Helical and Flat Structures from Chiral Dendronized Rectangular Oligo(phenylene ethynylene)s

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ABSTRACT
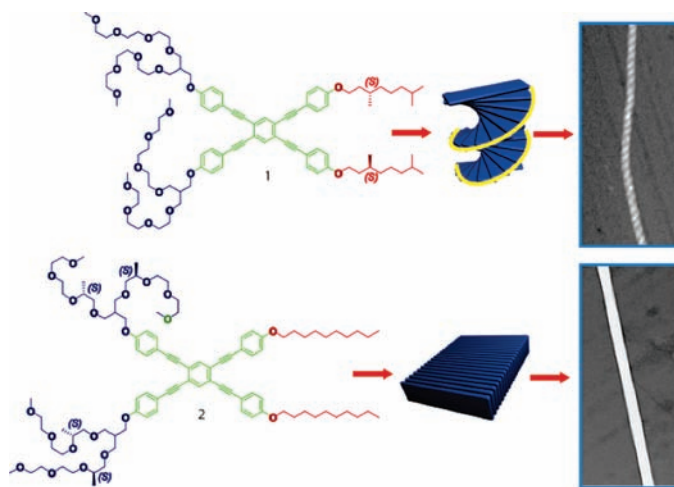
The synthesis of two chiral amphiphiles and their self-assembling features in solution and onto surfaces is reported. The different degree of interdigitation of the paraffinic substituents has an enormous influence in the chirality of the aggregates. Thus, while oligo(phenylene ethynylene) 1 shows a bisignated Cotton effect in solution and *P*-type helices onto surfaces, compound 2 lacks in any dichroic response at room temperature and self-assembles into flat ribbons.

Chirality is a topic of intense debate and study in chemistry, and particularly, the origin of homochirality is in the forefront of this research. Big efforts are being devoted to clarify the process that yielded asymmetric natural products from original achiral racemates.[1] The generation of chirality is related to an efficient transfer of chiral information from chiral units to complex supramolecular structures through noncovalent interactions.

To emulate the natural organization of biomolecules such as proteins or polysaccharides, a variety of organic systems

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(1) (a) Weissbuch, I.; Leiserowitz, L.; Lahav, M. *Top. Curr. Chem.* **2005**, *259*, 123–165. (b) Luisi, P. L. *The Emergence of Life: From Chemical Origins to Synthetic Biology*; Cambridge University Press: Cambridge, 2006. (c) Förster, S.; Plantenberg, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 688–714. (d) Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. *Chem. Rev.* **2001**, *101*, 4039–4070.

Scheme 1. Synthesis of Chiral Amphiphiles **1** and **2**
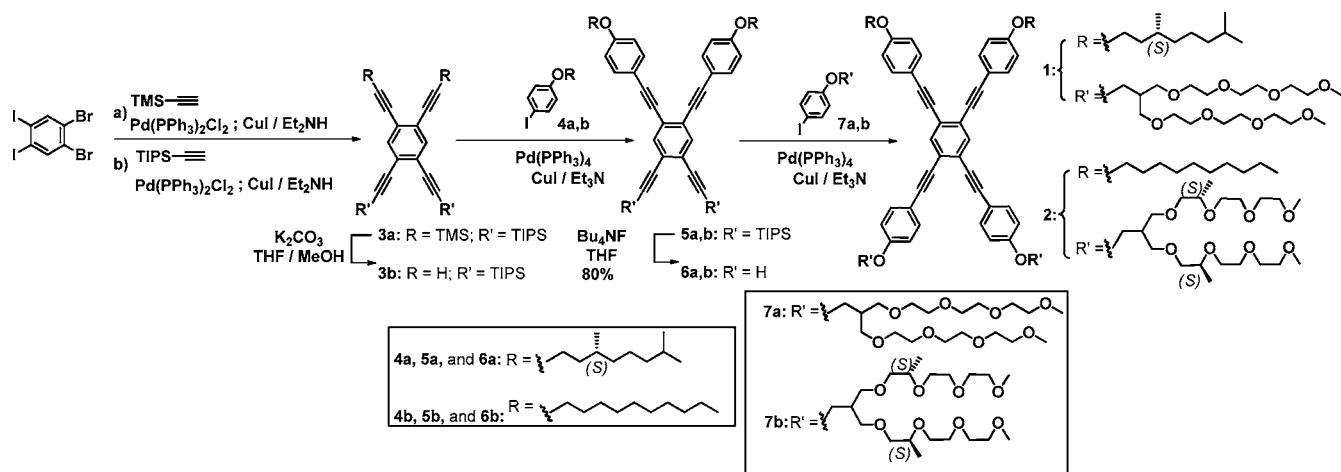
endowed with chiral paraffinic side chains can be found in the literature.[2] These studies demonstrate that the absolute configuration of the stereogenic centers conditions the handedness of the chiral supramolecular constructs. Considering that the original homochirality took place in aqueous media, ethylene oxide chains have been attached to those organic systems to generate nonionic amphiphiles.[3] We have incorporated this class of side chains to radial oligo(phenylene ethynylene) (OPE) platforms to construct supramolecular ensembles of modulated morphology and dimensionality.[4]

Herein, we report on the synthesis of nonionic amphiphiles based on a rectangular OPE scaffold peripherally substituted with chiral side chains of paraffinic or polar nature (compounds **1** and **2** in Scheme 1 and Figure S1 in Supporting Information). The chiral features of amphiphiles **1** and **2** in solution and onto surfaces have been investigated, and we have demonstrated that the interdigitation of the alkyl substituents exerts an enormous influence on the chirality of the self-assembled nanostructures.

The synthesis of the target OPEs starts with 1,2-dibromo-4,5-diiodobenzene,[5] which yields chiral amphiphiles with ste-

reogenic centers of absolute configuration *S* at the paraffinic chains (**1**) or at the ethylene oxide substituents (**2**) by sequential Sonogashira cross-coupling reactions[6] with the corresponding alkoxyiodobenzenes (**4a,b** or **7a,b**)[7] (Scheme 1).

The chemical structure of the new compounds has been confirmed by ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy and MALDI-TOF spectrometry. The symmetry of compounds **1** and **2** gives rise to simple ^{1}H NMR spectra with only three aromatic resonances at $\delta \approx 7.8$, 7.6, and 6.9. The methyl groups attached to the stereogenic centers appear as doublets at $\delta \approx 1.0$. The stretching bands corresponding to the CH_2 groups provide valuable information about the interdigitation degree of the paraffinic chains: while **1** shows two broad vibrations at ν 2923 and 2869 cm^{-1}, **2** presents sharper vibrations at 2925 and 2857 cm^{-1} (Figure S2 in Supporting Information) diagnostic of more efficient interdigitation of the alkyl chains.[8]

The self-assembly of **1** and **2** was first investigated by concentration-dependent UV−vis experiments in acetonitrile (MeCN) as solvent.[9] In these experiments, the appearance of bands at 329 and 360 nm is concomitant with the depletion of the band at ∼275 nm with increasing concentration, which implies the π-stacking of these amphiphiles (Figure S3 in Supporting Information). The variation of the molar fraction of aggregates (α_{aggr}) with the concentration of OPE is

(2) (a) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.* **2009**, *109*, 6275–6540. (b) Percec, V.; Imam, M. R.; Peterca, M.; Wilson, D. A.; Heiney, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 1294–1304. (c) Smulders, M. M. J.; Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2008**, *130*, 606–611. (d) Peterca, M.; Percec, V.; Imam, M. R.; Leowanawat, P.; Morimitsu, K.; Heiney, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 14840–14852. (e) Praveen, V. K.; Babu, S. S.; Vijayakumar, C.; Varghese, R.; Ajayaghosh, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1196–1211. (f) Ajayaghosh, A.; Chithra, P.; Varghese, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 230–233. (g) Ajayaghosh, A.; Varghese, R.; George, S. J.; Vijayakumar, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1141–1144. (h) Percec, V.; Dulcey, A. E.; Balagurusamy, V. S. K.; Miura, Y.; Smidrkal, J.; Peterca, M.; Nummelin, S.; Edlund, U.; Hudson, S. D.; Heiney, P. A.; Duan, H.; Maganov, S. N.; Vinogradov, S. A. *Nature* **2004**, *430*, 764–768. (i) George, S. J.; Ajayaghosh, A.; Jonkheijm, P.; Schenning, A. P. H. J.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3421–3425.

(3) Ryu, J.-H.; Hong, D.-J.; Lee, M. *Chem. Commun.* **2008**, 1043–1054.

(4) (a) Fernández, G.; García, F.; Sánchez, L. *Chem. Commun.* **2008**, 6567–6569. (b) García, F.; Aparicio, F.; Fernández, G.; Sánchez, L. *Org. Lett.* **2009**, *11*, 2748–2751. (c) García, F.; Fernández, G.; Sánchez, L. *Chem.—Eur. J.* **2009**, *15*, 6740–6747. (d) Fernández, G.; García, F.; Aparicio, F.; Matesanz, E.; Sánchez, L. *Chem. Commun.* **2009**, 7155–7157. (e) García, F.; Sánchez, L. *Chem.—Eur. J.* **2010**, *16*, 3138–3146.

(5) Miljanić, O. S.; Vollhardt, K. P.; Whitener, G. D. *Synlett* **2003**, 29–34.

(6) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(7) Compounds **3a**, **3b**, **4b**, and **6a** have been prepared by following previously reported procedures. See ref 4d. For the synthesis of the chiral dendritic polar chain present in compound **6b**, see: (a) Peterca, M.; Percec, V.; Imam, M. R.; Leowanawat, P.; Morimitsu, K.; Heiney, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 14840–14852. (b) Kim, H.-J.; Zin, W.-C.; Lee, M. *J. Am. Chem. Soc.* **2004**, *126*, 7009–7014.

(8) The asymmetric and symmetric stretching peaks corresponding to an *all-trans* conformation appear at 2918 and 2849 cm^{-1}, respectively. See: Nakanishi, T.; Michinobu, T.; Yoshida, K.; Shirahata, N.; Ariga, K.; Möhwald, H.; Kurth, D. G. *Adv. Mater.* **2008**, *20*, 443–446.

(9) Despite the polar chains incorporated into the aromatic framework of **1** and **2**, it is not possible to solubilize them in polar solvents such as H$_2$O, butanol, or THF at concentrations higher than 1×10^{-4} M.

sigmoidal in shape and fits to eq 1, corresponding to an isodesmic model (insets in Figure S3 in Supporting Information).[10] This analysis sheds values for the binding constant of ~5.4 × 10⁵ and 4.2 × 10⁵ M⁻¹ for **1** and **2**, respectively.

$$\alpha_{aggr} = 1 - \frac{2Kc_T + 1 - \sqrt{2Kc_T + 1}}{2(Kc_T)^2} \quad (1)$$

To further corroborate the mechanism experienced by these compounds to self-assemble, we exploited circular dichroism (CD) spectroscopy at different conditions of concentration and temperature (Figures 1, S4, and S5 in Supporting
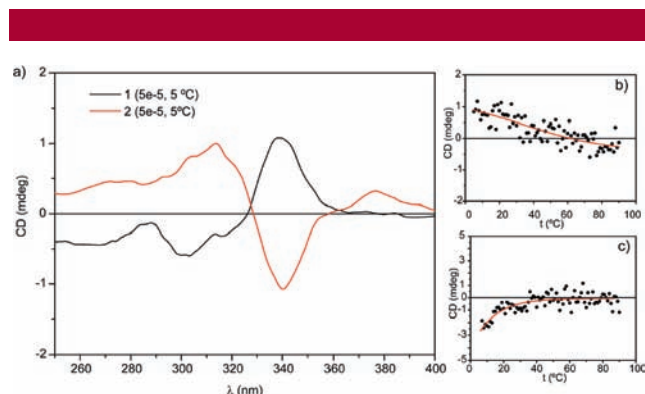

Figure 1. CD spectra (a) of **1** and **2** (H_2O, 5 × 10⁻⁵ M, 5 °C) and melting curves for **1** (b) and **2** (c) from 5 to 90 °C at intervals of 1 °C/min.

Information).[11] In aqueous solution, compound **1** presents a bisignated Cotton effect with a negative wave at around 300 nm and a positive wave at 340 nm indicative of a right-handed helical stacking.[12] Increasing temperature results in the desappearence of this CD signal (Figure 1b), and a turbid dispersion becomes visible. Thus, the dispersion is formed above the low critical solution temperature transition in aqueous media. In these conditions, the polar chains are dehydratated, generating new supramolecular ensembles less soluble in the aqueous solution.[13]

Surprisingly, chiral OPE **2** shows no CD signal at room temperature, despite the fact that it possesses four stereogenic centers (Figure 1c and S5 in Supporting Information). As occurs

for **1**, turbid dispersions appear above 30 °C, and no CD response is detected. However, at 10 °C and below, a bisignated Cotton signal is observed with positive and negative waves at 310 and 340 nm, respectively. This Cotton effect would be indicative of a left-handed helical columnar stack.

The presence of aggregated species in solution has been further corroborated by dynamic light scattering (DLS). CONTIN analysis of the DLS autocorrelation function of aqueous solutions of **1** (10⁻⁴ M) at 90° shows a broad distribution of hydrodynamic radii (R_H) of aggregates centered at ~30 nm (Figure S6 in Supporting Information). However, the similar analysis carried out for aqueous solution of **2** at the same concentration exhibits an extremely broad distribution from 10 nm to several micrometers and with maxima at 30 nm (similarly to **1**), 210 nm, and 1.4 μm (Figure S6 in Supporting Information). In both cases, the broad distribution of R_H could be indicative of a high degree of polydispersity.[14]

Finally, we have visualized the supramolecular aggregates detected in solution by transmission electron microscopy (TEM). TEM images taken from 1 × 10⁻⁴ M aqueous solutions of chiral OPE **1** show isolated thick rope-like structures (Figures 2 and S7 in Supporting Information). All

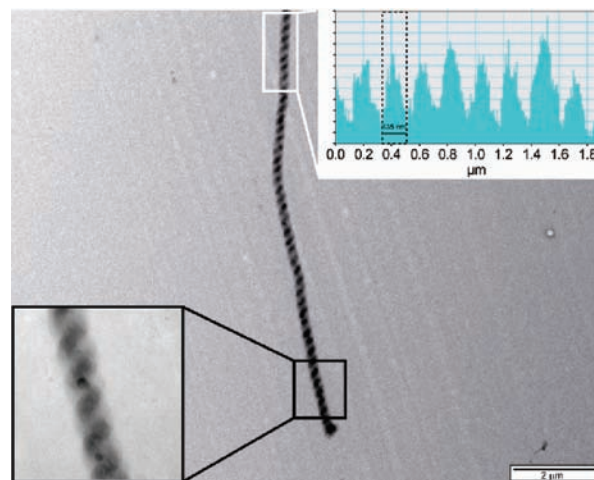**Figure 2.** TEM images showing the right-handed helical stacks formed from **1** (~10⁻⁴ M, H_2O, 25 °C) onto carbon-coated copper grids. The insets show a zoom TEM image (down) and the density profile (top).

of the helical columnar stacks are right-handed, in very good agreement with the CD data, and the density profiles indicate that the pitch of these *P*-type helices is ~135 nm. The apolar nature of the chiral paraffinic chains and the aromatic skeleton provokes the interdigitation of the chiral paraffinic chains and the π-stacking. These noncovalent forces produce chiral self-assembled fibers with a preferred helicity determined by the stereogenic centers.[15] The hydrophobic core of the aggregated species forces them to coil until forming the thick filaments that keep the original helical sense (Figure 3).[16]

(10) (a) De Greef, T. F. A.; Smulders, M. M. J.; Wolffs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, *109*, 5687–5754. (b) Martin, R. B. *Chem. Rev.* **1996**, *96*, 3043–3064. (c) Zhao, D.; Moore, J. S. *Org. Biomol. Chem.* **2003**, *1*, 3471–3491. (d) Chen, Z.; Lohr, A.; Saha-Möller, C. R.; Würthner, F. *Chem. Soc. Rev.* **2009**, *38*, 564–584.

(11) CD spectroscopy has been demonstrated to provide accurate data on the self-assembly mechanism followed by chiral compounds. For recent examples, see ref 2a and Jonkheijm, P.; van der Schoot, P.; Schenning, A. P. H. J.; Meijer, E. W. *Science* **2006**, *313*, 80–83.

(12) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: Chichester, U.K., 1994.

(13) (a) Dormidontova, E. E. *Macromolecules* **2002**, *35*, 987–1001. (b) Smith, G. D.; Bedrov, D. *J. Phys. Chem. B* **2003**, *107*, 3095–3097. (c) Aathimanikandan, S. V.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2005**, *127*, 14922–14929. (d) Jia, Z.; Chen, H.; Zhu, X.; Yan, D. *J. Am. Chem. Soc.* **2006**, *128*, 8144–8145. (e) Hirose, T.; Matsuda, K. *Chem. Commun.* **2009**, 5832–5834.

(14) Yagai, S.; Kubota, S.; Iwashima, T.; Kishikawa, K.; Nakanishi, T.; Karatsu, T.; Kitamura, A. *Chem.—Eur. J.* **2008**, *14*, 5246–5257.
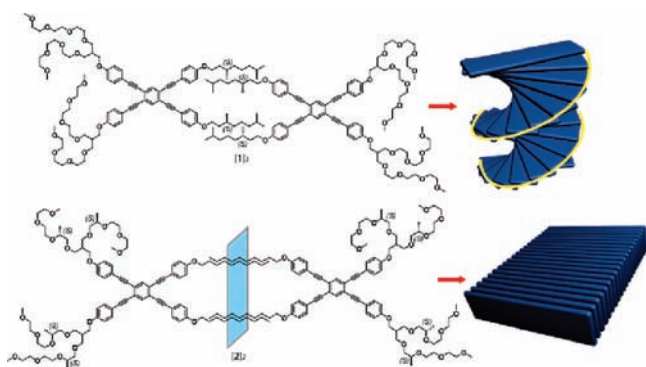
Figure 3. Schematic illustration of the dimers (represented as blue tablets) formed upon interdigitation of **1** and **2** and the subsequent aggregation. The plane of symmetry of the dimer of **2** is shown in light blue.

TEM images of aqueous solutions (1×10^{-4} M) of compound **2** demonstrate that this rectangular OPE does not form chiral nanostructures (Figures 4a and S8 in Supporting
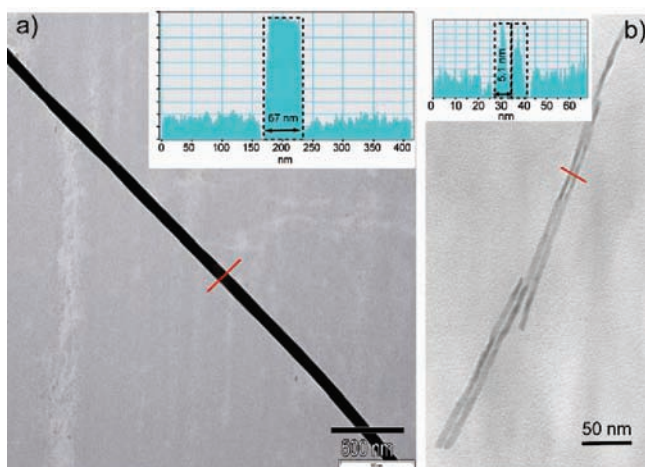

Figure 4. TEM images of amphiphilic OPE **2** in aqueous solution ($\sim 10^{-4}$ M, 25 °C) (a) and in MCH ($\sim 10^{-4}$ M) solution (b) onto carbon-coated copper grids. The insets in (a) and (b) shows the density profiles along the red lines.

Information). In contrast, ribbons with a uniform diameter of ~ 67 nm are observed. As indicated by the CD experiments at room temperature, the lack of chirality in solution is fairly translated to the surface. Considering the FTIR data, the aggregation of **2** involves an efficient interdigitation of the decyl chains that gives rise to self-assembled achiral bilayered fibers whose basic constitutive unit would be a symmetric dimer (Figure 3). These fibers would be stabilized

by the π-stacking of the aromatic framework and the van der Waals interactions of the decyl side chains. This hydrophobic structure constitutes the core of the aggregate being the hydrophilic dendritic chains pointing outward. The aggregated species thus formed are intrinsically achiral due to the presence of a symmetry plane in the basic dimeric unit that frustates a helical organization (Figure 3). Similarly to amphiphile **1**, the hydrophobic core of the aggregates avoids contacting with the polar environment by the interaction of the dendritic polar wedges forming a dense packing of tapes and the final thick ribbons appear.

The visualization of isolated self-assembled bilayer ribbons from **2** has been achieved by using the apolar methylcylcohexane (MCH) as solvent to prepare the samples for TEM imaging. In these conditions, the aromatic skeletons are interacting by π-stacking, the paraffinic chains would be entangled to a lesser extent and the polar dendritic wedges could be slightly coiled. All of these supramolecular forces direct the formation of long ribbons with typical diameters of ~ 7 nm diagnostic of the formation of a bilayered ribbon (Figures 4b and S9 in Supporting Information). In addition, some regions of the long ribbons present diameters of ~ 5 nm (red line and inset in Figure 4b). This value is too large for a single molecule and implies (1) the interaction of **2** forming a bilayer and (2) the formation of slightly twisted tapes with folded edges generated to avoid the steric constrains imposed in the columnar stacks by the dendritic polar wedges to avoid their steric hindrance.[4d,17]

In conclusion, we have synthesized two nonionic chiral amphiphiles that present opposite chiral features upon association. The presence of stereogenic centers at the alkyl chains impedes their efficient interdigitation. Thus, CD and TEM images demonstrate the formation of right-handed helices. Contrary to that, when chiral dendritic polar side chains and linear decyl substituents decorate the periphery of the aromatic framework, no CD response appears at room temperature and the aggregation of this chiral OPE forms achiral ribbons. These studies, which are opposite to those previously reported for referable chiral hexa-*peri*-bencoronnenes,[18] provide valuable information about the structural requirements participating in the translation of point chiral information from the molecular to the supramolecular level.

Supporting Information Available: Experimental details and supplementary figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Palmans, A. R. A.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 8948–8968.

(16) Bae, J.; Choi, J.-H.; Yoo, Y.-S.; Oh, N.-K.; Kim, B.-S.; Lee, M. *J. Am. Chem. Soc.* **2005**, *127*, 9668–9669.

(17) Ryu, J.-H.; Kim, H.-J.; Huang, Z.; Lee, E.; Lee, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5304–5307.

(18) Jin, W.; Fukushima, T.; Niki, M.; Kosaka, A.; Ishii, N.; Aida, T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10801–10806.