Use of unnatural β-peptides as a self-assembling component in functional organic fibres†

Elisabeth Torres,[a] Josep Puigmartí-Luis,[b] Ángel Pérez del Pino,[b] Rosa M. Ortuño*[a] and David B. Amabilino*[b]

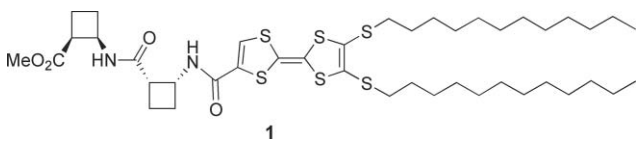
Received 2nd November 2009, Accepted 23rd December 2009
First published as an Advance Article on the web 5th February 2010
DOI: 10.1039/b922843h

A homochiral synthetic dipeptide incorporating two cyclobutyl rings has been used as an assembling unit for the π-electron-rich tetrathiafulvalene (TTF) moiety. The molecule was prepared and characterised to show all the features of the two components, whereby chirality and π-function are incorporated in the same species. Supramolecular fibres are formed by the compound, as proven by atomic force microscopy (AFM) and transmission electron microscopy. The dimensions of the nanostructures suggest that the molecules pack into dimeric tapes with the peptide head groups at the centre. Current-sensing AFM shows that once doped, films of the material are capable of conducting electricity.

Introduction

The use of unnatural peptides in molecular-based systems presents enormous possibilities for the preparation of new chiral materials with novel properties, because these products can adopt well-defined secondary and, in some cases, tertiary and quaternary structures.[1] Among them, β-peptides are prominent. Their propensity to fold, forming sheets, helices and reversed turns, has been established.[2] They present the advantage with respect to α-peptides that the number of residues usually needed to form foldamers is lower than that required in α-oligomers. In addition, careful design at the residue level can lead to enhanced secondary structural stability among the foldamers relative to conventional peptides.

In particular, the use of carbocycles[3] and heterocycles[4] incorporated into the β[2,3]-positions of the peptide backbone, combined with the control of chirality in the monomers, has allowed the synthesis of β-peptides with interesting structural features, including the formation of tertiary structures, such as nanosized fibrils and micelles.[5] The obtained results have permitted a better understanding of the combined influence of chirality and conformational constraint on the molecular and supramolecular arrangement of these compounds. The acquired knowledge has been useful in the preparation of several materials, such as nucleic acid mimics[6] and nanotubes.[7] However, the use of these peptide derivatives to generate chiral conducting materials is an unexplored area of great interest[8], and for this reason, we chose to prepare molecule **1**.

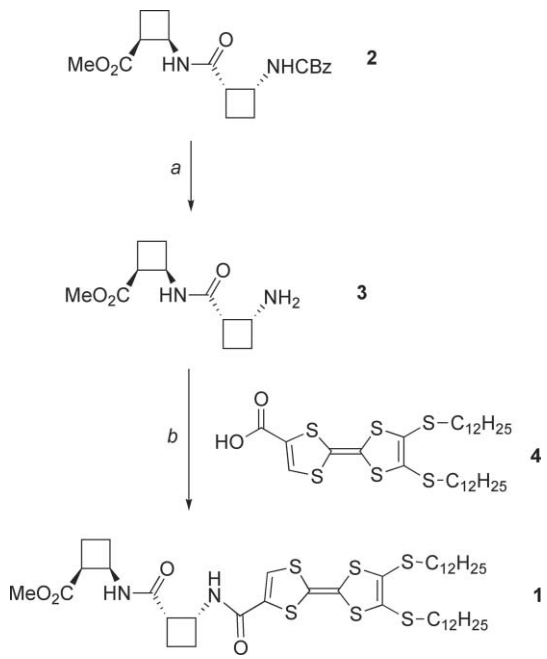


1

Compound **1** incorporates a dipeptide linked through an amide bond to a tetrathiafulvalene (TTF) residue, which is in turn functionalised with dodecyl chains to provide solubility in organic solvents. The choice of these components is based on simple amide derivatives of TTF which self-assemble into nanoscopic fibres.[9] The β-peptide promised to provide chirality and rigidity to the secondary structure.

Results and discussion

Compound **1** was prepared (Scheme 1) starting from the synthetic dipeptide **2**, which was prepared according to a known procedure,[10] and was subsequently deprotected using hydrogen and damp palladium hydroxide on carbon (Degussa type) to yield



Scheme 1 *Reagents and conditions*: (a) H_2 (6 atm), 20% $Pd(OH)_2$, EtOH (quantitative); (b) EDAC, Et_3N, HOBt, DMF (32%).

[a]*Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain. E-mail: rosa.ortuno@uab.es*
[b]*Institut de Ciència de Materials de Barcelona (CSIC), Campus UAB, 08193 Bellaterra, Spain, amabilino@icmab.es*

† Electronic supplementary information (ESI) available: NMR spectra and additional AFM images. See DOI: 10.1039/b922843h

amine **3**. Coupling of this compound with the TTF-derived acid **4**[11] afforded **1** in 32% yield. The compound is not stable for long periods of time, apparently because of the cleavage of the TTF-amide linkage, but it can be handled in air for periods of days.

The compound was characterised by all the usual analytical techniques, including NMR, polarimetry, mass spectrometry, and IR spectroscopy, which shows the typical bands of the amide bonds in the compound at 3317 (associated N*H*) and 1651 (associated-*H* NHC=O) cm^{-1}. Circular dichroism spectra of MeOH solutions of both compound **1** and **2**[10] (Fig. 1) show Cotton effects at around 205 nm. This result suggests a similar strand-type secondary structure for the peptide moiety in **1** as in the isolated compound **2**, and confirms the optical activity of **1**. The lack of temperature dependence observed in these spectra suggests that the molecules are not aggregated at the concentration used for the experiments.

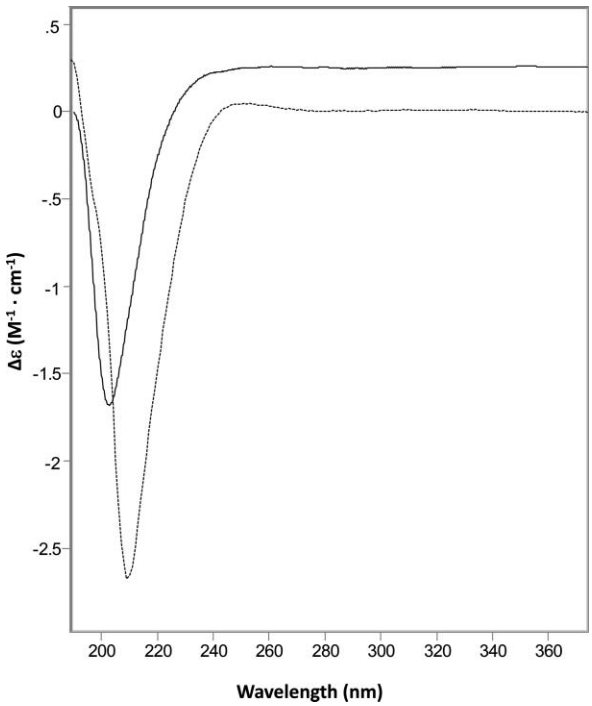


Fig. 1 Superimposed CD spectra of compound **1** (—) and dipeptide **2** (---) in methanol at 20 °C.

The interest in the material derived from **1** is to be able to prepare a fibrous system which is capable of conducting electricity, once doped (oxidised) to produce a conduction pathway.[12] This goal requires processing the material in such a way that long fibres are formed. The compound is completely soluble in a range of organic solvents, and importantly, this TTF derivative can form fibres.

When a drop of a chloroform solution of **1** was deposited onto a holey carbon transmission electron microscope (TEM) grid, the images of the sample showed the formation of a complex network of fibres (Fig. 2). The fibres are seen exclusively over the grid and do not cross over the holes, at least in the regions which were observed. The width of the fibres lie in the range 10–15 nm for apparently isolated objects, to around 60 nm for bundles, and the corresponding lengths are from a few hundred nanometres to well over a micron. All of the fibres are relatively straight. In these unstained images, there is no hint of regular chirality in the fibres[13] despite the chiral nature of the molecule.

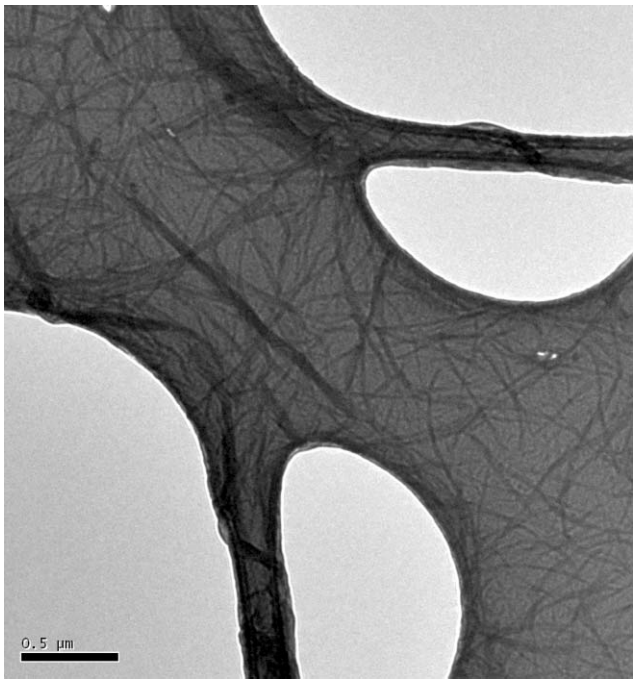


Fig. 2 TEM image of a sample of **1** deposited onto a holey carbon grid (the dark amorphous shape) showing the formation of nanofibres over the grid.

In order to study the properties of these fibres once doped, it was necessary for the fibres to be formed on a substrate, and we chose highly oriented pyrolytic graphite (HOPG). This conducting surface has been used by us previously for the study of the electrical properties of doped TTFs.[9] A 140 µM chloroform solution of **1** was deposited on HOPG by drop casting and was allowed to dry in air. Films with a complex morphology (see the ESI†) were observed by atomic force microscopy (AFM). The main part of the film is apparently amorphous because of the high concentration of the drop used for deposition, while on top, some clear indications of fibre formation are observed.

When the film was explored over small areas, indications of twisted fibres were obtained (Fig. 3), although they constitute the minor part of the sample. The fibres have minimum widths and heights of approximately 8 nm, corresponding to the size of head-to-head dimers seen in similar films of an achiral system.[14] It is noticeable in the image in Fig. 3 that sheet-like over-layers of the same width are also observed, indicating the formation of complex twisted bilayers of the compound in parts of the surface. The formation of twisted layers has been seen in other contexts in chiral systems, and has been assigned to deformation of the layers caused in part by the chiral nature of the molecular components.[15]

When the concentration of the chloroform solution of **1** was lowered to 28 µM and the solution was cast onto the HOPG, a very different texture was observed (Fig. 4). A homogeneous mesh of fibres was formed in which the coverage is uniformly arranged over relatively large areas, as seen in the 25 μm^2 image in Fig. 5 (top). Closer inspection of the sample reveals that the fibres are interwoven, leaving spaces between them. The bundles of fibres are between approximately 100 and 200 nm wide, while the height is approximately 8 nm, corresponding to the head-to-head bilayer-type structure alluded to earlier.

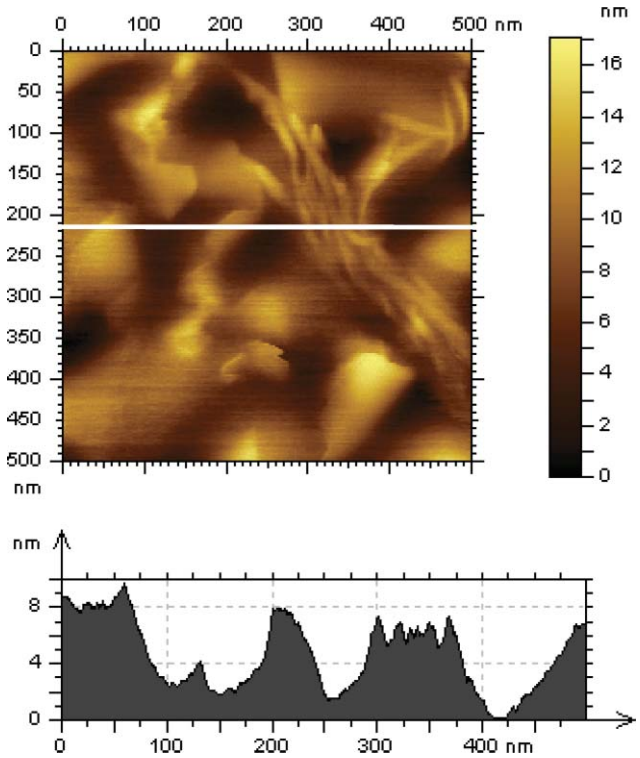


Fig. 3 Close-up topographic AFM image of a film of **1** cast onto graphite from a solution in chloroform (140 μM) (top) and the corresponding profile (below).

The texture of the sample can be appreciated even more clearly in the phase image of the film shown in Fig. 4c, in which individual fibres breaking away from one bundle and fusing into others can be seen. The fibres are not very straight, but seem always to curve, sometimes in quite dramatic fashion. This observation supports the idea forwarded above (when discussing the more concentrated casting), which suggests structural twisting at the supramolecular level leading to deformation from straight fibres, possibly as a result of the structure of the molecule, though no obvious sign of a preferred chirality is observed in the film.

The conductivity of the samples can be probed once charge carriers have been introduced by doping (oxidising) the films of **1** with iodine vapour (for two minutes). This process led to dark metallic films which were allowed to stand for several hours before the measurements were made. Current-sensing atomic force microscopy (CS-AFM) was used to explore the films on HOPG. In Fig. 5, the slight conductivity of the sample can be appreciated from the current–potential curve performed with the tip of the microscope. The measured conductance was approximately 0.3 nS at around 0 V, at the lower end of typical values for this kind of nanostructured organic material. Indeed, IR studies of a film cast onto a KBr disc and doped with iodine show a very weak charge transfer band, which implies a poor interaction between the aromatic moieties that are responsible for the charge transport. The corresponding current map in the CS-AFM does show that the film is uniformly conducting over hundreds of square nanometres, an important aspect of these materials if they are to have applications.

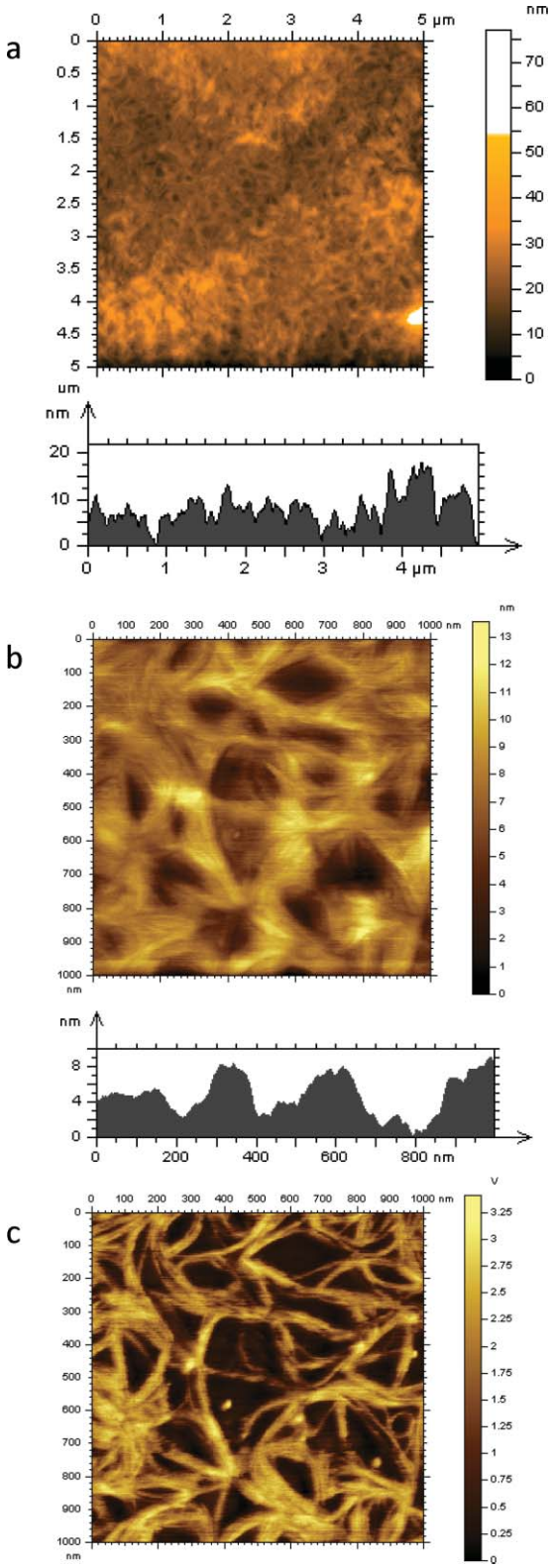


Fig. 4 AFM images and profile of fibres formed by casting a 28 μM chloroform solution of **1** onto HOPG. (a) And (b) AFM topographic images and profiles corresponding to the white lines in the images; (c) the phase signal of the image in (b), revealing the interwoven nature of the fibril network.

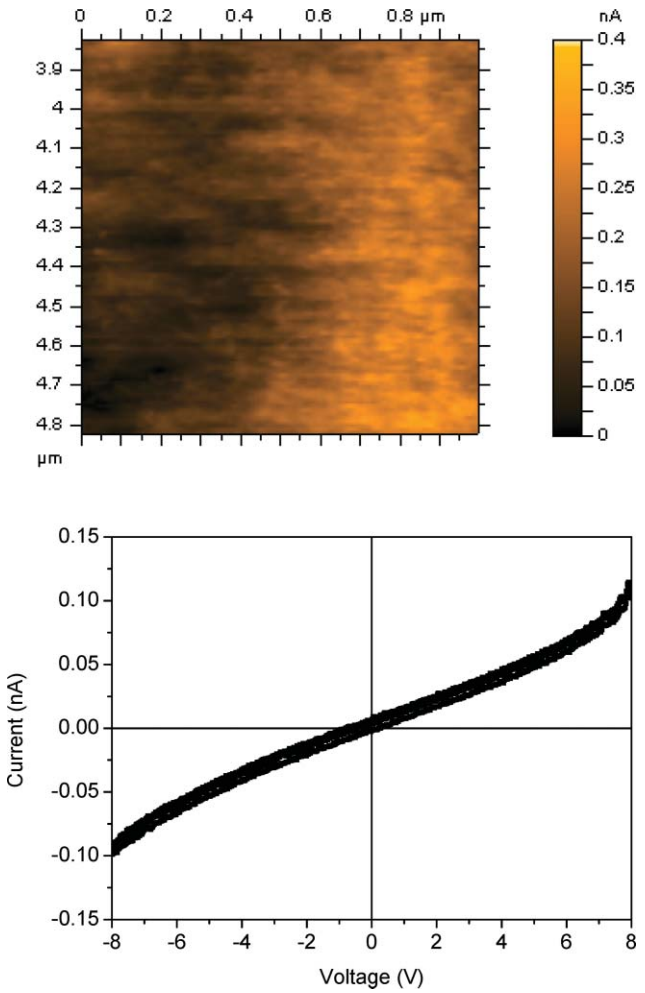


Fig. 5 CS-AFM image (at 5 V applied potential) of a doped film of **1** on HOPG (top) and a representative spectroscopy curve (below).

Conclusions

The incorporation of unnatural peptide derivatives in the side-chains of functional molecular units can aide in their self-assembly upon deposition on surfaces. Compound **1** shows well-structured fibres when deposited onto HOPG. The chirality in the molecule is evident in the circular dichroism spectrum in solution. The nature of the aggregates depends critically on the concentration of the compound in chloroform from which the cast films are prepared.

Doping of the material leads to a conducting film, where the charge is passed along stacks of TTF units. The head-to-head nature of the fibres (implied in the AFM images) may be a cause of the relatively high resistance of the sample (when observed by CS-AFM), where the peptide portion separates two rows of TTF moieties. This factor must be taken into account in the design of other compounds which might be prepared to have conducting properties.

Experimental

Compound 1

Bis(cyclobutane) β-peptide **2** (390 mg, 1.1 mmol) was dissolved in EtOH (30 mL), and 20% $Pd(OH)_2/C$ was added (40 mg). The mixture was stirred under hydrogen (P = 6 atm), at room temperature for 12 h. After that, the catalyst was removed by filtering through a Celite® filter aide, and washed with MeOH. Then, the resulting mixture was concentrated under reduced pressure, obtaining the free amine as a yellowish oil in quantitative yield. This product (**3**) was used in the next step without further purification. The free amine (50 mg, 0.22 mmols) and the carboxylic acid **4** (145 mg, 0.2 mmol) were dissolved in anhydrous DMF (15 mL). Then, TEA (0.17 mL), EDAC (127 mg, 0.7 mmol) and HOBt (45 mg, 0.3 mmol) were added. The mixture was stirred under a nitrogen atmosphere for 8 d. After this period of time, EtOAc was added (15 mL) and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography through Baker silica gel using a mixture of hexane–EtOAc (4 : 1) as eluent, to afford the compound **1** (60 mg, 32%) as an oil. $[\alpha]_D^{25} = -46$ (c 0.43, CH_2Cl_2). IR ($CHCl_3$): ν 3317, 2925, 2854, 1729, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J = 2.5 Hz, 6H), 1.21-1.63 (complex signal, 44H), 1.94-2.43 (complex signal, 8H), 3.41 (m, 2H), 3.72 (broad s, 4H), 4.75 (m, 1H), 6.61 (d, J = 5 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.8, 19.0, 21.7, 22.6, 28.5, 29.1, 29.7, 31.9, 35.1, 43.6, 44.5, 51.4, 77.0, 175.0. LDI-TOF/MS m/z (%) for [M^+ + 1, 100]: calcd., 858.39, found, 858.54.

TEM measurements

TEM images were acquired with a Jeol JEM 2011 microscope on unstained samples. Holey carbon grids were used, where the solution samples were dropped onto the grid and allowed to dry, and the gel sample was deposited as such and then dried.

AFM experiments

The atomic force microscopy (AFM) images were recorded on a PicoSPM system (Molecular Imaging). The intermittent contact mode was used close to the resonance frequencies of the silicon cantilevers (Nanosensors, FM-type force constant 1.2–3.5 N m^{-1} and tip diameter 5 nm) of around 60–70 kHz. All the images were recorded under atmospheric conditions. The images were processed using Mountains software from Digital Surf.

CS-AFM measurements

Current images of the doped samples on graphite substrates were obtained by using the same AFM system. A contact mode with a bias voltage applied to the sample, while scanning with a grounded conducting Pt–Ir coated silicon tip (force constant around 1.2 N m^{-1}) is necessary in order to perform such experiments. Contact to the sample was made using a stainless steel clamp pressed onto the surface of the doped xerogel. All the measurements were carried out in a dry nitrogen gas atmosphere in order to avoid artefacts introduced by humidity.

Acknowledgements

The authors thank financial support from the Spanish Ministerio de Ciencia e Innovación (grant CTQ2007-61704/BQU) and the Generalitat de Catalunya (grant 2009 SGR 733 and 2009 SGR

158). They are also grateful to the European Union for COST Action CM0803. Time allocated in the Servei de Ressonància Magnètica Nuclear and Servei de Microscòpia Electrónica (UAB) is gratefully acknowledged.

References

1 For a definition of secondary and tertiary structures in peptides, see, for instance: (*a*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173. For recent reports on helix bundle quaternary structures of β- and α/β peptides see: (*b*) D. S. Daniels, E. J. Petersson, J. X. Qiu and A. Schepartz, *J. Am. Chem. Soc.*, 2007, **129**, 1532; (*c*) W. S. Horne, J. L. Price, J. L. Keck and S. H. Gellman, *J. Am. Chem. Soc.*, 2007, **129**, 4178; (*d*) S. H. Gellman, *Abstracts of Papers, 237th ACS National Meeting*, American Chemical Society, Salt Lake City, UT, United States, March 22–26, 2009.

2 See, for instance: (*a*) S. Izquierdo, M. J. Kogan, T. Parella, A. Moglioni, V. Branchadell, E. Giralt and R. M. Ortuño, *J. Org. Chem.*, 2004, **69**, 5093; (*b*) S. Izquierdo, F. Rúa, A. Sbai, T. Parella, Á. Álvarez-Larena, V. Branchadell and R. M. Ortuño, *J. Org. Chem.*, 2005, **70**, 7963; (*c*) M. A. Gellman and S. H. Gellman, in *Enantioselective Synthesis of* β-*Amino Acids,*, ed. E. Juaristi and V. A. Soloshonok, John Wiley and Sons, New Jersey, 2nd edn, 2005, pp. 527–585.; (*d*) D. Seebach, D. F. Hook and A. Glattli, *Biopolymers*, 2006, **84**, 23; (*e*) P. Le Grel and G. Guichard, in *Foldamers: Structure, Properties and Applications*, ed. S. Hecht and I. Huc, Wiley-VCH, 2007, pp. 35–74; (*f*) D. Seebach and J. Gardiner, *Acc. Chem. Res.*, 2008, **41**, 1366; (*g*) W. S. Horne and S. H. Gellman, *Acc. Chem. Res.*, 2008, **41**, 1399; (*h*) I. M. Mándity, E. Wéber, T. Martinek, G. Olajos, G. K. Tóth, E. Vass and F. Fülöp, *Angew. Chem., Int. Ed.*, 2009, **48**, 2171; (*i*) E. Torres, E. Gorrea, E. Da Silva, P. Nolis, V. Branchadell and R. M. Ortuño, *Org. Lett.*, 2009, **11**, 2301; (*j*) E. Torres, C. Acosta-Silva, F. Rúa, Á. Álvarez-larena, T. Parella, V. Branchadell and R. M. Ortuño, *Tetrahedron*, 2009, **65**, 5669.

3 For some representative references, see: (*a*) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1996, **118**, 13071; (*b*) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 6206; (*c*) 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; (*d*) K. Möhle, R. Günther, M. Thormann, N. Sewald and H.-J. Hofmann, *Biopolymers*, 1999, **50**, 167; (*e*) J. J. Barchi Jr., X. Huang, D. H. Appella, L. A. Christianson, S. L. Durrell and S. H. Gellman, *J. Am. Chem. Soc.*, 2000, **122**, 2711; (*f*) T. A. Martinek, G. Tóth, E. Vass, M. Hollósi and F. Fülöp, *Angew. Chem., Int. Ed.*, 2002, **41**, 1718; (*g*) R. J. Doerksen, B. Chen, J. Yuan, J. D. Winkler and M. L. Klein, *Chem. Commun.*, 2003, 2534; (*h*) M. A. Schmitt, S. H. Choi, I. A. Guzei and S. H. Gellman, *J. Am. Chem. Soc.*, 2006, **128**, 4538; (*i*) F. Fülöp, T. A. Martinek and G. K. Tóth, *Chem. Soc. Rev.*, 2006, **35**, 323.

4 See, for instance: T. D. W. Claridge, J. M. Goodman, A. Moreno, D. Angus, S. F. Barker, C. Taillefumier, M. P. Watterson and G. W. Fleet, *Tetrahedron Lett.*, 2001, **42**, 4251.

5 (*a*) A. Hetényi, I. M. Mándity, T. A. Martinek, G. K. Tóth and F. Fülöp, *J. Am. Chem. Soc.*, 2005, **127**, 547; (*b*) T. A. Martinek, I. M. Mándity, L. Fülöp, G. K. Tóth, E. Vass, M. Hollósi, E. Forró and F. Fülöp, *J. Am. Chem. Soc.*, 2006, **128**, 13539; (*c*) T. A. Martinek, A. Hetényi, L. Fülöp, I. M. Mándity, G. K. Tóth, I. Dékány and F. Fülöp, *Angew. Chem., Int. Ed.*, 2006, **45**, 2396; (*d*) F. Rúa, S. Boussert, T. Parella, I. Díez-Pérez, V. Branchadell, E. Giralt and R. M. Ortuño, *Org. Lett.*, 2007, **9**, 3643.

6 A. M. Brückner, P. Chakraborty, S. H. Gellman and U. Diederichsen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4395.

7 T. Hirata, F. Fujimura and S. Kimura, *Chem. Commun.*, 2007, 1023.

8 N. Avarvari and J. D. Wallis, *J. Mater. Chem.*, 2009, **19**, 4061.

9 (*a*) J. Puigmartí-Luis, A. Minoia, A. Pérez del Pino, G. Ujaque, C. Rovira, A. Lledós, R. Lazzaroni and D. B. Amabilino, *Chem.–Eur. J.*, 2006, **12**, 9161; (*b*) J. Puigmartí-Luis, V. Laukhin, A. Pérez del Pino, J. Vidal-Gancedo, C. Rovira, E. Laukhina and D. B. Amabilino, *Angew. Chem., Int. Ed.*, 2007, **46**, 238.

10 E. Torres, E. Gorrea, K. K. Burusco, E. Da Silva, P. Nolis, F. Rúa, S. Boussert, I. Díez-Pérez, S. Dannenberg, S. Izquierdo, E. Giralt, C. Jaime, V. Branchadell and R. M. Ortuño, *Org. Biomol. Chem.*, 2010, **8**, 564.

11 M. M. S. Abdel-Mottaleb, E. Gomar-Nadal, M. Surin, H. Uji-I, W. Mamdouh, J. Veciana, V. Lemaur, C. Rovira, J. Cornil, R. Lazzaroni, D. B. Amabilino, S. De Feyter and F. C. De Schryver, *J. Mater. Chem.*, 2005, **15**, 4601.

12 (*a*) T. Kitamura, S. Nakaso, N. Mizoshita, Y. Tochigi, T. Shimomura, M. Moriyama, K. Ito and T. Kato, *J. Am. Chem. Soc.*, 2005, **127**, 14769; (*b*) T. Kitahara, M. Shirakawa, S.–i. Kawano, U. Beginn, N. Fujita and S. Shinkai, *J. Am. Chem. Soc.*, 2005, **127**, 14980; (*c*) T. Akutagawa, K. Kakiuchi, T. Hasegawa, S.-i. Noro, T. Nakamura, H. Hasegawa, S. Mashiko and J. Becher, *Angew. Chem., Int. Ed.*, 2005, **44**, 7283; (*d*) M. Iyoda, M. Hasegawa and H. Enozawa, *Chem. Lett.*, 2007, **36**, 1402; (*e*) H. Enozawa, Y. Honna and M. Iyoda, *Chem. Lett.*, 2007, **36**, 1434; (*f*) I. Danila, F. Riobé, J. Puigmartí-Luis, Á. Pérez del Pino, J. D. Wallis, D. B. Amabilino and N. Avarvari, *J. Mater. Chem.*, 2009, **19**, 4495.

13 A. Brizard, R. Oda and I. Huc, *Top. Curr. Chem.*, 2005, **256**, 167.

14 C. Munuera, J. Puigmartí-Luis, M. Paradinas, L. Garzón, D. B. Amabilino and C. Ocal, *Small*, 2009, **5**, 214.

15 (*a*) L. E. Hough, M. Spannuth, M. Nakata, D. A. Coleman, C. D. Jones, G. Dantlgraber, C. Tschierske, J. Watanabe, E. Körblova, D. M. Walba, J. E. Maclennan, M. A. Glaser and N. A. Clark, *Science*, 2009, **325**, 452; (*b*) L. E. Hough, H. T. Jung, D. Krüerke, M. S. Heberling, M. Nakata, C. D. Jones, D. Chen, D. R. Link, J. Zasadzinski, G. Heppke, J. P. Rabe, W. Stocker, E. Körblova, D. M. Walba, M. A. Glaser and N. A. Clark, *Science*, 2009, **325**, 456; (*c*) D. B. Amabilino, *Science*, 2009, **325**, 402.