Poschalko, M. Piotto, J. P. Briand, J. Raya, K. Elbayed, A. Bianco, G. Guichard, *Chem. Eur. J.* **2008**, *14*, 3874 – 3882.
[20] L. J. Smith, K. A. Bolin, H. Schwalbe, M. W. MacArthur, J. M. Thornton, C. M. Dobson, *J. Mol. Biol.* **1996**, *255*, 494 – 506.
[21] P. Kumar, M. Bansal, *J. Biomol. Struct. Dyn.* **2012**, *30*, 773 – 783.
[22] Addition of small amounts of [D_6]DMSO did not improve the quality of the spectra of **11a** and **11b**; even in 100 % [D_6]DMSO, ^{1}H NMR spectra were still poorly resolved (see the Supporting Information).
[23] a) N. E. Shepherd, H. N. Hoang, G. Abbenante, D. P. Fairlie, *J. Am. Chem. Soc.* **2005**, *127*, 2974 – 2983; b) C. A. Rohl, R. L. Baldwin, in *Methods Enzymol.*, *Vol. 295* (Ed.: G. K. Ackers, M. L. Johnson), Academic Press, San Diego, **1998**, pp. 1 – 26.
[24] Note added in proof: A similar case of conformational cooperativity between helical domains was reported independently by the Clayden group for chimeras made of oligomers of 2-aminoisobutyric acid (Aib) residues and oligoureas: J. Maury, B. A. F. Le Bailly, R. James, J. Clayden, *Chem. Commun.* **2015**, DOI: 10.1039/C5CC02995C.

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