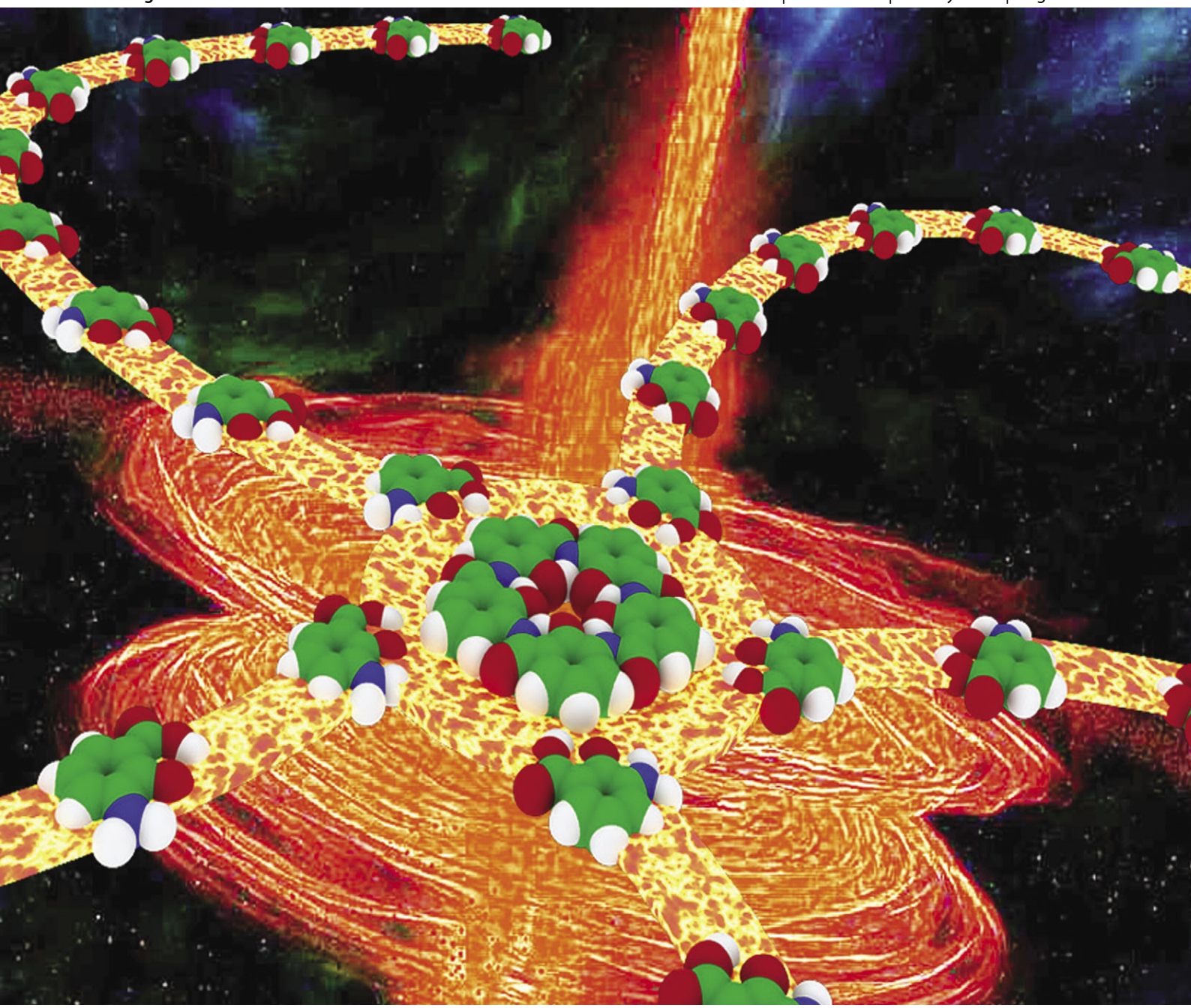
ChemComm

Chemical Communications

www.rsc.org/chemcomm

Volume 47 | Number 19 | 21 May 2011 | Pages 5345–5636



ISSN 1359-7345

COMMUNICATION

Huaqiang Zeng *et al.*

Highly selective one-pot synthesis of H-bonded pentagon-shaped circular aromatic pentamers

1359-7345(2011)47:19;1-C

ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2011, **47**, 5419–5421

www.rsc.org/chemcomm

COMMUNICATION

Highly selective one-pot synthesis of H-bonded pentagon-shaped circular aromatic pentamers†

Bo Qin,[a] Wei Qiang Ong,[a] Ruijuan Ye,[a] Zhiyun Du,[b] Xiuying Chen,[c] Yan Yan,[a] Kun Zhang,[b] Haibin Su[c] and Huaqiang Zeng*[a]

Received 26th December 2010, Accepted 20th January 2011
DOI: 10.1039/c0cc05791f

One-pot, multi-molecular macrocyclization allows the highly selective preparation of pentagon-shaped circular aromatic pentamers mediated by an inward-pointing continuous hydrogen-bonding network.

Recently, we[1a–d] and others[1e,f] described a series of folding molecules with their helically or circularly folded structures enforced by internally placed continuous H-bonding networks. A unique structural feature shared by these folding molecules and recently elucidated by us[1a–d] lies in an intrinsic peculiarity, needing five identical repeating units to form either a macrocycle[1a,b] or helical turn.[1c,d] In particular, the nearly planar pentagon shape found in these macrocyclic pentamers[1a,b] is very unusual among shape-persistent macrocycles,[2] and bears no precedent among either H-bonded macrocycles[3] or synthetic foldamers[4] except for very recently reported *fivefold*-symmetric Schiff base macrocycles.[5a] Inspired by the prominent examples of one-pot, H-bonding assisted multi-molecular macrocyclization reactions,[3d,g,k] we became interested in investigating the possibility to efficiently and selectively produce H-bond rigidified pentagon-shaped macrocyclic pentamers in one-pot from their monomeric building blocks. Our interest in this work is not only due to the recurring challenges associated with the efficient one-pot preparation of shape-persistent macrocycles, in particular, H-bonded ones that are currently very limited in scope and applicable to only a few monomer building blocks, but also due to their proven ability to (i) bind neutral[3h,r] or organic cationic species,[5b] (ii) serve as an ion transporter across cell membranes,[5c] (iii) stabilize DNA G-quadruplex structures[5d] and (iv) very recently selectively recognize alkali metal ions.[1b] Additionally, the *fivefold* symmetry built into the aromatic backbone should promise some unique applications in such as targeting biological pentamers.[1a]

Compared to one-pot macrocyclization systems involving symmetric monomers,[3d,g,k] our system is further complicated by (i) the presence of both acid and amine groups on the same unsymmetrical bifunctional monomers, forcing us to look beyond the classical conditions for acid chloride generation, (ii) the H-bonding enforced, more curved backbone that either lowers down the reactivity of both acid and amine or introduces the steric hindrance in the backbone, rendering the typical amide coupling agents (DCC, EDC, HATU, *etc.*; Table 1) totally ineffective, and (iii) the additional steric hindrance originating from five sticking-out interior methyl groups,[1a] increasing the energetic barrier for macrocyclization and possibly impeding its efficient cyclization, especially when combined with the remote steric hindrance between the end residues.[3g] This likelihood can be manifested by the

Table 1 Searching suitable conditions[a] for one-pot preparation of circular pentamer **1** from monomer **1a**

Entry	Coupling reagent	Base	Solvent	Yield[b] (%)
1	DCC	—[c]	CH_2Cl_2	—[d]
2	EDC	—[c]	CH_2Cl_2	—[d]
3	HATU	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
4	BOP	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
5	HATU/HOBt	DIEA	DMF/CH_2Cl_2 (1 : 1)	Trace
6	TSTU	DIEA	DMF/CH_2Cl_2 (1 : 1)	Trace
7	CDI	DIEA	DMF/CH_2Cl_2 (1 : 1)	Trace
8	$P(OPh)_3$	Pyridine	NMP	—[d]
9	Ph_3PCl_2	—[c]	$CHCl_3$	—[d]
10	Ph_3PCl_2	—[c]	THF	—[d]
11	$POCl_3$	—[c]	THF	—[d]
12	$POCl_3$	—[c]	Toluene	5
13	$POCl_3$	—[c]	CH_2Cl_2	6
14	$POCl_3$	DIEA	CH_2Cl_2	10
15	$POCl_3$	DIEA	CH_3CN	36
16	*$POCl_3$*	*TEA*	*CH_2Cl_2*	*25*
17	*$POCl_3$*	*TEA*	*CH_3CN*	*46*
18	$POCl_3$	Pyridine	CH_2Cl_2 or CH_3CN	Trace
19	$POCl_3$	NMM	CH_2Cl_2 or CH_3CN	Trace
20	$POCl_3$	DMAP	CH_2Cl_2	6
21	$POCl_3$	DMAP	CH_3CN	Trace

[a] Reaction conditions: **1a** (0.2 mmol), coupling reagents (0.4 mmol), base (0.6 mmol), solvent (2.0 ml), room temperature, 12 h. [b] Isolated yield by flash column chromatography. [c] No base is used. [d] No product can be detected. NMP = *N*-methylpyrrolidone; NMM = *N*-methylmorpholine.

[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] *Faculty of Chemical Engineering and Light Industry, Guang Dong University of Technology, Guang Dong, 510006, China*
[c] *Division of Materials Science, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798. E-mail: HBSu@ntu.edu.sg; Fax: +65 6790-9081; Tel: +65 6790-4346*

† Electronic supplementary information (ESI) available: Synthetic procedures and a full set of characterization data including ^{1}H NMR, ^{13}C NMR, MS, H–D exchange and molecular modelling. See DOI: 10.1039/c0cc05791f

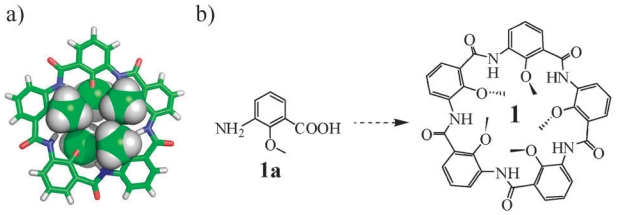


Fig. 1 (a) Top view of crystal structure of **1** with methoxy methyl groups in CPK representations,[1a] showing the steric crowding involving the interior methyl groups. (b) Illustration of one-pot synthesis of pentamer **1** from its monomer precursor **1a**.

considerable difficulty we encountered during the last step end-to-end amide coupling reaction that transforms the acyclic pentamer precursor into circular pentamer **1** by intramolecular cyclization (Fig. 1).†[1a]

Peptide coupling reagents first came to our mind because of the simplicity in procedures and mild conditions under which amide bonds form from carboxylic acids and amines. The well known coupling reagents of varying types were tested that, in some cases (entries 1–4 in Table 1), failed to produce detectable amounts of circular pentamer **1**, and in other cases (entries 5–7) yielded **1** in a trace amount. The initial screening of phosphorus-based reagents, allowing the *in situ* generation of acid chloride, turned out to be unsuccessful (entries 8–11). The subsequent screening of phosphoryl trichloride, $POCl_3$, in either toluene (entry 12) or dichloromethane (CH_2Cl_2, entry 13) gave rise to a very encouraging yield of 5% and 6%, respectively. Addition of three equivalent organic bases such as diisopropylethylamine (DIEA, entry 14) increased the chemical yield to 10% in CH_2Cl_2. Replacement of CH_2Cl_2 with CH_3CN further increased the chemical yield of **1** to 36% (entry 15). A further screening of various bases (entries 16–23) in both CH_2Cl_2 and CH_3CN led to the discovery of triethylamine (TEA) as the powerful organic base that allowed the efficient production of **1** under a high concentration of 100 mM in good and excellent yields of 25% and 46%, respectively. A chemical yield of 46% is considered excellent with respect to the stepwise construction of **1** that gives an overall yield of ~5% after months of dedicated effort.[1a]

The one-pot macrocyclization reaction is influenced significantly by the amount of coupling reagent ($POCl_3$) and base (TEA) used (Table 2). While 1 : 2 : 3 ratio of **1a** : $POCl_3$: TEA (entry 2) produced **1** with 25% and 46% yields in dichloromethane and acetonitrile, respectively, only a trace amount or a low yield of 5% for **1** can be obtained in the same solvents when the amount of $POCl_3$ was reduced from two to one equivalents (entry 1). The use of either more of $POCl_3$ (entry 3) or less of TEA (entry 4) lowered down the chemical yields significantly when compared to entry 2. Other solvents permitting one-pot preparation of **1** include acetone (12%), THF (14%), $CHCl_3$ (20%) and toluene (17%). No cyclization product **1** can be generated when DMSO is used as the solvent possibly due to its strong H-bonding ability that disrupts the crescent conformation in the intermediate oligomers, a prerequisite for the efficient backbone cyclization.

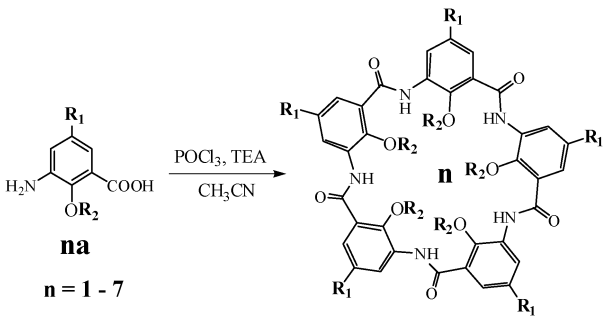
Table 2 Effects of coupling reagent ($POCl_3$) and base (TEA)[a] on one-pot preparation of circular pentamer **1** from monomer **1a**

			Yield[b] (%)	
Entry	$POCl_3$/equiv.	TEA/equiv.	CH_2Cl_2	CH_3CN
1	1.1	3.0	Trace	5
2	*2.0*	*3.0*	*25*	*46*
3	3.0	3.0	21	35
4	2.0	2.0	18	28

[a] Reaction conditions: **1a** (0.2 mmol = 1 equiv.), $POCl_3$, TEA, CH_3CN (2.0 ml), room temperature, 12 h. [b] Isolated yield by flash column chromatography.

The general utility of one-pot macrocyclization conditions was demonstrated by the satisfactory preparation of other circularly folded aromatic pentamers **2–7**, sharing the same aromatic backbone but differing by interior (R_1) and exterior (R_2) side chains (Table 3). Pentamer **5** with a poor solubility of <0.04 mM in CH_3CN was produced in a comparably much lower yield of 24%. Bulky groups such as isopropyl groups and ethyl groups decreased the production yields of **4** and **6** considerably to 31% and 32%, respectively. In addition to bulky ethyl groups in its interior, the poor yield of **7** *via* one-pot condensation possibly can be accounted for by its poor solubility (<0.25 mM) in CH_3CN. The evidences that (i) no circular tetramers or heptamers were observed during the synthesis of **1–7** and (ii) 6% of hexamer was only obtained during the preparation of **1** but not **2–7** suggest that the pentameric macrocycle consisting of five identical repeating units is energetically more favored over other four-, six- and seven-residue macrocycles. Consistent with this experimental

Table 3 One-pot preparation[a] of circular aromatic pentamers **1–7** from their respective monomers **1a–7a**, and the half-lives (h) of H–D exchange[b] of amide protons in **1–7**



				Half-life[b]/h	
Aromatic pentamer	R_1	R_2	Yield[c] (%)	2.0 mM	0.2 mM
1	H	Me	46 (6)[d]	6.3	1.49
2	O*n*-C_8H_{17}	Me	42	8.7	4.28
3	OMe	Me	45	—[e]	5.74
4	Oi-Pr	Me	31	31.6	7.50
5	Me	Me	24	—[e]	2.40
6	H	Et	32	5.2	0.22
7	OMe	Et	26	∞[f]	12.4

[a] Reaction conditions: ***n*a** (0.2 mmol), $POCl_3$ (0.4 mmol), TEA (0.6 mmol), CH_3CN (2.0 ml), room temperature, 12 h. [b] Half-lives of H–D exchange data were measured at 2.0 mM or 0.2 mM in 5% D_2O/47.5% DMSO-d_6/47.5% $CDCl_3$ (v/v) at room temperature. [c] Isolated yield by flash column chromatography. [d] Yield of the hexamer. [e] Not soluble at 2.0 mM. [f] No H–D exchange was observed over three days.

observation, theoretical treatments of circularly folded macrocycles containing from 4 to 7 residues at the B3LYP/6-31G* level show that the relative stability per repeating unit increases in the order of tetramer **9** < heptamer **11** < hexamer **10** < pentamer **1** with or without explicit solvents.†

The strength of these internally located intramolecular H-bonds in **1–7** was quantitatively measured by amide proton–deuterium (H–D) exchange experiments carried out at 2.0 mM (Table 3).[1a,c,d] Since the intermolecular aggregation in **1–7** is an unlikely event,†[1a] the half-lives of H–D exchange should enable the direct correlation between the H–D half-life and H-bond strength. From entry 6, it is evidenced that the steric crowding involving bulkier ethoxy groups in **6** does not impede the efficient H–D exchange, and amide protons can be accessed well by D_2O molecules. The determined half-life values show that the H-bond strength among **1–7** highly likely increases in the order of **6** < **1** < **5** < **2** < **3** < **4** < **7**.

A further examination of these H–D exchange values shows that the exteriorly located electron-donating alkoxy side chains (i) cause a large variation in H-bond strength and (ii) make intramolecular H-bonds in pentamers **2–4** and **7** stronger than those found in pentamers **1** and **6** that carry no side chains. These findings agree well with the similar trends seen for a series of H-bonding stabilized crescent-shaped oligomers recently reported by us.[1d] Comparison of H–D exchange data for amide protons in **1** ($t_{1/2}$ = 1.49 h) and **6** ($t_{1/2}$ = 0.22 h) suggests much weakened intramolecular H-bonds in **6** relative to those in **1**. Largely, this may be due to the bulkier interior ethyl groups in **6** that cause a larger backbone distortion and so weaken the H-bonds in **6** more than those in **1**. Computationally, the aromatic backbone in **6** is more distorted than that in **1**.†

Our current investigation makes possible the highly selective production of circularly folded aromatic pentamers *via* H-bonding assisted one-pot macrocyclization reactions with excellent yields of ~50% under mild conditions within a day. This greener protocol is far more cost-effective and time-saving than the lengthy step-by-step process, giving circular pentamers in about 5% yields after months of effort as previously reported by us.[1a,b] The established one-pot macrocyclization protocol should enable a facile access to diverse pentamers for targeting biological pentamers,[1a] and for fine-tuning their already demonstrated high ion-binding affinity and selectivity,[1b] especially when coupled with the demethylating methodologies for the selective removal of interior methyl groups that are currently under investigation.

Financial support of this work by the NUS AcRF Tier 1 grants (R-143-000-375-112 and R-143-000-398-112 to H.Z.), A*STAR BMRC research consortia (R-143-000-388-305 to H.Z.) and A*STAR SERC grant (M47070020 to H.S.) is acknowledged.

Notes and references

1 (*a*) 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; (*b*) 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; (*c*) 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; (*d*) 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; (*e*) J.-L. Hou, H.-P. Yi, X.-B. Sha, C. Li, Z.-Q. Wu, X.-K. Jian, L.-Z. Wu, C.-H. Tung and Z.-T. Li, *Angew. Chem., Int. Ed*., 2006, **45**, 796; (*f*) D. Kanamori, T. A. Okamura, H. Yamamoto and N. Ueyama, *Angew. Chem., Int. Ed*., 2005, **44**, 969.

2 For some reviews on shape-persistent macrocycles, see: (*a*) J. L. Sessler and D. Seidel, *Angew. Chem., Int. Ed*., 2003, **42**, 5134; (*b*) R. Misra and T. K. Chandrashekar, *Acc. Chem. Res*., 2008, **41**, 265; (*c*) W. Zhang and J. S. Moore, *Angew. Chem., Int. Ed*., 2006, **45**, 4416; (*d*) N. E. Borisova, M. D. Reshetova and Y. A. Ustynyuk, *Chem. Rev*., 2007, **107**, 46; For pillar[5]arene-based macrocycles whose pentameric backbone is 3D-shaped rather than 2D planar, see: (*e*) C. Han, F. Ma, Z. Zhang, B. Xia, Y. Yu and F. Huang, *Org. Lett*., 2010, **12**, 4360; (*f*) Z. Zhang, Y. Luo, B. Xia, C. Han, Y. Yu, X. Chena and F. Huang, *Chem. Commun*., 2011, DOI: 10.1039/c0cc03732j.

3 For H-bonded macrocycles, see: (*a*) Z. T. Li, J. L. Hou, C. Li and H. P. Yi, *Chem.–Asian J*., 2006, **1**, 766; (*b*) S. M. Hecht and I. Huc, *Foldamers: Structure, Properties and Applications*, Wiley-VCH, 2007; (*c*) B. Gong, *Acc. Chem. Res*., 2008, **41**, 1376; (*d*) L. Yuan, W. Feng, K. Yamato, A. R. Sanford, D. Xu, H. Guo and B. Gong, *J. Am. Chem. Soc*., 2004, **126**, 11120; (*e*) A. M. Zhang, Y. H. Han, K. Yamato, X. C. Zeng and B. Gong, *Org. Lett*., 2006, **8**, 803; (*f*) H. C. Ahn, S. M. Yun and K. Choi, *Chem. Lett*., 2008, 10; (*g*) W. Feng, K. Yamato, L. Q. Yang, J. S. Ferguson, L. J. Zhong, S. L. Zou, L. H. Yuan, X. C. Zeng and B. Gong, *J. Am. Chem. Soc*., 2009, **131**, 2629; (*h*) H. Jiang, J. M. Leger, P. Guionneau and I. Huc, *Org. Lett*., 2004, **6**, 2985; (*i*) L. Y. Xing, U. Ziener, T. C. Sutherland and L. A. Cuccia, *Chem. Commun*., 2005, 5751; (*j*) J. K. H. Hui and M. J. MacLachlan, *Chem. Commun*., 2006, 2480; (*k*) J. S. Ferguson, K. Yamato, R. Liu, L. He, X. C. Zeng and B. Gong, *Angew. Chem., Int. Ed*., 2009, **48**, 3150; (*l*) A. Filarowski, A. Koll and L. Sobczyk, *Curr. Org. Chem*., 2009, **13**, 172; (*m*) F. J. Carver, C. A. Hunter and R. J. Shannon, *J. Chem. Soc., Chem. Commun*., 1994, 1277; (*n*) F. Bohme, C. Kunert, H. Komber, D. Voigt, P. Friedel, M. Khodja and H. Wilde, *Macromolecules*, 2002, **35**, 4233; (*o*) A. Srinivasan, T. Ishizuka, A. Osuka and H. Furuta, *J. Am. Chem. Soc*., 2003, **125**, 878; (*p*) J. B. Lin, X. N. Xu, X. K. Hang and Z. T. Li, *J. Org. Chem*., 2008, **73**, 9403; (*q*) E. Berni, C. Dolain, B. Kauffmann, J.-M. Lger, C. Zhan and I. Huc, *J. Org. Chem*., 2008, **73**, 2687; (*r*) Y. Y. Zhu, C. Li, G. Y. Li, X. K. Jiang and Z. T. Li, *J. Org. Chem*., 2008, **73**, 1745; (*s*) L. Q. Yang, L. J. Zhong, K. Yamato, X. H. Zhang, W. Feng, P. C. Deng, L. H. Yuan, X. C. Zeng and B. Gong, *New J. Chem*., 2009, **33**, 729; (*t*) F. Li, Q. Gan, L. Xue, Z.-M. Wang and H. Jiang, *Tetrahedron Lett*., 2009, **50**, 2367.

4 For some recent reviews on foldamers, see (*a*) S. H. Gellman, *Acc. Chem. Res*., 1998, **31**, 173; (*b*) K. D. Stigers, M. J. Soth and J. S. Nowick, *Curr. Opin. Chem. Biol*., 1999, **3**, 714; (*c*) B. Gong, *Chem.–Eur. J*., 2001, **7**, 4336; (*d*) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev*., 2001, **101**, 3893; (*e*) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev*., 2001, **101**, 3219; (*f*) M. S. Cubberley and B. L. Iverson, *Curr. Opin. Chem. Biol*., 2001, **5**, 650; (*g*) A. R. Sanford and B. Gong, *Curr. Org. Chem*., 2003, **7**, 1649; (*h*) A. R. Sanford, K. Yamato, X. Yang, L. Yuan, Y. Han and B. Gong, *Eur. J. Biochem*., 2004, **271**, 1416; (*i*) C. Schmuck, *Angew. Chem., Int. Ed*., 2003, **42**, 2448; (*j*) I. Huc, *Eur. J. Org. Chem*., 2004, 17; (*k*) C. M. Goodman, S. Choi, S. Shandler and W. F. DeGrado, *Nat. Chem. Biol*., 2007, **3**, 252; (*l*) Z. T. Li, J. L. Hou and C. Li, *Acc. Chem. Res*., 2008, **41**, 1343; (*m*) W. S. Horne and S. H. Gellman, *Acc. Chem. Res*., 2008, **41**, 1399; (*n*) X. Li, Y.-D. Wu and D. Yang, *Acc. Chem. Res*., 2008, **41**, 1428; (*o*) I. Saraogi and A. D. Hamilton, *Chem. Soc. Rev*., 2009, **38**, 1726; (*p*) X. Zhao and Z. T. Li, *Chem. Commun*., 2010, **46**, 1601.

5 (*a*) S. Guieu, A. K. Crane and M. J. MacLachlan, *Chem. Commun*., 2010, **46**, 1169; (*b*) A. R. Sanford, L. Yuan, W. Feng, K. Yamato, R. A. Flowersb and B. Gong, *Chem. Commun*., 2005, 4720; (*c*) A. J. Helsel, A. L. Brown, K. Yamato, W. Feng, L. H. Yuan, A. J. Clements, S. V. Harding, G. Szabo, Z. F. Shao and B. Gong, *J. Am. Chem. Soc*., 2008, **130**, 15784; (*d*) P. S. Shirude, E. R. Gillies, S. Ladame, F. Godde, K. Shin-Ya, I. Huc and S. Balasubramanian, *J. Am. Chem. Soc*., 2007, **129**, 11890.