Chemical Science

Cite this: *Chem. Sci.*, 2012, **3**, 2042

www.rsc.org/chemicalscience

EDGE ARTICLE

Chiral crystallization of aromatic helical foldamers *via* complementarities in shape and end functionalities†

Huaiqing Zhao,‡[a] Wei Qiang Ong,‡[a] Feng Zhou,[b] Xiao Fang,[a] Xueyuan Chen,[c] Sam F. Y. Li,[a] Haibin Su,[b] Nam-Joon Cho[b] and Huaqiang Zeng*[a]

Received 22nd February 2012, Accepted 28th March 2012
DOI: 10.1039/c2sc20219k

Biomolecules such as α-helices are exclusively right-handed without contamination by their left-handed counterparts. Within the abiotic world, chiral or external perturbations have to be applied to the abiotic helical foldamers or polymers to control and bias their helical screw sense. Otherwise, it is not possible to separate racemic helical foldamers composed of achiral building blocks. By designing two complementary "sticky" groups, incorporating them into the ends of helical pentamers and taking advantage of the energetically more favored full overlap, which involves helical backbones, we succeeded in demonstrating, for the first time, a spontaneous resolution of racemic helices into their enantiopure single-handed helical forms *via* chiral crystallization without the use of chiral auxiliary or external stimuli.

Introduction

Biological macromolecules such as DNA and α-helices are largely expressed asymmetrically as right-handed helices and are controlled by their homochiral constituents, *e.g.*, D-sugars and L-amino acids, to yield their characteristic biological functions. The design of bio-inspired abiotic helical foldamers[1] aims at not only reproducing the one-handed helicity observed in nature but also aims at rendering good properties for applications in sensing, catalysis, data storage, optical devices *etc.* While diverse approaches have been adopted in producing optically active helical polymers,[2] controlling and biasing the helical screw sense in oligomeric helices have been achieved mostly by 1) using chiral monomers[3a,3b] or those carrying chiral side chains,[3c] 2) introducing chiral groups in the middle[4a,4b] or at the end that act covalently[4c,4d] or noncovalently,[4e–h] 3) light *via* incorporation of both a chiral end group and a photo-sensitive azobenzene motif[5] and 4) binding to anions[6] or chiral guests.[7]

In the absence of chiral or external perturbations, synthetic helical foldamers made up of achiral building blocks typically exist as a racemic mixture, and strategies allowing for their separation into enantiopure single-handed helical forms have yet to be demonstrated.[8] We present here a bottom up tactic for obtaining unprecedented conglomerate-forming helical foldamers that, upon chiral crystallization, spontaneously resolve into helices of single handedness without using any chiral auxiliary or external stimuli.

It has been generally observed that helices of opposite handedness pack densely in the solid state *via* partial, *e.g.*, side-by-side, overlap of aromatic backbones by virtue of aromatic π–π stacking forces (Fig. 1a). This side-by-side overlap, however, seems to be energetically inefficient (see Table 1) and should not be favored over the full overlap of aromatic backbones that is only possible for helices of the same handedness (Fig. 1b). The exclusive occurrence of the former in the solid state is therefore a scientifically bewildering reality that remains to be understood at a fundamental level. A careful look into many helical foldamers with known crystal structures[9] reveals a possible explanation for this perplexing fact and a possible means to realize induction of one handedness. Our examination shows that most of the helices contain exterior or interior bulky side chains that prevent the aromatic backbone from an efficient overlap among helices of the same handedness, and in all the cases studied, the helices contain two end groups (*e.g.*, aromatic protons and other larger groups) that repel each other through electrostatic interactions. We therefore envisioned that, by eliminating exterior and interior bulky side chains and incorporating two "sticky" groups at the helical ends containing electrostatically complementary functional groups, the resultant helices might be able to efficiently pile up to form energetically more stable 1D columnar stacks of the same handed helices that can further associate to form 3D ordered chiral crystal lattices.

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore. E-mail: chmzh@nus.edu.sg; Fax: +65-6779-1691; Tel: +65-6516-2683*
[b]*Division of Materials Science, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798*
[c]*Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian, China 350002*

† Electronic supplementary information (ESI) available. CCDC reference numbers 838391–838393 and 865971–865973. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc20219k

‡ These authors contributed equally to this work.

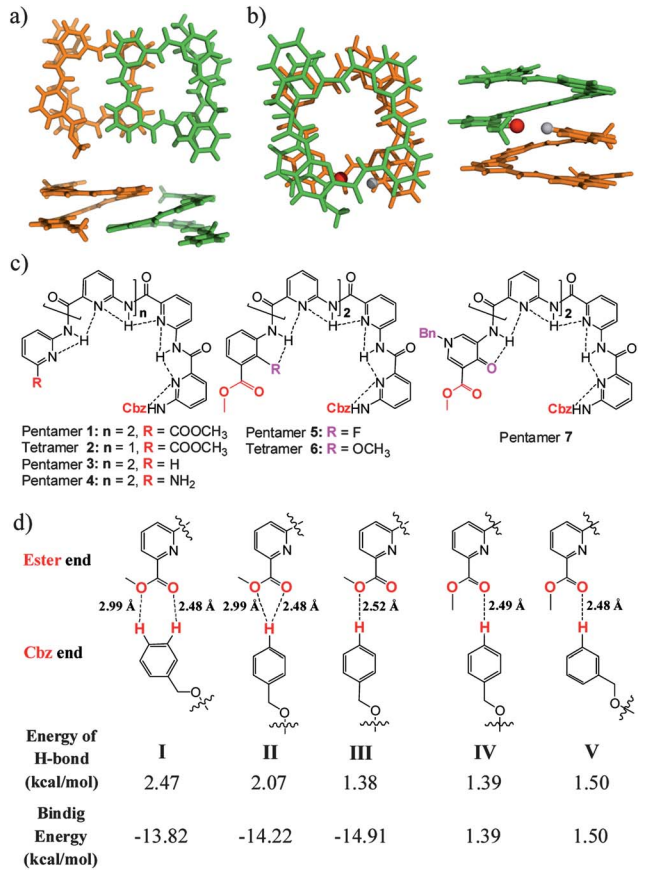
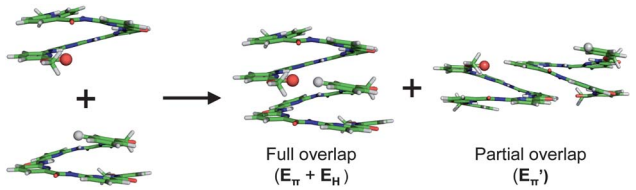


Fig. 1 Schematic illustrations of (a) partial edge and (b) "sticky end"-mediated full edge overlap of aromatic backbones of synthetic helices as well as (c) structures of pyridine-based helical foldamers **1–7** and (d) possible H-bonding modes and distances formed between the two complementary "sticky" end groups by virtue of partially charged O-atoms as H-bond acceptors from ester groups and aromatic protons as H-bond donors from Cbz groups as found in **1**, **2** and **5–7**. The energies of H-bonds in H-bonded structures **I–III** and in **IV** and **V** listed in d) were obtained with respect to their *E* and *Z* conformations, respectively. The binding energies arising from the formation of H-bonded structures **I–V** show that both **IV** and **V**, where the ester group adopts the *Z* conformation, are more stable than structures **I–III** by 15.21–16.30 kcal mol^{-1}. **IV** and **V** both form weakly stable complexes, releasing energies of 1.39 and 1.50 kcal mol^{-1}, respectively, upon complex formation while **I–III** are unlikely to form stable H-bonded structures. Also note that both **3** and **4** in c) contain no complementary end groups.

Results and discussion

To test the above hypothesis, the H-bond-rigidified pyridine-based pentamer **1** containing two complementary "sticky" ends (ester and Cbz, Fig. 1c and 1d) was conceived and used to help visualize the unprecedented foldamer-based chiral crystallization *via* complementarities in both shape and end functionalities, and was used for comparison with the recently reported crystal structures of tetramer **2**[9c] that does not contain a full helical turn (Fig. 1c) and pentamers **3**[9c] and **4**[9e] that contain a full helical turn but no "sticky" ends (Fig. 1c) to better appreciate the important structural factors influencing the chiral crystallization in synthetic helical foldamers. The two "sticky" ends were designed to form weak H-bonds between ester O-atoms and Cbz aromatic protons, computationally stabilizing the helical stacks by 1.3–2.5 kcal mol^{-1} at the B3LYP/6-311G(2d,p) level (Fig. 1d). This is not a very substantial energetic contribution but we thought that the two "sticky" helical ends only needed to be "sticky" enough to not repel each other as found in other synthetic helices. Under this hypothetical scenario, the attractive end-to-end interactions may cooperatively work with strong π–π stacking forces to promote efficient 1D chiral stacking among the helices of the same, rather than the opposite, handedness.

Table 1 Computationally determined driving forces dictating the energetic profiles[a] associated with full and partial overlaps involving helical backbones



	*M***1**·MeOH	*M***1**·CH_2Cl_2	*P***1**·CH_2Cl_2
E_π (kcal mol^{-1})	30.11	29.80	29.95
E_π' (kcal mol^{-1})	22.91	22.75	
E_H (kcal mol^{-1})	1.15[b]	1.14[b]	1.14[b]
E_{IC} (kcal mol^{-1})	45.57	45.03	46.74

[a] These energies originate from fully overlapped aromatic π–π stackings (E_π) and the weak intermolecular H-bond formed between the two "sticky" end groups (E_H), both of which dictate the formation of 1D chiral stacks of the same handed helices. Also computed are the partially overlapped aromatic π–π stackings (E_π') and the binding energy per helical pentamer (E_{IC}) responsible for the formation of the ordered 3D chiral lattice *via* intercolumnar edge-to-edge contacts. All these energies were calculated using Dreiding force field.[10] [b] Obtained after single point energy calculations at the level of B3LYP/6-311G(2d,p). The crystallographically determined distance of the H-bond between the two "sticky" end groups is 2.42 Å for *M***1**·MeOH and 2.44 Å for both *M***1**·CH_2Cl_2 and *P***1**·CH_2Cl_2.

The folding backbones of oligomers **1–4** are rigidified by internally placed high-strength intramolecular H-bonds between the pyridine N-atoms and amide protons (Fig. 1c and Fig. 2a), and **1** was synthesized using the experimental procedures recently established by us[9c,9d] (Scheme S1†). Crystals of **1** suitable for X-ray diffraction were initially grown by slow diffusion of methanol into **1**-containing dichloromethane solution. All the crystals obtained were verified to have a chiral space group, $P2_12_12_1$, and contain a discrete chain of methanol molecules residing in the helical interior of **1**. Due to an absence of heavy atoms, only one crystal with a Flack value of 0.0(11) can be confirmed to arise from the pure left-handed helices (*M***1**·MeOH, Fig. 2a), and the absolute handedness of all the other methanol-containing chiral crystals made up of either left- or right-handed (*M* or *P*) helices cannot be confidently deduced. To help determine the absolute handedness of the crystals, atoms of heavy elements, such as chlorine, need to be incorporated into the crystal lattices in a regular array. In this regard, some **1**-based crystals were purposely grown by slow evaporation or diffusion of hexane, acetone, or ethyl acetate into **1**-containing dichloromethane (CH_2Cl_2). Gratifyingly, slow diffusion of acetone or

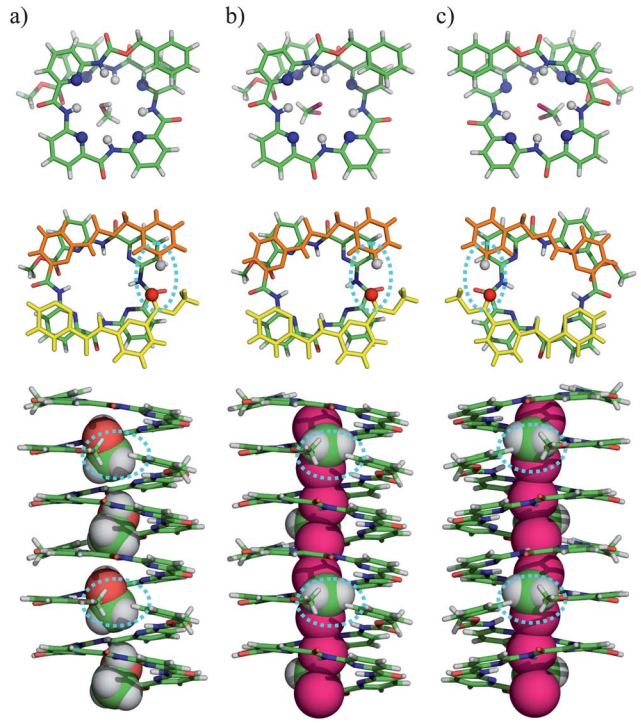


Fig. 2 Crystal structures and 1D columnar packing by helically folded pentamer **1** containing either MeOH or CH_2Cl_2 in their helical interiors. (a) and (b) are the left-handed helices of **1** (*M*-**1**·MeOH and *M*-**1**·CH_2Cl_2), and (c) describes the right-handed helices of **1** (*P*-**1**·CH_2Cl_2). Top, an individual pentamer molecule of **1** that illustrates the formation of an intramolecular H-bonding network by pyridine N-atoms (blue balls) and amide protons (grey balls), inducing a helical structure in **1**. Middle, complementary end groups from helical fragments in dotted ovals, illustrating the formation of a weak intermolecular H-bond of C=O···H–C type (d_{O-H} = 2.44 Å, also see type **V** H-bond in Fig. 1d) between the end ester O-atom (red ball) and Cbz aromatic proton (grey ball). The efficient full-edge overlap among helical backbones is clearly visible too. Bottom, The complementary "sticky" end groups highlighted in dotted ovals "glue" single-handed helical pentamers, *via* numerous weak H-bonds of 2.44 Å in length, into an infinite single-handed helical chiral column along the crystallographic *a* axis, enclosing small molecules in a chain-like fashion.

ethyl acetate into CH_2Cl_2 did lead to the chiral crystals containing regularly arrayed CH_2Cl_2 molecules that produce anomalous dispersion effects, allowing the corresponding helical structures to be unambiguously determined to be left- or right-handed, *e.g*, *M*-**1**·CH_2Cl_2 (Fig. 2b) or *P*-**1**·CH_2Cl_2 (Fig. 2c), respectively.

From the crystal structures of *M*-**1**·MeOH, *M*-**1**·CH_2Cl_2 and *P*-**1**·CH_2Cl_2, the existence of a strong intramolecular H-bonding network in **1** is apparent that restricts the conformational freedom of the amide bonds and causes the aromatic backbone of **1** to curve in one direction, and eventually into a helical conformation (top and bottom, Fig. 2) as demonstrated similarly by helical pentamer **3**.[9c] The enclosed cavity of about 2.75 Å in radius allows small guest molecules, such as methanol or dichloromethane, to sit inside the helical interior *via* stabilizing H-bonds between **1** and trapped guest molecules.

Importantly, the end groups designed to be complementary and "sticky" turned out to be complementary to each other, and to stick to each other to form a weak H-bond between the ester carbonyl O-atom and Cbz aromatic proton (middle, Fig. 2) by virtue of the type **V** H-bonding mode (Fig. 1d). These numerous feeble but "attractive" H-bonding forces enable the helices of the same handedness to efficiently pack on top of each other *via* full overlap of helically folded aromatic backbones to form a one-handed helical column (bottom, Fig. 2).

As represented by the left-handed crystal structure of *M*-**1**·CH_2Cl_2 in Fig. 3a, all the 1D chiral columnar stacks contain two sets of identical complementary "sticky" end groups located in front of and behind the helical columns. They "seamlessly" glue numerous helices of the same handedness into a 1D chiral stack that appears to be built from a single chiral polymeric backbone, rather than from a copious amount of short oligomers (Fig. 3b). This points to a potentially realizable strategy for constructing single-handed chiral polymers by introducing some reactive chemical handles into the exterior of the pentameric backbone and cross-linking, through chemical conjugation reactions, these one-dimensionally arrayed pentamers to form a "seamlessly" integrated chiral polymeric backbone. In the 3D sense, the 1D chiral columns are regularly spaced with a centre-to-centre distance of 13.7 Å to form a pseudo-hexagonal arrangement. These pseudo-hexagons recur in the 2D space, leading to the formation of a 3D chiral crystal lattice.

Obtaining these chiral crystals suggests a selection process that differentiates helices of opposite handedness during the crystal growth. Presumably, this selection is governed by both attractive end-to-end interactions and favorable aromatic π–π stacking forces. For comparison, tetramer **2**, whose main backbone, excluding the Cbz group, is too short to furnish a helical turn, probably lacks sufficient driving forces from aromatic π–π contacts despite the fact that **2** does contain complementary "sticky" end groups. Accordingly, **2** does not form 1D chiral stacks and only racemic helices sterically induced by Cbz groups are found in the crystals where the Cbz groups adopt two

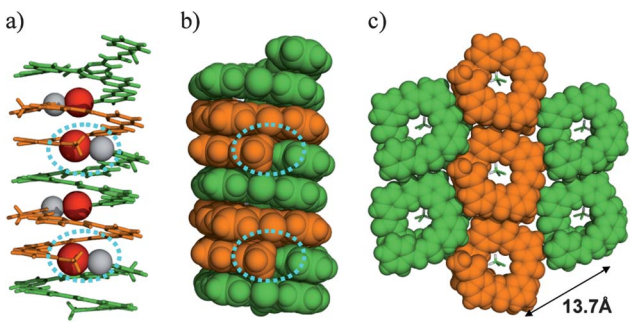


Fig. 3 1D and 3D chiral packing by **1** in *M*-**1**·CH_2Cl_2 *via* complementary "sticky" end groups, aromatic π–π stacking forces and inter-columnar edge-to-edge contacts. (a) 1D chiral stack containing two sets of complementary "sticky" end groups in front of (dotted ovals) and behind the column; (b) CPK representation illustrating a seamlessly formed 1D chiral stack that appears to be made up of a single polymeric chiral backbone rather than numerous short oligomers; (c) intercolumnar edge-to-edge contacts *via* partially charged exterior oxygen and hydrogen atoms that lead to the formation of a pseudo-hexagonal arrangement of the 1D chiral stacks from (b). In green columns in (c), Cbz end groups point up, while in orange columns, it is the ester group that points up.

different orientations that are roughly perpendicular to or parallel to the main backbone.[9c] On the other hand, pentamers **3**[9c] and **4**[9e] are long enough to take up a helical shape, and thereby have adequate driving forces for full overlap involving helical backbones. Undesirably, the two end groups composed of aromatic or amine protons repel each other, resulting in the disruption of otherwise possibly formed chiral stacks. In this case, achiral crystals are also found where helices of opposite handedness interact more strongly than the corresponding helices of the same handedness.[9c,9e]

To assess the generality of the design principle, and to examine our above hypothesis on the possible disruption of the chiral crystallization by either exterior or interior side chains, three closely related pentamers **5–7** were also synthesized by replacing the end pyridine unit with other monomeric repeating units derived from fluorobenzene,[11a,11b] methoxybenzene[11c–i] and pyridine motifs, respectively.[11j,11k] Highly desirably, the "sticky" ends in **5** carrying no side chains are also capable of directing the aromatic helical backbones to pack on top of each other, forming 1D chiral stacks of left-handedness (Fig. 4a) and subsequently a 3D chiral crystal lattice. However, the presence of either interior methoxy side chain as in **6** or exterior benzyl side chain as found in **7** "overrides" the directing power of "sticky" end groups by disallowing the full-edge overlap of helical backbones in **6** (Fig. 4b) and **7** (Fig. 4c), thereby causing the helices of opposed handedness to interact more favourably with each other than with the helices of the same handedness. Accordingly, only achiral crystals were obtained for both **6** and **7**.

A quantitative understanding of the driving forces underlying the formation of both 1D chiral stacks and 3D chiral lattices was provided by carrying out computational investigations using Dreiding force field on pentamer **1** (Table 1).[10] Single point energy calculations on the corresponding structural motifs directly taken from their crystal structures yield the binding energies of varying components (E_π for aromatic π–π stacking *via* full overlap and E_{IC} for the formation of the ordered 3D chiral lattice *via* intercolumnar edge-to-edge contacts as illustrated in Fig. 3c). To derive the binding energy (E_H, Table 1) of the weak H-bond formed between the ester carbonyl O-atom and Cbz aromatic proton from the two "sticky" ends (middle, Fig. 2), short fragments identical to type **V** in Fig. 1d were taken directly from the crystal structure and were computed at the level of B3LYP/6-311G(2d,p). The binding energies (E_π', Table 1) for the partially overlapped helical backbones were computed based on the helical structural motifs from the crystal structures that have been computationally optimized to furnish a dimer structure comprising both left- and right-handed helices (Fig. 1a and Table 1). From the energies tabulated in Table 1, it can be seen that efficient aromatic stacking is the major driving force, contributing ~30 kcal mol^{-1} per helical pentamer into the 1D chiral stack that is further stabilized by weak yet indispensable intermolecular H-bonds of ~1.1 kcal mol^{-1} in strength. Association of the formed 1D chiral stacks into a 3D chiral crystal lattice *via* inter-columnar edge-to-edge contacts is greatly facilitated by the exterior, arrayed and partially charged O- and H-atoms, which provide a binding energy of ~46 kcal mol^{-1} per helical pentamer and allow the pseudo-hexagonal arrangement involving seven pentamers (Fig. 3c) to repeatedly extend over the 2D space. As a good reference, partial overlap of helical backbones generates ~23 kcal mol^{-1} per pentamer (Fig. 1a and Table 1), a value that is ~7 kcal mol^{-1} less than the full overlap.

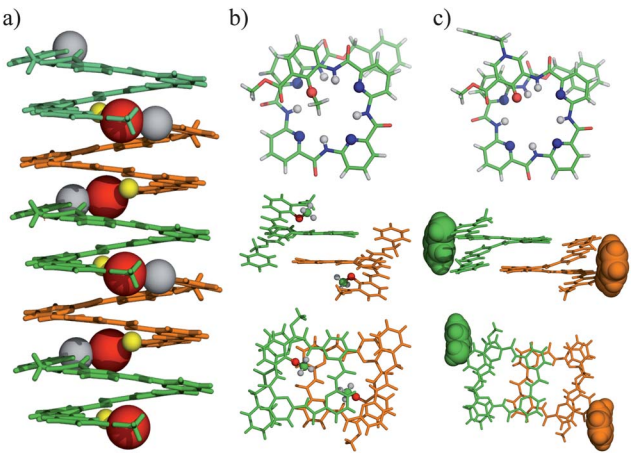


Fig. 4 (a) 1D chiral stack formed by **5** in its left-handed chiral crystals *via* complementary "sticky" end groups, shown as red and grey balls, and aromatic π–π stacking forces; fluorine atoms are indicated by small yellow balls and disordered solvents (MeOH and CH_2Cl_2) trapped in the interior hollow cavity are omitted. (b) and (c) illustrate the H-bond-enforced helical geometries adopted by both **6** and **7** as well as the partial-edge overlaps among their helical backbones in the solid state. Due to the presence of interior or exterior side chains, both **6** and **7** were found to produce achiral crystals.

Conclusions

As demonstrated by helical pentamers **1** and **5**, we provide here the very first examples of synthetic helical foldamers where chiral crystallization apparently proceeds without resorting to chiral or external perturbations by utilizing two complementary "sticky" groups at the two ends of the helically folded molecular strands and by further taking advantage of the fact that full overlap of helical backbones is energetically more favored than the corresponding partial overlap by ~7 kcal mol^{-1} in the case of pentamer **1**. In contrast, without these complementary "sticky" groups as evidenced by **3** and **4** or with the presence of exterior side chains as in **6** and interior side chains as in **7**, intra-columnar packing turns out to be greatly impeded, and chiral crystallization does not occur. This strategy may have uses in yielding single-handed helices not only in synthetic foldamers of varying types that are oligomeric in nature[1] but also in polymers,[2] and therefore may open a new avenue for creating optically active materials for interesting applications.

Acknowledgements

Financial support of this work to H.Z. was provided by The National Research Foundation (R-154-000-529-281), NUS AcRF Tier 1 grants (R-143-000-419-646 and R-143-000-442-112) and Singapore Environment and Water Industry Development Council and Economic Development Board (SPORE, COY-15-EWI-RCFSA/N197-1).

Notes and references

1 (*a*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; (*b*) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; (*c*) M. S. Cubberley and B. L. Iverson, *Curr. Opin. Chem. Biol.*, 2001, **5**, 650; (*d*) A. R. Sanford, K. Yamato, X. Yang, L. Yuan, Y. Han and B. Gong, *Eur. J. Biochem.*, 2004, **271**, 1416; (*e*) C. Schmuck, *Angew. Chem., Int. Ed.*, 2003, **42**, 2448; (*f*) I. Huc, *Eur. J. Org. Chem.*, 2004, 17; (*g*) R. P. Cheng, *Curr. Opin. Struct. Biol.*, 2004, **14**, 512; (*h*) C. Z. Li, X. K. Jiang, Z. T. Li, X. Gao and Q. R. Wang, *Chin. J. Org. Chem.*, 2007, **27**, 188; (*i*) C. M. Goodman, S. Choi, S. Shandler and W. F. DeGrado, *Nat. Chem. Biol.*, 2007, **3**, 252; (*j*) B. Gong, *Acc. Chem. Res.*, 2008, **41**, 1376; (*k*) Z. T. Li, J. L. Hou and C. Li, *Acc. Chem. Res.*, 2008, **41**, 1343; (*l*) W. S. Horne and S. H. Gellman, *Acc. Chem. Res.*, 2008, **41**, 1399; (*m*) I. Saraogi and A. D. Hamilton, *Chem. Soc. Rev.*, 2009, **38**, 1726; (*n*) D. Haldar and C. Schmuck, *Chem. Soc. Rev.*, 2009, **38**, 363; (*o*) H. Juwarker and K.-S. Jeong, *Chem. Soc. Rev.*, 2010, **39**, 3664; (*p*) X. Zhao and Z. T. Li, *Chem. Commun.*, 2010, **46**, 1601; (*q*) G. Guichard and I. Huc, *Chem. Commun.*, 2011, **47**, 5933.

2 (*a*) T. Nakano and Y. Okamoto, *Chem. Rev.*, 2001, **101**, 4013; (*b*) E. Yashima, K. Maeda, H. Iida, Y. Furusho and K. Nagai, *Chem. Rev.*, 2009, **109**, 6102.

3 (*a*) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 6206; (*b*) D. H. Appella, L. A. Christianson, D. A. Klein, M. R. Richards, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 7574; (*c*) R. B. Prince, L. Brunsveld, E. W. Meijer and J. S. Moore, *Angew. Chem., Int. Ed.*, 2000, **39**, 228.

4 (*a*) Z. Dong, G. P. A. Yap and J. M. Fox, *J. Am. Chem. Soc.*, 2007, **129**, 11850; (*b*) H.-Y. Hu, J.-F. Xiang, Y. Yang and C.-F. Chen, *Org. Lett.*, 2008, **10**, 69; (*c*) C. Dolain, H. Jiang, J. M. Leger, P. Guionneau and I. Huc, *J. Am. Chem. Soc.*, 2005, **127**, 12943; (*d*) A. M. Kendhale, L. Poniman, Z. Dong, K. Laxmi-Reddy, B. Kauffmann, Y. Ferrand and I. Huc, *J. Org. Chem.*, 2011, **76**, 195; (*e*) Y. Inai, K. Tagawa, A. Takasu, T. Hirabayashi, T. Oshikawa and M. Yamashita, *J. Am. Chem. Soc.*, 2000, **122**, 11731; (*f*) Y. Inai, Y. Ishida, K. Tagawa, A. Takasu and T. Hirabayashi, *J. Am. Chem. Soc.*, 2002, **124**, 2466; (*g*) Y. Inai, N. Ousaka and T. Okabe, *J. Am. Chem. Soc.*, 2003, **125**, 8151; (*h*) Y. Inai, H. Komori and N. Ousaka, *Chem. Rev.*, 2007, **7**, 191.

5 E. D. King, P. Tao, T. T. Sanan, C. M. Hadad and J. R. Parquette, *Org. Lett.*, 2008, **10**, 1671.

6 (*a*) H. Miyake, K. Yoshida, H. Sugimoto and H. Tsukube, *J. Am. Chem. Soc.*, 2004, **126**, 6524; (*b*) V. R. Naidu, M. C. Kim, J.-M. Suk, H.-J. Kim, M. Lee, E. Sim and K.-S. Jeong, *Org. Lett.*, 2008, **10**, 5373; (*c*) R. M. Meudtner and S. Hecht, *Angew. Chem., Int. Ed.*, 2008, **47**, 4926; (*d*) J.-M. Suk, V. R. Naidu, X. Liu, M. S. Lah and K.-S. Jeong, *J. Am. Chem. Soc.*, 2011, **133**, 13938.

7 (*a*) C. Li, G.-T. Wang, H.-P. Yi, X.-K. Jiang, Z.-T. Li and R.-X. Wang, *Org. Lett.*, 2007, **9**, 1797; (*b*) M. S. Gin, T. Yokozawa, R. B. Prince and J. S. Moore, *J. Am. Chem. Soc.*, 1999, **121**, 2643; (*c*) R. B. Prince, S. A. Barnes and J. S. Moore, *J. Am. Chem. Soc.*, 2000, **122**, 2758; (*d*) J. L. Hou, X. B. Shao, G. J. Chen, Y. X. Zhou, X. K. Jiang and Z. T. Li, *J. Am. Chem. Soc.*, 2004, **126**, 12386; (*e*) H. Abe, N. Masuda, M. Waki and M. Inouye, *J. Am. Chem. Soc.*, 2005, **127**, 16189; (*f*) S. J. Wezenberg, G. Salassa, E. C. Escudero-Adán, J. Benet-Buchholz and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2011, **50**, 713; (*g*) Y. Ferrand, A. M. Kendhale, B. Kauffmann, A. Grlard, C. Marie, V. Blot, M. Pipelier, D. Dubreuil and I. Huc, *J. Am. Chem. Soc.*, 2010, **132**, 7858.

8 For non-foldamer molecules, at most 5–10% of racemic solutions spontaneously resolve into chiral crystals, a process that still remains poorly understood, see: J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, 3rd ed.; Krieger Publishing Co.: Malabar, FL, 1994.

9 (*a*) Y. Yan, B. Qin, Y. Y. Shu, X. Y. Chen, Y. K. Yip, D. W. Zhang, H. B. Su and H. Q. Zeng, *Org. Lett.*, 2009, **11**, 1201; (*b*) Y. Yan, B. Qin, C. L. Ren, X. Y. Chen, Y. K. Yip, R. J. Ye, D. W. Zhang, H. B. Su and H. Q. Zeng, *J. Am. Chem. Soc.*, 2010, **132**, 5869; (*c*) W. Q. Ong, H. Q. Zhao, Z. Y. Du, J. Z. Y. Yeh, C. L. Ren, L. Z. W. Tan, K. Zhang and H. Q. Zeng, *Chem. Commun.*, 2011, **47**, 6416; (*d*) W. Q. Ong, H. Q. Zhao, X. Fang, S. Woen, F. Zhou, W. L. Yap, H. B. Su, S. F. Y. Li and H. Q. Zeng, *Org. Lett.*, 2011, **13**, 3194; (*e*) H. Q. Zhao, W. Q. Ong, X. Fang, F. Zhou, M. N. Hii, S. F. Y. Li, H. B. Su and H. Q. Zeng, *Org. Biomol. Chem.*, 2012, **10**, 1172.

10 S. L. Mayo, B. D. Olafson and W. A. Goddard III, *J. Phys. Chem.*, 1990, **94**, 8897.

11 (*a*) C. L. Ren, F. Zhou, B. Qin, R. J. Ye, S. Shen, H. B. Su and H. Q. Zeng, *Angew. Chem., Int. Ed.*, 2011, **50**, 10612; (*b*) C. L. Ren, S. Y. Xu, J. Xu, H. Y. Chen and H. Q. Zeng, *Org. Lett.*, 2011, **13**, 3840; (*c*) B. Qin, X. Y. Chen, X. Fang, Y. Y. Shu, Y. K. Yip, Y. Yan, S. Y. Pan, W. Q. Ong, C. L. Ren, H. B. Su and H. Q. Zeng, *Org. Lett.*, 2008, **10**, 5127; (*d*) B. Qin, C. L. Ren, R. J. Ye, C. Sun, K. Chiad, X. Y. Chen, Z. Li, F. Xue, H. B. Su, G. A. Chass and H. Q. Zeng, *J. Am. Chem. Soc.*, 2010, **132**, 9564; (*e*) B. Qin, W. Q. Ong, R. J. Ye, Z. Y. Du, X. Y. Chen, Y. Yan, K. Zhang, H. B. Su and H. Q. Zeng, *Chem. Commun.*, 2011, **47**, 5419; (*f*) B. Qin, C. Sun, Y. Liu, J. Shen, R. J. Ye, J. Zhu, X.-F. Duan and H. Q. Zeng, *Org. Lett.*, 2011, **13**, 2270; (*g*) B. Qin, S. Shen, C. Sun, Z. Y. Du, K. Zhang and H. Q. Zeng, *Chem.–Asian J.*, 2011, **6**, 3298; (*h*) B. Qin, L. Jiang, S. Shen, C. Sun, W. Yuan, S. F. Y. Li and H. Q. Zeng, *Org. Lett.*, 2011, **13**, 6212; (*i*) Y. Liu, B. Qin and H. Q. Zeng, *Sci. China: Chem.*, 2012, **55**, 55; (*j*) C. L. Ren, V. Maurizot, H. Q. Zhao, J. Shen, F. Zhou, W. Q. Ong, Z. Y. Du, K. Zhang, H. B. Su and H. Q. Zeng, *J. Am. Chem. Soc.*, 2011, **133**, 13930; (*k*) Z. Y. Du, C. L. Ren, R. J. Ye, J. Shen, Y. J. Lu, J. Wang and H. Q. Zeng, *Chem. Commun.*, 2011, **47**, 12488.

