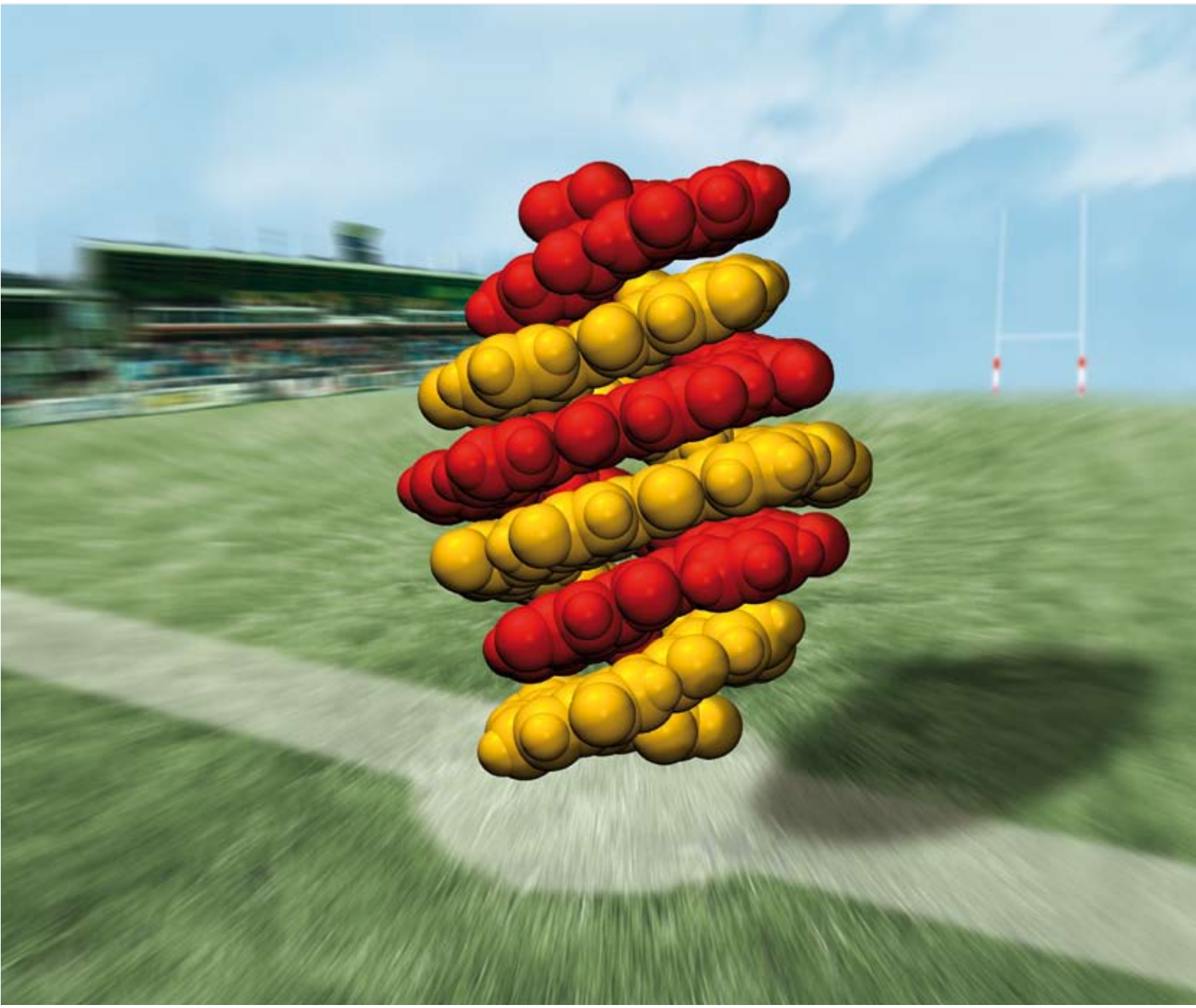
ChemComm

Chemical Communications

www.rsc.org/chemcomm

Number 17 | 7 May 2008 | Pages 1937–2060



ISSN 1359-7345

RSC Publishing

1359-7345(2008)17;1-2

Interpenetrating single helical capsules†

Emanuela Berni,[a] Joachim Garric,[a] Corinne Lamit,[a] Brice Kauffmann,[b] Jean-Michel Léger[c] and Ivan Huc*[a]

Received (in Cambridge) 2nd January 2008, Accepted 8th February 2008
First published as an Advance Article on the web 28th February 2008
DOI: 10.1039/b719712h

An aromatic oligoamide sequence designed to adopt a helically folded conformation surrounding a hollow space is shown to undergo hybridization into a double helical duplex in which the two strands fill each other's hollow.

Aromatic oligoamide foldamers are an emerging class of oligomers which adopt well defined, highly tunable and predictable conformations.[1] They open unprecedented perspectives to rationally design large and complex architectures through the covalent assembly of sequences of monomers that impart specific structural features.[1,2] For example, several groups have shown that the diameter of helically folded aromatic oligoamides can be tuned at will upon adjusting the size—one, two or three fused rings—of the monomer units or the relative orientation of acid and amine substituents on each unit.[3,4] Such helices with a large diameter define a cavity that may host various molecules and offer a new entry into the design of artificial receptors.[5,6]

We have recently extended this concept by combining various monomers into a helically folded sequence so that the diameter of the helix is larger in the centre than at each extremity, thus creating a closed shell that can encapsulate small guests.[7] These objects amount to helical capsules and were compared to molecular apple peels. Unlike helices with open hollows, they completely wrap around their guests and isolate them from the surrounding medium. Binding and release of the guest becomes a slow process as it requires partial unfolding of the helical capsule. As an example, compound **2b** is comprised of a helical heptameric pyridine sequence with a polar hollow flanked by two quinoline dimers that cap the hollow at each extremity (Fig. 1). It was shown to encapsulate two water molecules or small polar guests such as methanol or formic acid.[7b]

For the purpose of enlarging the helix hollow and recognizing more sizeable guests, we designed compound **2a**, an analogue of **2b** in which the central pyridine unit has been replaced by a larger 1,8-diaza-anthracene unit. A molecular model of the capsule in its single helical conformation is shown in the supporting information†. In the following, we report on the unanticipated ability of **2a** to form double helical dimers in which each strand fills the other strand's hollow by a reciprocal intercalation process, resulting in a duplex with no cavity that is thus unable to act as a capsule.

Oligomer **2a** was prepared from precursor **1a**[8] by removal of the terminal Boc protections and subsequent coupling with a quinoline dimer acid chloride following procedures similar to those employed in the synthesis of **2b** from **1b** (see supporting information†).[7b] The chromatographic purification of **2a** reproducibly yielded two products with distinct retention coefficients but with analytical data both consistent with the formula of **2a**. The mass spectra both showed peaks corresponding to the expected molecular mass; one of the two mass spectra also showed peaks corresponding to a dimer. NMR spectra of the two species are also both consistent with the formula of **2a** but differ in terms of signal multiplicity. One spectrum suggests a symmetrical structure in which equivalent protons at one or the other end of the sequence give rise to degenerate signals (Fig. 2d). The other spectrum showed twice as many signals, suggesting that the two halves of the sequence are not equivalent (Fig. 2a). Additionally, the two species were observed to slowly yet reversibly interconvert. Spectra of a 0.47 mM $CDCl_3$ solution of the unsymmetrical species show that it slowly converts into the symmetrical species (Fig. 2). Over several days, the equilibrium can be quantitatively reverted upon increasing the concentration up to the solubility limit.

Single crystals of **2a** were grown from a number of different solvents. Three structures could be solved from DMSO, dichloroethane and pyridine, using methanol or water as precipitants, that showed essentially identical double helical

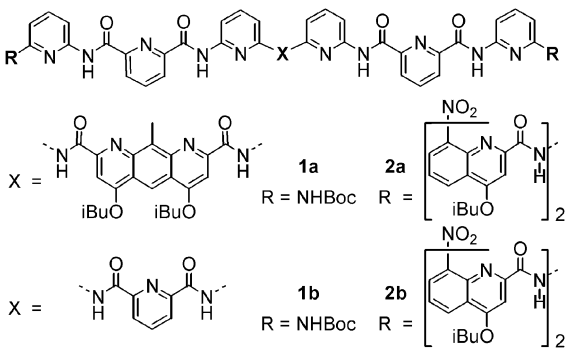


Fig. 1 Helical foldamer sequences based on pyridine, quinoline and diaza-anthracene monomers.

[a] *Université Bordeaux 1 – CNRS UMR5248, Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, 33607 Pessac, France. E-mail: i.huc@iecb.u-bordeaux.fr; Fax: +33 (0)5 4000 2215; Tel: +33 (0)5 4000 2219*
[b] *Université Bordeaux 1 – Université Victor Segalen Bordeaux 2 – CNRS UMS3033, Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, 33607 Pessac, France*
[c] *Université Victor Segalen Bordeaux 2, Laboratoire de Pharmacochimie, 146 rue Léo Saignat, 33076 Bordeaux, France*
† Electronic supplementary information (ESI) available: experimental procedure, Fig. S1–5 and crystallographic data. See DOI: 10.1039/b719712h

 This journal is © The Royal Society of Chemistry 2008

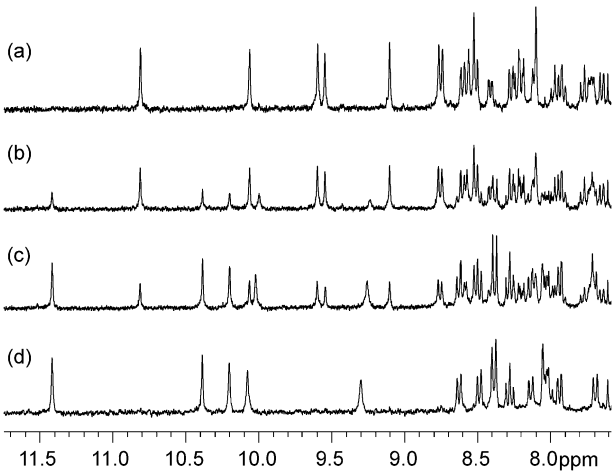


Fig. 2 Part of the 300 MHz ^{1}H NMR spectrum of **2a** in $CDCl_3$ (0.47 mM) showing the quantitative conversion of a double helical conformer (a) to a single helical conformer after 7 h (b), 74 h (c) and 167 h (d).

architectures. Only the structure based on the best data set was fully refined and is shown in Fig. 3.‡ The two strands of the duplex are not crystallographically equivalent but are overall superimposable, resulting in a pseudo C_2-symmetrical duplex. NMR spectra of freshly dissolved crystals allowed us to establish that the least symmetrical structure in solution is that of the double helical duplex. Consistent with the multiplicity of the ^{1}H NMR signals, the two strands are identical in the crystal structure but the two halves of one strand are different: one of the two terminal quinoline dimers lies on the top of the helix whereas the other quinoline dimer is buried in

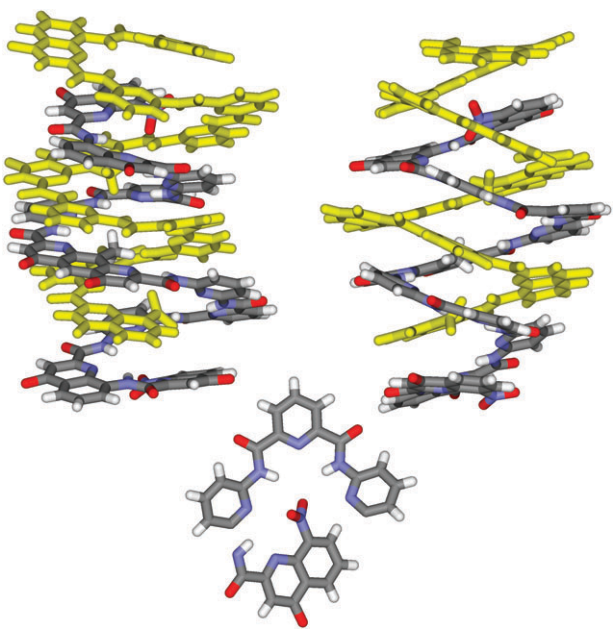


Fig. 3 Side views of the solid state structure of $(\mathbf{2a})_2$ crystallized from dichloroethane/methanol.‡ The relative position of the terminal nitroquinolines buried in the duplex and a 2,6-pyridinecarboxamide unit belonging to the other strand are shown at the bottom. Isobutyl side chains and included solvent molecules have been omitted for clarity.

the structure, its nitro group forming two hydrogen bonds with a pyridinedicarboxamide unit of the opposite strand (d_{N-O} = 3.1–3.3 Å). The dissymmetrical structure of each strand in the duplex gives rise to quite uneven twists between consecutive aryl moieties in the sequence, with torsion angles ranging from less than 5° to more than 40° (see supporting information†).

Based on these results and taking into account the hybridization properties of pyridinecarboxamide oligomers,[8,9] we concluded that the species having a symmetrical structure in solution is the single helical conformer of **2a**. It prevails at low concentration and its NMR signals are shifted downfield from those of $(\mathbf{2a})_2$ indicating less extensive intramolecular ring current effects in the single helix than in the duplex. The proportions between **2a** and $(\mathbf{2a})_2$ at various concentration yielded a hybridization constant K_{dim} = 320 L mol^{-1}.

The ability of pyridinecarboxamide oligomers such as **1b** to hybridize into double helical hybrids has been largely documented.[9] However, the hybridization of **2a** came as a surprise because this process had never been observed in the numerous quinoline-derived amide foldamers that we have studied.[2,4] We recently reported that boc-terminated oligomer **1a** possesses an ability to hybridize at least five orders of magnitude higher than **1b**.[8] This spectacular difference was assigned to the large diameter of **1a** imparted by its central diaza-anthracene unit. The large diameter goes together with a lower tilt angle of the strand with respect to the helix axis for the same vertical rise (3.5 and 7 Å per turn in the single and in the double helix, respectively) which result in lower torsion angles at each aryl-amide linkage, and thus in a much lower enthalpic cost of the spring-like extension necessary to double the helical pitch and undergo hybridization. The strong propensity of aromatic amide helices with a large diameter to undergo spring-like extension and hybridization was recently confirmed by the characterization of a quadruplex structure in oligoamides derived from 8-fluoroquinoline.[10] Conversely, because of their high curvature, quinoline oligomers possess a low number or rotatable bonds per helical turn, giving rise to larger dihedral angles at aryl-amide linkages that result in their apparent inability to undergo spring-like extension and hybridization. For example, oligomer **1b** has a K_{dim} value of 120 mol L^{-1} in $CDCl_3$,[9f] but its analogue **2b** flanked with two quinoline dimers shows no detectable hybridization.[7b] In the case of **2a**, the two terminal quinoline dimers also considerably reduce the dimerization, but this process is so effective in the case of **1a** ($K_{dim} > 10^7$ mol L^{-1} in $CDCl_3$) that it remains significant in **2a** (320 mol L^{-1}).

A side view of $(\mathbf{2a})_2$ (Fig. 3, top right) clearly illustrates the egg shape of the structure associated with the variation of helix diameter from the centre of the sequence to its termini, and thus its potential to act as a capsule when in a single conformation. However, the two strands completely fill each other's hollow in the duplex and no space remains to accommodate even the smallest guest. Thus, the hybridization amounts to a reciprocal filling of the capsules' hollows by the other strand. The single helical conformer of **2a** was expected to possess a sizeable cavity. Unfortunately, efforts to grow crystals of the single helical form of **2a** proved unsuccessful. Even at low concentration when the single helix

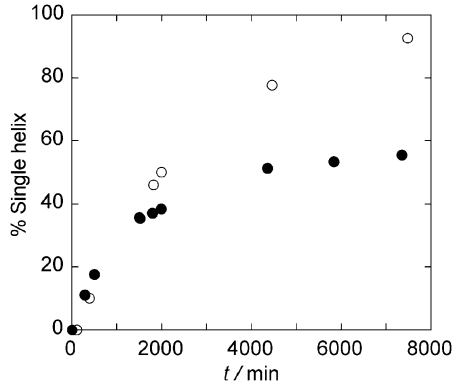


Fig. 4 Kinetics of duplex dissociation of $(\mathbf{2a})_2$ monitored by ^{1}H NMR at 25 °C in 6.7 mM (●) and 0.47 mM (○) $CDCl_3$ solutions.

is largely dominant and in solvents such as pyridine that disfavour hybridization, all crystals consist of the duplex which presumably possess a much lower solubility or, to the least, a higher propensity at crystal nucleation. No direct observation could be made of the size of the hollow of **2a**.

Another unusual feature of the hybridization of **2a** are the kinetics of hybridization and strand dissociation that are slow enough to perform a chromatographic separation of the single and double stranded species at room temperature. This contrasts with the behaviour of most organic double helical hybrids.[9–12] Related equilibria in pyridinecarboxamide oligomers were generally found to be slow on the NMR time scale but never so on the chromatographic time scale.[9] The slow kinetics could be monitored by ^{1}H NMR allowing the estimation of the first order rate constant of duplex dissociation and the second order rate constant of duplex formation to be 3.6×10^{-4} min^{-1} and 0.12 L mol^{-1} min^{-1}, respectively (see Fig. 4).

Such slow kinetics presumably arise from the large size of duplex $(\mathbf{2a})_2$, in which each strand spans about three helical turns and from its particular egg-like shape. A slippage mechanism involving a series of roller-coaster like discrete steps has been proposed for the hybridization of pyridine oligomers.[9c] During hybridization, intramolecular π–π stacking interactions within the single helical monomer are replaced by intermolecular aromatic stacking when the extremity of one of the strands proceeds inside the other single helical strand in an eddy-like process. This process is expected to become increasingly slow as oligomer length increases. Moreover, the fact that the diameter of **2a** varies from the extremities to the centre of the sequence might also create kinetic barriers to strand association and dissociation due to diameter mismatch on the way to and from the stable duplex.

Our discovery of the hybridization of **2a** further expands the registry of aromatic units that are compatible with double helix formation and the variety of sizes and shapes of these double helices. In order to isolate single helical capsules for the purpose of molecular recognition, we speculate that hybridization will be inhibited through the introduction of a third quinoline ring at each end of the strand or through the replacement of the terminal nitro groups by bulkier Boc protected amines. Development along these lines will be reported in due course.

Notes and references

‡ Crystal data were collected on a Rigaku Rapid axis diffractometer with a Cu generator and Varimax optics, standard procedures were followed. Crystal data for $(\mathbf{2a})_2$: $(C_{113}H_{104}N_{24}O_{20})_2(C_2H_4Cl_2)_8(CH_3OH)$, M_r = 5060.06, T = 133(2) K, monoclinic space group $P2_1/c$, a = 23.634(2), b = 37.289(4), c = 29.467(3) Å, β = 111.432(6)°, V = 24 173(4) Å^3, ρ_{calc} = 1.390 g cm^{-3}, μ = 2.360 mm^{-1}, Z = 4, reflections collected: 86 679, independent reflections: 37 901 (R_{int} = 0.0901), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.1228, w$R2$ = 0.3707, R indices (all data) $R1$ = 0.2032, w$R2$ = 0.3792. CCDC 673596. For crystallographic data in cif or other formats, see DOI: 10.1039/b719712h

1 For reviews, see: L. Cuccia and I. Huc, in *Foldamers: Structure, Properties and Applications*, ed. S. Hecht and I. Huc, Wiley-VCH, Weinheim, 2007, ch. 1, pp. 3–33; Z.-T. Li, J.-L. Hou, C. Li and H.-P. Yi, *Chem.–Asian J.*, 2006, **1**, 766; I. Huc, *Eur. J. Org. Chem.*, 2004, 17; B. Gong, *Chem.–Eur. J.*, 2001, **7**, 4336.

2 N. Delsuc, J.-M. Léger, S. Massip and I. Huc, *Angew. Chem., Int. Ed.*, 2007, **46**, 214; V. Maurizot, C. Dolain, Y. Leydet, J.-M. Léger, P. Guionneau and I. Huc, *J. Am. Chem. Soc.*, 2004, **126**, 10049; C. Dolain, J.-M. Léger, N. Delsuc, H. Gornitzka and I. Huc, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 16146.

3 B. Gong, H. Zeng, J. Zhu, L. Yuan, Y. Han, S. Cheng, M. Furukawa, R. D. Parra, A. Y. Kovalevsky, J. L. Mills, E. Skrzypczak-Jankun, S. Martinovic, R. D. Smith, C. Zheng, T. Szyperski and X. C. Zeng, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 11583.

4 (*a*) H. Jiang, J.-M. Léger and I. Huc, *J. Am. Chem. Soc.*, 2003, **125**, 3448; (*b*) H. Jiang, J.-M. Léger, C. Dolain, P. Guionneau and I. Huc, *Tetrahedron*, 2003, **59**, 8365; (*c*) T. Buffeteau, L. Ducasse, L. Poniman, N. Delsuc and I. Huc, *Chem. Commun.*, 2006, 2714.

5 J.-L. Hou, X.-B. Shao, G.-J. Chen, X.-Y. Zhou, X.-K. Jiang and Z.-T. Li, *J. Am. Chem. Soc.*, 2004, **126**, 12386; M. Inouye, M. Waki and H. Abe, *J. Am. Chem. Soc.*, 2004, **126**, 2022; H.-P. Yi, X.-B. Shao, J.-L. Hou, C. Li, X.-K. Jiang and Z.-T. Li, *New J. Chem.*, 2005, **29**, 1213; H. Abe, N. Masuda, M. Waki and M. Inouye, *J. Am. Chem. Soc.*, 2005, **127**, 16189; C. Li, G.-T. Wang, H.-P. Yi, X.-K. Jiang, Z.-T. Li and R.-X. Wang, *Org. Lett.*, 2007, **9**, 1797; M. Waki, H. Abe and M. Inouye, *Angew. Chem., Int. Ed.*, 2007, **46**, 3059.

6 R. B. Prince, S. A. Barnes and J. S. Moore, *J. Am. Chem. Soc.*, 2000, **122**, 2758; A. Tanatani, M. J. Mio and J. S. Moore, *J. Am. Chem. Soc.*, 2001, **123**, 1792; A. Tanatani, T. S. Hughes and J. S. Moore, *Angew. Chem., Int. Ed.*, 2002, **41**, 325; T. Nishinaga, A. Tanatani, K. Oh and J. S. Moore, *J. Am. Chem. Soc.*, 2002, **124**, 5934; M. T. Stone and J. S. Moore, *Org. Lett.*, 2004, **6**, 469.

7 (*a*) J. Garric, J.-M. Léger and I. Huc, *Angew. Chem., Int. Ed.*, 2005, **44**, 1954; (*b*) J. Garric, J.-M. Léger and I. Huc, *Chem.–Eur. J.*, 2007, **13**, 8454.

8 E. Berni, B. Kauffmann, C. Bao, J. Lefeuvre, D. M. Bassani and I. Huc, *Chem.–Eur. J.*, 2007, **13**, 8463.

9 (*a*) V. Berl, I. Huc, R. G. Khoury, M. J. Krische and J.-M. Lehn, *Nature*, 2000, **407**, 720; (*b*) V. Berl, I. Huc, R. G. Khoury and J.-M. Lehn, *Chem.–Eur. J.*, 2001, **7**, 2810; (*c*) A. Acocella, A. Venturini and F. J. Zerbetto, *J. Am. Chem. Soc.*, 2004, **126**, 2362; (*d*) H. Jiang, V. Maurizot and I. Huc, *Tetrahedron*, 2004, **60**, 10029; (*e*) D. Haldar, H. Jiang, J.-M. Léger and I. Huc, *Angew. Chem., Int. Ed.*, 2006, **45**, 5483; (*f*) C. Zhan, J.-M. Léger and I. Huc, *Angew. Chem., Int. Ed.*, 2006, **45**, 4625; (*g*) C. Dolain, C. Zhan, J.-M. Léger and I. Huc, *J. Am. Chem. Soc.*, 2005, **127**, 2400; (*h*) D. Haldar, H. Jiang, J.-M. Léger and I. Huc, *Tetrahedron*, 2007, **63**, 6322.

10 Q. Gan, C. Bao, B. Kauffmann, A. Grélard, J. Xiang, S. Liu, I. Huc and H. Jiang, *Angew. Chem., Int. Ed.*, 2008, **47**, 1715.

11 Y. Tanaka, H. Hatagiri, Y. Furusho and E. Yashima, *Angew. Chem., Int. Ed.*, 2005, **44**, 3867; H. Goto, H. Katagiri, Y. Furusho and E. Yashima, *J. Am. Chem. Soc.*, 2006, **128**, 7176.

12 For another example of slow hybridization kinetics, see: H. Sugiura, Y. Nigorikawa, Y. Saiki, K. Nakamura and M. Yamaguchi, *J. Am. Chem. Soc.*, 2004, **126**, 14858.

This journal is © The Royal Society of Chemistry 2008