Dedicated to Prof. Sorin Rosca on the occasion of his 70th birthday

Helical Diastereomerism in Self-organization of Molecular Strands

MIHAIL BARBOIU[1]*, JEAN-MARIE LEHN[2]

[1] Institut Européen des Membranes - IEM-CNRS 5635, Place Eugène Bataillon, CC 47, F-34095 Montpellier, France

[2] ISIS, Université Louis Pasteur, CNRS UMR 7006, 8, Allée Gaspard Monge, F-67000 Strasbourg, France

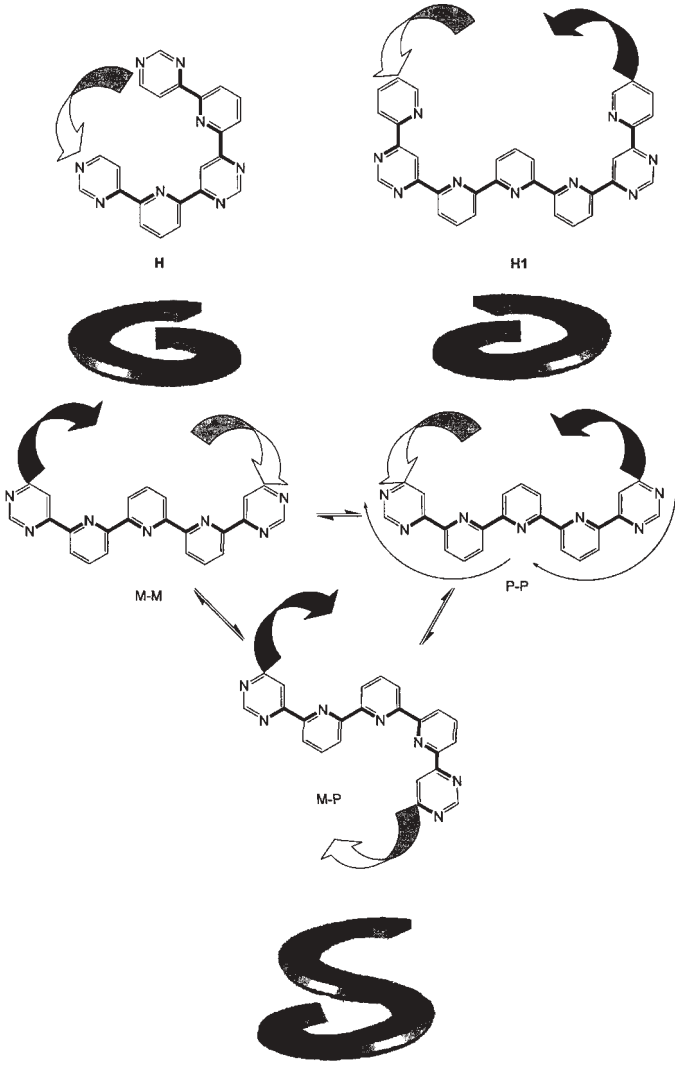
*The polyheterocyclic molecule **2** reported in this paper is a helically-wrapped molecular strand presenting two helical substrands of same helicity separated in space thus forming P-P and M-M helical enantiomers. It represents the case of a molecule presenting two chiral centers of helical type. The dimerization process of the compound described in this paper appears to give rise to heterodimeric and homodimeric species. At high and room temperature the formation of dimeric species is accompanied by folding-unfolding interconversion of single molecular strands. Sliding of the monomers along one another without dissociation at low temperature allows each of two helical partners to associate in dimers stabilized by pronounced π–π stacking interactions between the internal heterocycles of the strands.*

Keywords: supramolecular chemistry , helical structures, heterocyclic ligands, molecular dynamics

Supramolecular chirality may be obtained from suitable achiral molecular constituents associated through a dissymmetrizing interaction mode. [1a, b] The transfer of chiral information [1c] between achiral or chiral molecules at supramolecular level through non covalent interactions has attracted great interest. For instance polymeric, [1d] amphiphilic, [1e, f] H-bonded, [1g, h] π–π stacked, [1i] and cage-type [1j, k] chiral supramolecular systems have been described recently.

The intrinsic features of *helical structures* as well as their occurrence in many biological systems such as nucleic acids, oligosaccharides and proteins involved in numerous natural architectures (such as ion channels and pumps) has made the understanding of the factors governing their chiral self-organization particularly attractive and significant. [2] Helical organization in synthetic systems can be controlled and directed both by structural and conformational information encoded in the molecule and by specific intermolecular interactions undergoing hierarchical self-assembly at the supramolecular level [3, 4]. Hydrogen bonding [3a,c, 5] solvophobic effects [3b], cation binding [3d, 4j, 4h] and specific molecular groups [3e,f] and in particular heterocyclic helicity condons [4a-4d] may be used to generate helical entities at molecular and supramolecular level. In our group we have pursued several approaches to the generation of helical molecular strands [4] involving oligoheterocyclic pyridine-pyrimidine, [4a-d] pyridine-pyridazine, [4e,f] pyridine-naphthyridine, [4g] sequences, oligopyridines-dicarboxamides [5] and hydrazone-pyrimidine oligomers [6]. One of the most developed strategies for helicity induction implements "helicity condons" [4a-4d] based on preferred NC-CN *transoid* conformations in structural motifs consisting of alternating pyridine (py) and pyrimidine (pym) subunits connected in α,α' positions (scheme 1).

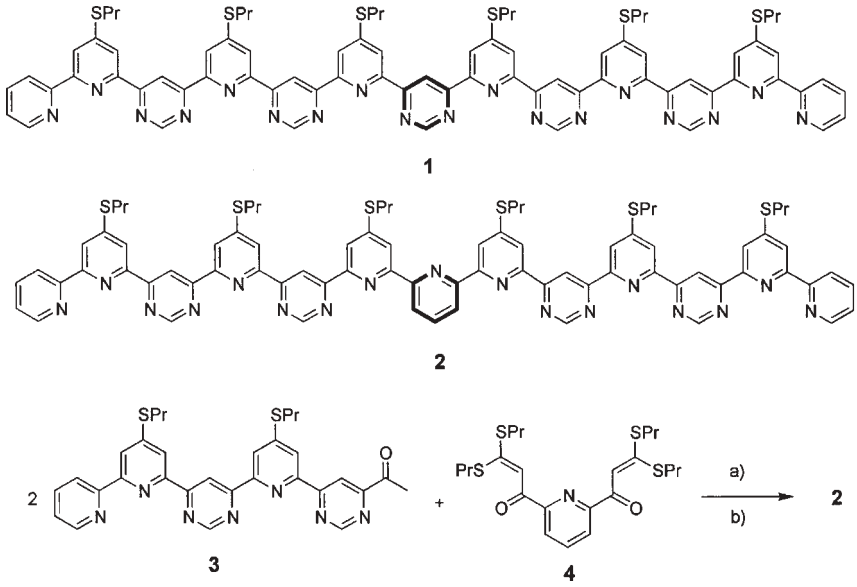
It has been shown that strands of the type **1** [4b, c] indeed adopt one [4a], two [4a-c], three- and four-turn [4d] helical structures, **H** respectively, in solution and in the solid state (scheme 1, 2). The same holds for strands incorporating a hydrazone subunit as surrogate for the py



Scheme 1

groups [6]. Generally, in the helical oligomers of type **1** the prime helicity inducing factor is the preferred *transoid*

* *email: mihai.barboiu@iemm.univ-montp2.fr*



Scheme 2. a) *t*BuOK, 18-crown-6, THF; b) AcOH/NH_4OAc, reflux

conformation around the NC-CN bond connecting two successive heterocycles [4] It may in addition further stabilized by long–range *intramolecular* π–π stacking interactions between successive helical turns. Recently, we have shown that the introduction of asymmetric centers in a oligopyridine-dicarboxamide chain results in chirality induction into the helical strand [5d]. Furthermore, we have found supplementary interactional motifs could perturb the supramolecular interaction between enantiomeric helical oligomers. Thus, the arrangement of the phenyl-pyrimidine substituted helices in the solid state is different from helical channel-type superstructures, resulting in the formation of the π–π stacked dimeric aggregates [7b]. In the dimer, the supramolecular interactions between right- and left-handed individual helices involve important phenyl ring overlaps.

In strands such as **1**, all helical turns have the same sense, so that such entities represent a single helicity center. Replacing a central pyrimidine group of a py-pym strand with a pyridine one as in compound **2** makes use of the strongly favored *transoid* [4, 7, 8] conformation around the connecting NC–CN bond in α–α ’- bipyridine (bipy), α–α’-(py,pym) units to introduce a py unit between two curved fragments, that may have the same or opposite helicity. Thus, such strands present two helicity centers and generate helical diastereoisomers. The polyheterocyclic strand **2** thus presents three features:

a) α–α’-linked, extended (py-pym) sequences strongly enforce helical winding of the strand [4];

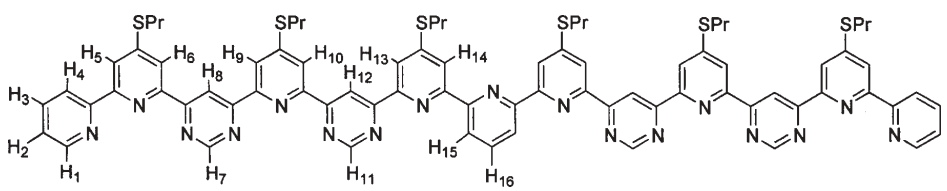
b) the two helical sub-strands of same helicity connected to the central Py are separated in space (Scheme 1, **H1**), favoring the intermolecular interactions between helical strands over the intramolecular overlaps of multiturn structures;

c) the P-P and M-M enantiomers (all *transoid*) should be energetically favored over the P-M diastereoisomer (*cisoid-transoid*, scheme 1).

Experimental Part

General methods: All reagents were obtained from commercial suppliers and used without further purification. THF was distilled over benzophenone/Na. All organic solutions were routinely dried by using sodium sulfate (Na_2SO_4).Column chromatography was carried out on Merck alumina activity II-III. ^1H and ^{13}C NMR, COSY and ROESY spectra were recorded on an ARX 500 MHz Bruker spectrometer in $CDCl_3$, with the use of the residual solvent peak as reference. The numerotations used for the assignments of the ^1H NMR signals (according to the corresponding COSY and ROESY spectra) are given below. Mass spectrometric studies were performed FAB mode using a quadrupole mass spectrometer (Micromass, Platform II). The microanalyses were carried out at Service de Microanalyses, Institut Charles Sadron, Strasbourg.

Synthesis of ligand 2: Compounds **3** [4c] and **4** [7] were prepared according to the procedures described in the literature. *Compound 2:* To a refluxing solution of **3** (120 mg, 0.20 mmol), **4** (50 mg, 0.11 mmol) and [18]crown-6 (54 mg, 0.20 mmol) in dry THF (20 mL), a solution of *t*BuOK (46.4 mg, 0.40 mmol) in dry THF (15 mL) was added under argon over a period of 2 h. The solution was stirred overnight at room temperature and acetic acid (3 mL) and NH_4OAc (1.7g) were added to the reaction. The mixture was refluxed for 90 min., cooled, poured into water (100 mL) extracted with chloroform (3 . 100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL) and dried with Na_2SO_4. After evaporation the crude material was purified by flash chromatography (alumina/chloroform) to give **2** (87 mg, 58%). ^1H NMR ($CDCl_3$) at 333K: δ = 10.03 (s, 2H, H11), 9.77 (s, 2H, H7), 9.43 (s, 2H, H12), 9.40 (s, 2H, H8), 8.52 (d, 4H, H5,6), 8.45 (d, 2H, H9), 8.18 (d, 2H, H13), 8.13 (d, 2H, H10), 8.09 (d, 2H, H4), 7.88 (d, 2H, H14), 7.82 (d, 2H, H1), 6.73 (m, 4H, H15, 16, H3), 6.06 (dt, 2H, H2), 3.24 (t, *J*=7.9, 8H), 1.88 (sext, *J*=7.9, 8H), 1.21 (t, *J*=7.9, 12H); ^{13}C NMR ($CDCl_3$): δ = 13.85, 13.93, 22.02, 22.24, 29.97, 33.10,



33.24, 114.16, 114.47, 117.47, 118.69, 119.74, 122.07, 123.50, 135.54, 138,34 146.32, 151.84, 152.11, 152.43, 153.44, 154.19, 158.32, 158.34, 162.44, 162.62, 162.72, 162.81. FAB-MS: m/z (%): 1452.4 (100) $[M+H]^+$; $C_{79}H_{73}N_{17}S_6$ (1452.9 g/mol):calcd C 65.31, H 5.06, N, 16.39; found C 65.40, H 5.16, N 16.20.

X-Ray Crystallographic data for ligand 2

Single crystals of **2**, $[C_{79}H_{73}N_{17}S_6 \bullet CHCl_3]$ were grown from acetonitrile / chloroform. Crystals were placed in oil and a single colourless crystal of dimension 0.20 . 0.16 . 0.10 mm was selected, mounted on a glass fibre and placed in a low-temperature N_2 stream. The unit cell was triclinic with a space group of P-1. Cell dimensions: a=13.6908(2)Å, b=16.4792(3)Å, c=19.6718(4)Å, α=88.549(5)°, β=71.551(5) °, γ=66.352(5)°, V= 3830.2(1)Å^3 , and Z=2 (FW is 1640, ρ=1.36 gcm^{-3}). Reflections were collected from 2.5°≤ θ ≤ 27.50° for a total of 17449 of which 9136 were unique having I>3σ(I) ; number of parameters is 946. Final R factors were R_1=0.083 (based on observed data), wR_2=0.094 (based on all data), GOF=1.030, maximal residual electron density is 1.373 eÅ^{-3}.

X-ray diffraction data for **2** were collected on a Nonius Kappa charge-coupled device (CCD) diffractometer with a graphite monochromatized MoKa radiation (λ=0.71073 Å). φ scans at 173, at the Laboratoire de Cristallochimie, Université Louis Pasteur, Strasbourg. The structure of **2** were determined using direct methods and refined (based on F^2 using all independent data) by full matrix least square methods (SHELXTL 97). Hydrogen atoms were included at calculated positions by using a riding model.

Results and discussions

Synthesis of compound 2 and self-assembly NMR studies: Compound **2** was synthesized using Potts' methodology [9] following the strategy developed earlier [4, 7]: repetitive twofold reaction of the bifunctional central pyridine bis-Michael acceptor units **4** [9] with two methyl ketone building blocks **3** [4c] yield **2** (58%).

We anticipated that a pyridine moiety inserted between two (py-pym) strands would define in the molecular structure of **2**, a spatially separated disposition of two helical strands relative to its own position. Moreover, based on preferential *transoid* conformation both helical substrands of **2** present the same handedness P-P and M-M showing the same NMR signals (see fig. 1).

To understand the helix interconversion and self-assembly phenomena of **2** in solution, a variable temperature NMR study was performed. The NMR spectrum of a 4 mM $CDCl_3$ solution of **2** at 298 K displays only one set of rather broad signals (fig. 1), consistent with the presence of different species in solution. This suggest the compound **2** aggregates in solution, but this aggregate is labile on the NMR time scale at 298 K and that its signals are averaged with the signals of the P-P or the M-M enantiomers in fast exchange in solution. Upon heating the solution of **2** in $CDCl_3$ features a relatively sharp ^{1}H NMR spectrum at 333 K. All 16 proton resonances could be assigned on the basis of COSY and NOESY spectra at 333 K and is consistent with the presence of a helical conformation of the monomeric P-P and M-M strands. As expected, on the basis of previous results, [4b-c, 5] a strong shielding is observed for the terminal and central pyridines hydrogens H2 and H3 at δ=6.06 and 6.70 and at δ=6.72 and 6.74, respectively (for numerotation of the hydrogens, see experimental section). Moreover, distinct NOE effects are found between the protons oriented towards the interior of the helix, e.g. between H_4, H_8 and H_{12} and between H_{15} and H_{12}. On the basis of these NMR data one may conclude that the molecular strand **2** adopts in solution a helical conformation of about 1 turn for both oligoheterocyclic substrands connected to the central pyridine moiety.

Upon cooling the above observed monomeric NMR signals decrease and broaden, the coalescence being reached at about 263 K. Below this temperature the signals of aromatic protons shifts up to about 0.6 ppm upfield at 203 K; this effect agrees with the occurrence of strong aggregation of compound **2** at low temperature. Two new sets of resonances of equal proportion appear and the NMR signals of monomeric **2** completely disappear.

This suggests that at low temperature the (P-P)$\rightleftarrows$(M-M) interconversion is considerably slowed down and that

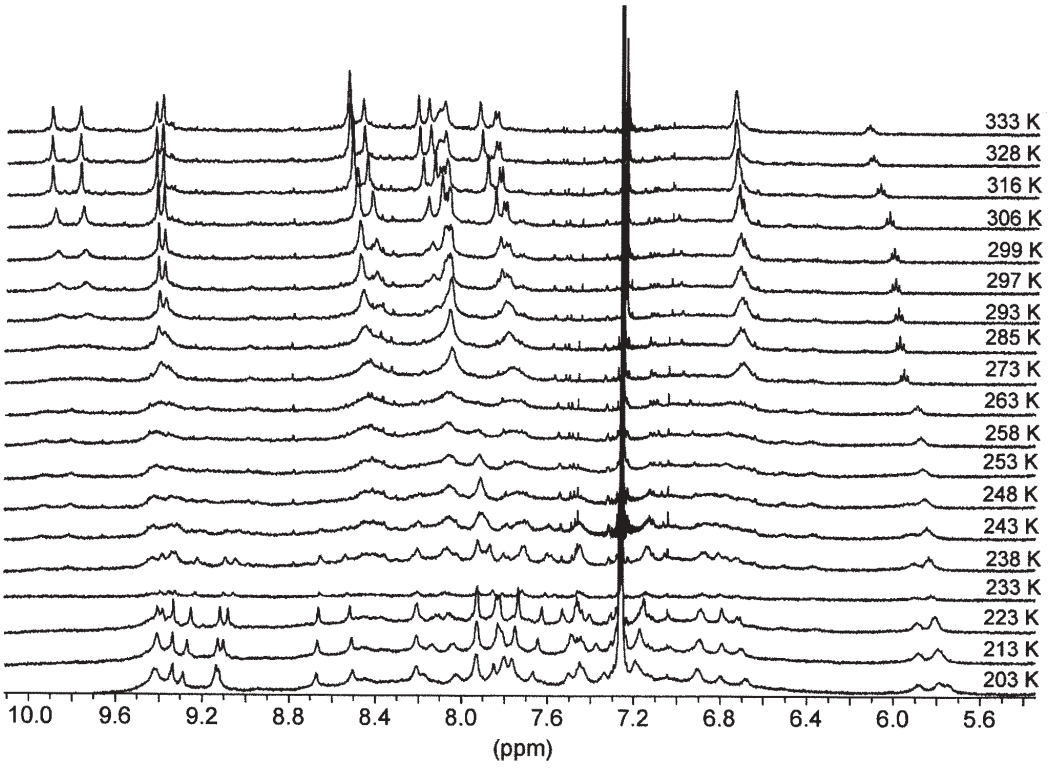


Fig. 1. 500 MHz ^{1}H NMR spectra of a 4 mM solution of 2 at various temperatures

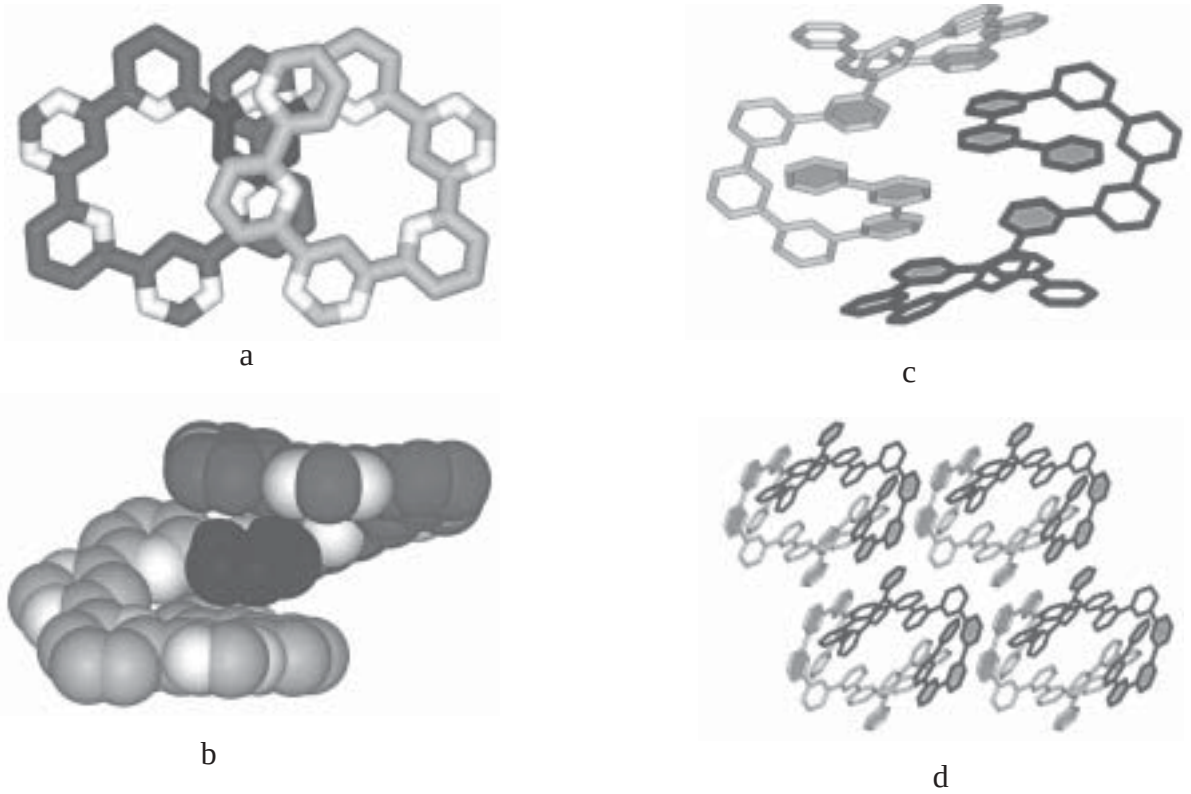


Fig. 2. Crystal structure of bis-helical strand 2 showing the (M-M) enantiomer of the diasteroisomeric entity: a) stick representation; (b) space-filling representation. Representation of the diastereoisomeric heterodimer [(P-P)(M-M)] intradimer; c) and interdimer (d) packing of dimers. Grey aromatic moieties represent the stacks mentioned in the text. The SnPr substituents and hydrogen atoms have been omitted for clarity

compound **2** is present in solution only as associated enantiomeric homodimers [(P-P)(P-P)] or [(M-M)(M-M] and a heterodimer [(P-P)(M-M)] representing a supramolecular *meso*-type diasteroisomer, based on two helical centers. It appears that long range aromatic overlapping contributes to the dimer formation, as well as imparts greater intrinsic magnetic nonequivalence between the diastereoisomeric dimers. In agreement with a statistical distribution of 25 : 50 : 25, [(P-P)(P-P)] : [(P-P)(M-M)] :[(M-M)(M-M] of dimers in solution, the proportion between the two sets of signals are identical, indicating that the three species; two homodimers and a heterodimer fastly interconvert in solution. Related processes were observed for binary associations occuring under conditions of fast interassociate exchange in enantiomeric mixtures of aminoacids [10a] and of amines/porphyrin [10b] complexes. Crystals of **2** suitable for X-ray structure determination were obtained by slow diffusion of acetonitrile into a solution of **2** in chloroform at room temperature. The molecular structure and packing are presented in figure 2.

Solid state structure of compound 2: The unit cell contains two molecules of **2** together with two $CHCl_3$ molecules. The helical sub-strands, of the same helical sense, are positioned on opposite sites of the interconnecting central pyridine moiety (fig. 2a, b). The molecule does not present a center of symmetry in the solid state, as the terminal pyridines and the central pyridine ring overlap non-symmetrically (centroid-centroid distances of about 3.78Å and 4.02Å, respectively). This feature suggests that supplementary intermolecular π-π and C-H...π interactions play a role in the cohesion of the structure and in the crystal packing.

Because the heterodimeric diastereoisomer [(P-P)(M-M)] is statistically predominant in solution we expected this species to crystallize. As shown in figure 2c, the right- and left-handed individual helices are π-π stacked in dimeric aggregates presenting four intradimer aromatic ring overlaps between the $(Py2)_P$-$(Pym3)_M$ and the $(Pym3)_P$-$(Py4)_M$ of each strand (centroid-centroid distance of about 3.75Å and 3.66 Å, respectively). Each dimer interacts with four neighboring ones (fig. 2d) : in the *b* direction by four interdimer aromatic ring overlaps between $(Py4)_P$-$(Pym5)_M$ of each strand (centroid-centroid distance of about 3.65 Å;) and in the *a* direction by two $(Py1)_P$-$(Pym3)_P$ and $(Py1)_M$-$(Pym3)_M$ (centroid-centroid distance of about 3.69 Å). The last overlap interaction concerns the less intradimer-associated terminal pyridine and represents a "communication" between strands of the same helical sense. The S*n*Pr groups fill the interstices between the helical strands, so that all available void space between the dimer components is filled. Accordingly, arrays of π-π stacked racemic helical heterodimers are generated in the solid state and in the solution from achiral strands **2** by self-organization.

Related intermolecular interactions between multiturn helical artchitectures have been identified in the self-aggregation of the collagen [2c-e] as well as in the cooperative and hierarchical self-assembly of pyridine-pyridazine strands into extended supramolecular fibers [4e, f].

In view of these data, the dimerization process of compound **2** is expected to give rise to heterodimeric and homodimeric species. At high and room temperature, the formation of dimeric species is accompanied by folding-unfolding interconversion of single molecular strands. Sliding of the monomers along one another without dissociation at low temperature allows each of two helical partners to associate in dimers stabilized by pronounced π–π stacking interactions between the internal heterocycles of the strands. Related sliding processes occur in the formation of the gramicidin A dimer [11], as cation

selective channel across lipid bilayers, as well as in the double-helical oligopyridine-dicarboxamide [4h, i] and Py-Pym–Ag [5b] architectures previously reported by our group.

In conclusion, the polyheterocyclic molecule **2** is a helically-wrapped molecular strand presenting two helical substrands of same helicity separated in space thus forming P-P and M-M helical enantiomers. It represents the case of a molecule presenting two chiral centers of helical type.

Furthermore dynamic conformational and association equilibria occur between the two spatially distinct helical sub-strands and intermolecular chiral interactions take place between strands of the same (homodimers) and opposite (heterodimers) helical sense.

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8.*** The cisoid-transoid energy difference is about 7 kcal/mol - see ref 4f for details and references.

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