

## Molecular Helicity: a General Approach for Helicity Induction in a Polyheterocyclic Molecular Strand

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The structural and conformational features of the non-chiral polyheterocyclic molecule **1** induce a helical shape in the molecular strand both in solution and in the solid state, as shown by the crystal structure.

Molecular helicity is of interest because of its special chiral geometrical features and of its occurrence in biological species, as in the  $\alpha$ -helix of proteins and the double helix of nucleic acids.<sup>1,2</sup>

Our work has been concerned with the spontaneous generation of double helical<sup>3</sup> and triple helical<sup>4</sup> metal complexes, termed helicates, by self-assembly from linear ligand strands and appropriate metal ions; and with triple helical supramolecular polymers formed by polyassociation of complementary components through hydrogen bonding.<sup>5,6</sup>

In these cases, helicity results either from the design of the ligand and choice of metal ion, or from carbon asymmetry in the molecular components. Of special interest is the definition of structural and conformational features that may direct the induction of helical features into flexible linear molecules.<sup>7</sup>

We present here a general principle for curling up a non-chiral linear molecule into a helical shape. It makes use of three basic features: (a) an alternating sequence of pyridine (py) and pyrimidine (pym) units; (b) linkage of these units at appropriate positions; (c) *transoid* conformation around the linkage bonds based on the preference for a *trans* orientation of nitrogen sites and concomitant *cisoid* orientation of CH and N sites as found in 2,2'-bipyridine (bpy) and shown in Fig. 1

These features are present in the bpy-pym-py-pym-bpy sequence **1** of seven heterocyclic groups linked through 2,6-positions of the py units and the 4,6-positions of the pym units. Preference for *transoid* orientation around the single bonds connecting the subheterocyclic moieties should necessarily lead to a helically twisted overall conformation. Molecule **1** was synthesized following the sequence of reactions shown in Scheme 1.

6-Lithio-2,2'-bipyridine **2b**, made by the slow addition of *n*-butyllithium to 6-bromo-2,2'-bipyridine **2a** in THF at  $-78^\circ\text{C}$ , was transmetallated by the addition of tributyltin chloride giving 6-tributylstannyl-2,2'-bipyridine **2c** in 90% yield. Palladium catalysed heterocoupling<sup>8</sup> of **2c** with one equiv. of 4,6-dichloropyrimidine in DMF at  $90^\circ\text{C}$  gave the 4-(2',2''-bipyrid-6'-yl)-6-chloropyrimidine **3** in 45% yield after sublimation ( $110^\circ\text{C}$  at 0.01 torr). Bis-2,6-tributylstannylpyridine† **4** and **3** (2 equiv.) were treated in an analogous fashion giving **1** in 31% yield.

The assignments for the  $^1\text{H}$  NMR spectrum were deduced by  $^1\text{H}$  decoupling and NOE experiments. All the chemical shifts were consistent for pyrimidine and pyridine polyheterocycles except for two unexpectedly high upfield proton shifts assigned to  $\text{H}_{5''}$  and  $\text{H}_{4''}$  of the terminal pyridines (Fig. 2). As noted above, one can expect an all *transoid* conformation that will lead to a helical structure, giving rise to terminal pyridine overlap and significant shielding effects. ROESY NMR experiments provided evidence that in  $\text{CDCl}_3$  solutions  $\text{H}_{3''}$  of the terminal pyridine and  $\text{H}_{5'}$  of the pyrimidine were interacting by

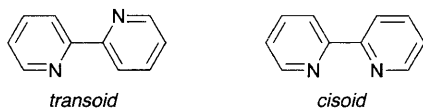
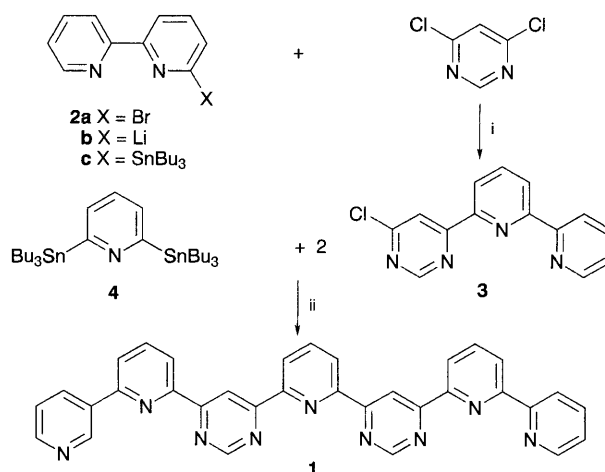


Fig. 1

NOE. No other intramolecular NOE interactions were present, supporting an all *transoid* conformation and therefore a helical shape in solution. Since the individual rotational barriers are expected to be low, there is fast exchange on the NMR time scale between the two enantiomeric helices.

In order to investigate the nature of **1** in the solid state, its crystal structure was determined (Fig. 3).‡ The unit cell is centrosymmetric and contains two enantiomeric helices. The molecule has a two-fold rotation axis passing through N(5) and C(17) and adopts a helical overall conformation in which the nitrogen sites have the expected orientation about the connecting single bonds.§ Preference for *transoid* over *cisoid* arrangements may result from a combination of factors: electrostatic repulsion between N sites and steric interaction between CH sites in the *cisoid* arrangement and (weak) attraction between N and CH sites and antiparallel orientation of N-sites dipoles in the *transoid* arrangement. As a result the interior of the helical strand is lined with alternating CH and N sites. The central cavity is  $5.42 \text{ \AA}$  across (terminal pyridine N to pyrimidine  $\text{C}_5$ )



Scheme 1 Reagents and conditions: i, DMF,  $\text{Pd}^{\text{II}}(\text{PPh}_3)_2\text{Cl}_2$ ,  $90^\circ\text{C}$ ; ii, DMF,  $\text{Pd}^{\text{II}}(\text{PPh}_3)_2\text{Cl}_2$ ,  $120^\circ\text{C}$

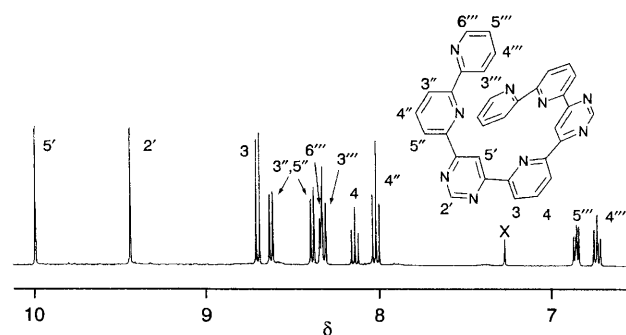


Fig. 2 400 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of **1** with chemical shift assignments (residual  $\text{CHCl}_3$  indicated by X)

and of a comparable size to that of cyclohexypyridine and 18-crown-6.

The orientation of the terminal pyridines lies between an edge to face and a face to face interaction.<sup>¶</sup> This directs H<sub>3''</sub> into the cavity formed by the helix, giving a distance of 3.0 and 3.4 Å between H<sub>3''</sub> and both H<sub>5'</sub> sites. Also, H<sub>4''</sub> is placed on top of the N(2') pyridine ring, and H<sub>3''</sub>, H<sub>5''</sub> and H<sub>6''</sub> lie above the other terminal pyridine; these interactions lead to upfield shifts in the <sup>1</sup>H NMR spectrum. Based on these observations, we conclude that the solid state and solution structures of this molecule are helical and similar.

Several interesting developments may be envisaged: (a) the internal void may serve to include guest species that could induce the screw sense of the helix; (b) attaching long chains at the exterior of the structure (at position 4 of the py groups and 2 of the pym groups) may generate helical liquid crystalline phases; (c) replacement of the pym units by 1,3,5-triazines (connected at the 2,4-positions to neighbouring py groups) would provide a full lining of the internal void with nitrogen sites thus providing a continuous polar surface for binding metal ions and representing an approach to potential (helical) ion channels; in this case of course the orientational preference around single bonds may be less clear cut.

The present results confirm that the structural principle enunciated above leads to the induction of helicity into chains of heterocyclic groups such as **1**. By extension, other general approaches may be sought with the goal of generating a desired overall molecular shape on the basis of the geometry of the constituting components and of local conformational preferences under the control of intramolecular non-covalent inter-

actions like amino-acid units, peptide links and hydrogen bonds lead to the  $\alpha$ -helix and other forms of proteins.

G. S. H. thanks the NSERC (Canada) for a doctoral fellowship.

Received, 15th December 1994; Com. 4/07654K

## Footnotes

† Synthesised by quenching a solution of 2,6-dilithiopyridine<sup>9</sup> with tributyltin chloride at -70 °C in THF (for the analogous synthesis of 2-tributylstannylpyridine see ref. 10).

‡ X-Ray data for **1**: (C<sub>33</sub>H<sub>21</sub>N<sub>9</sub>), *M* = 543.6, colourless crystals, monoclinic, *a* = 12.396(3), *b* = 12.307(3), *c* = 17.358(5) Å,  $\beta$  = 95.49(2), *V* = 2636.0 Å<sup>3</sup>, *Z* = 4,  $\rho_{\text{calc}}$  = 1.370,  $\mu$  = 6.502 cm<sup>-1</sup>, space group *C2/c*. A suitable crystal of **1**, (0.28 × 0.20 × 0.14 mm<sup>3</sup>) was mounted on the end of a glass fibre. 2891 + *h* ± *k* ± *l* reflections were collected on a Philips PW1100/16 instrument at 20 °C with Cu graphite monochromated radiation ( $\lambda$  = 1.5418 Å),  $\theta/2\theta$  flying step scans, step width = 0.03°, scan speed = 0.020° s<sup>-1</sup>, scan width = 0.80 + 0.14 tg( $\theta$ )°, 3° <  $\theta$  < 52°. Three standard reflections measured every hour during the data collection period showed no significant trend. The raw data were converted to intensities and corrected for Lorentz and polarization factors. The structure was solved using direct methods. 1036 independent reflections with *I* > 3 $\sigma$ (*I*) were used to determine and refine the structure. Hydrogen atoms were introduced as fixed contributors by their computed coordinates (C-H = 0.95 Å) and isotropic temperature factors such as *B*<sub>H</sub> = 1.3 *B*<sub>eqv</sub>(C) Å<sup>2</sup>. Empirical absorption corrections were applied (DIFABS). Molen<sup>11</sup> on a Vax computer was used for all calculations. Final *R*(*F*) = 0.035. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ Recent work with poly-*m*-phenylenes indicated a helical shape in the solid state structure of this class of compounds to which **1** is structurally related.<sup>12</sup>

¶ The dihedral angle between the planes of the terminal pyridines is 38.8°.

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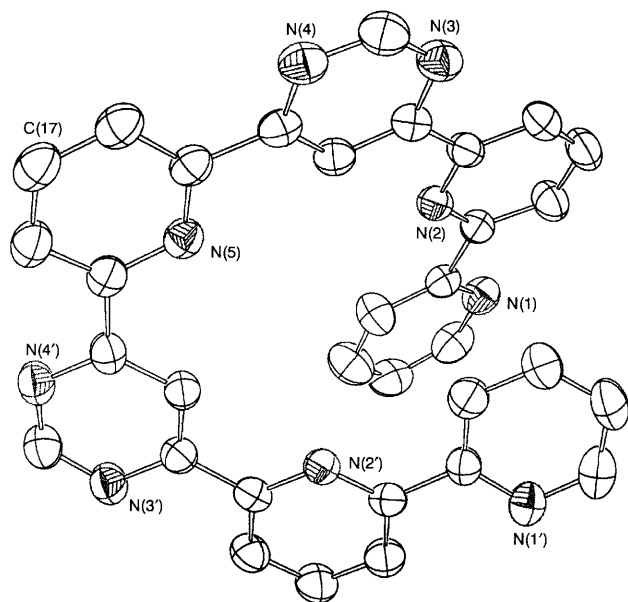


Fig. 3 ORTEP Drawing of **1** with nitrogen labels (hydrogens and carbon labels, except for C(17) have been omitted for clarity)