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Structural codons: linearity/helicity interconversion by pyridine/pyrimidine exchange in molecular strands†

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Pyridine and pyrimidine groups connected through amide functions can be combined into specific sequences that self-organize into either helical or linear structures enforced by the formation of intramolecular hydrogen bonds.

The control of the folding of molecular strands into well-defined architectures has been a subject of great interest in recent years in view of both its importance in molecular design and its significance for the understanding of the conformational features of biomolecules.[1] Various intramolecular non-bonded interactional effects can be combined into specifically designed structure enforcing units, "structural codons", capable of inducing into molecular strands well-defined shapes spanning the domain between helicity and linearity. In our laboratory, we have in particular made use of "helicity codons" involving specific combinations of heterocycles[2] and pyridine carboxamide sequences[3] to enforce helicity through respectively internal rotational preferences and hydrogen bond formation. Thus, molecular strands composed of alternating 2,6-diaminopyridine and 2,6-pyridinedicarbonyl units have been shown to adopt a helical conformation both in solution and in the solid state.[3]

We now report three new oligoamide model sequences showing that the exchange of pyridine by pyrimidine units results in a modification of the conformation of molecular strands, resulting in linearity/helicity interconversion.

The four pyridine and pyrimidine derived diamino and dicarbonyl groups shown in Fig. 1 may be classified as "linear" or "curved" units, according to the relative orientation of their termini in the conformation imposed by their hydrogen bonding pattern. These units can be combined in four different manners to give four different structural motifs. Thus, alternating linear units result in the formation of a linear strand; the alternating curved units lead to undulating forms; and finally, the two possible combinations of one linear and one curved unit generate helical oligoamide strands.

The corresponding four types of trimers[4] shown in Fig. 2 are a representative example of these sequences. In each case the strand is represented in the conformation in which a maximum number of favourable electrostatic interactions (akin to markedly bent hydrogen bonds) can be established. The amide protons are in all the cases oriented so as to be surrounded by two aromatic nitrogen atoms, and the carbonyl oxygens are located at the same time between two aromatic protons, presenting respectively two favourable N–H···N and (weaker) C–H···O interactions.

These oligomers (**5–8**) were prepared from the corresponding diacid[5] chloride and Boc-monoprotected diamine,[6] following the procedure described for compounds **5a,b** (Fig. 2) in ref. 3*b*. Their analytical and spectroscopic data (NMR, mass) are in agreement with the assigned structure.

The conformations of compounds **5–8** were found to be as represented in Fig. 2 both in solution and in the solid state. Analysis of their ^{1}H NMR and NOESY spectra clearly indicated, as expected, the absence of any short range H,H interactions. The conformations were confirmed by determination of the crystal structures of compounds **6b**,[7] **7a** and **8a**[8] (Fig. 3).‡ As seen, in all the cases the relative orientation of the heterocycles and the amide linkages is as depicted in Fig. 2.

These spectroscopic and structural data indicate that the patterns of favourable electrostatic interactions enforce the predicted orientation of the different residues and that the replacement of a pyridine ring by a pyrimidine indeed interconverts the conformation of the tris-heterocyclic entities between the linear and the helical ones.

It is worth noting that the previously developed py–py strands[3] fold so that the carbonyl oxygens are directed *outside* the helix whereas in the pym–pym strands these oxygens are oriented towards the *inside*, which makes them suitable for metal ion

† Electronic supplementary information (ESI) available: spectroscopic (^{1}H,^{13}C-NMR, mass) data for compounds **6a,b**; **7a,b** and **8a,b**. See http://www.rsc.org/suppdata/cc/b3/b311045a/

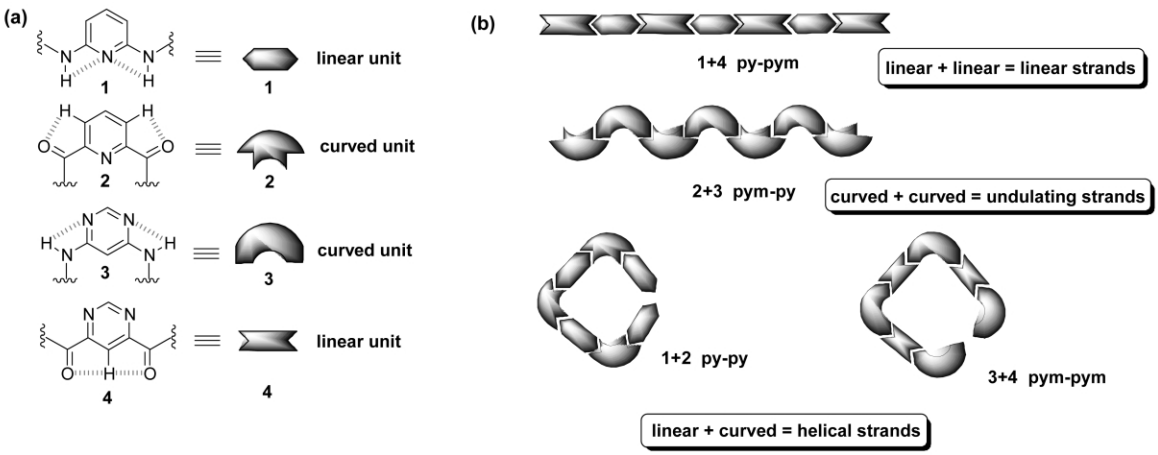

Fig. 1 Schematic representation of: (a) the four pyridine and pyrimidine-based monomeric units, and (b) four structurally different molecular strands composed of the combination of these monomeric units. The broken lines are meant to represent favourable electrostatic interactions.

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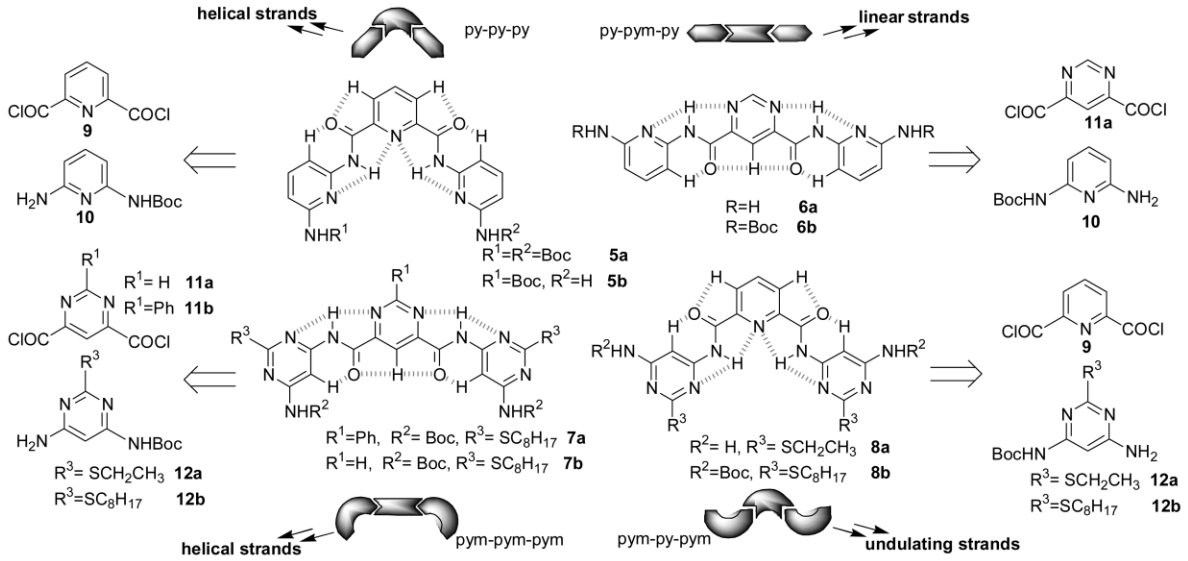

Fig. 2 Schematic representation, pattern of favourable electrostatic interactions and retrosynthetic pathway for the four types of trimers.

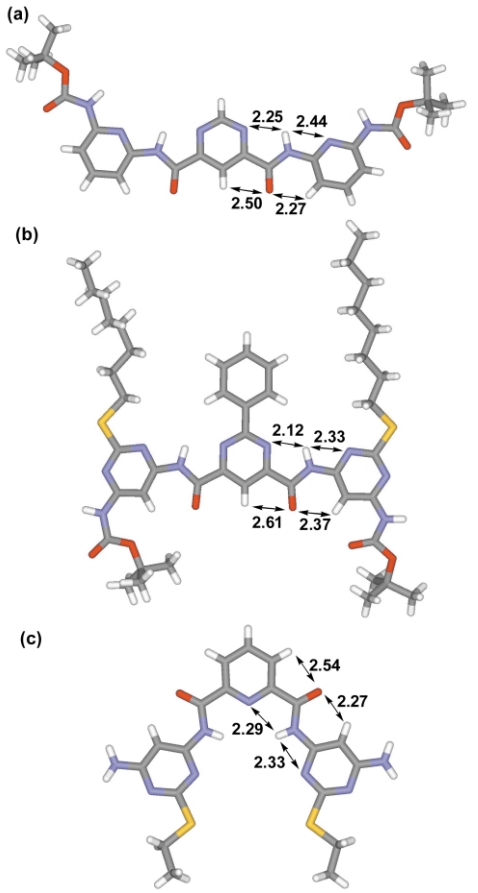

Fig. 3 Views of the structure of one of the two independent molecules in the crystals of **6b** (a), of **7a** (b) and **8a** (c). Some non-bonded N···H and O···H distances are given in Å.

coordination and promising building blocks for the construction of ion channels.

In conclusion, three new sequences of oligoamides have been designed, which, by the appropriate choice of monomeric units, open up the possibility of constructing molecular strands designed to generate linear, undulating or helical shapes. The results obtained further extend the ability to direct the folding of molecular strands for both chemical and biological purposes.

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Notes and references

‡ Crystallographic data: **6b** $C_{26}H_{30}N_8O_6\cdot0.375CH_2Cl_2\cdot0.125H_2O$, M = 584.67, orthorhombic, a = 25.0498(1), b = 20.9704(3), c = 11.7186(3) Å, V = 6155.8(2) Å^3, space group $P2_12_12$, Z = 8, μ = 0.141 mm^{-1}, 18009 data measurements, 8581 data measurements with $I > 3\sigma(I)$, R = 0.087, Rw = 0.111; **7a** $C_{46}H_{64}N_{10}O_6S_2\cdot CH_2Cl_2$, M = 1002.15, orthorhombic, a = 13.5362(2), b = 18.8739(2), c = 41.3548(7) Å, V = 10565.4(3) Å^3, space group $Pbca$, Z = 8, μ = 0.257 mm^{-1}, 15327 data measurements, 4705 data measurements with $I > 3\sigma(I)$, R = 0.086, Rw = 0.103; **8a** $C_{19}H_{21}N_9O_2S_2\cdot H_2O$, M = 489.58, monoclinic, a = 11.4672(3), b = 29.3393(8), c = 7.8434(3) Å, V = 2280.4(1) Å^3, space group $C12/c1$, Z = 4, μ = 0.276 mm^{-1}, 5616 data measurements, 1426 data measurements with $I > 3\sigma(I)$, R = 0.043, Rw = 0.068. CCDC 219231–219233. See http://www.rsc.org/suppdata/cc/b3/b311045a/ for crystallographic data in .cif or other electronic format.

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4 Synthesis and structural characterization of longer oligomers are in progress.

5 The acid chlorides **11a** and **11b** were formed by boiling the corresponding diacids in $SOCl_2$ for 24 h and recrystallized from hexane. For the preparation of 4,6-pyrimidinedicarboxylic acid see: R. R. Hunt, J. F. W. McOmie and E. R. Sayer, *J. Chem. Soc.*, 1959, 525. The 2-phenyl substituted diacid was prepared analogously from 4,6-dimethyl-2-phenylpyrimidine.

6 Compounds **12a,b** were prepared from 4,6-diamino-2-mercaptopyrimidine and the corresponding alkyl bromide using a procedure described by: R. A. Nugent, S. T. Schlachter, M. J. Murphy, G. J. Cleek, T. J. Poel, D. G. Wishka, D. R. Graber, Y. Yagi, B. J. Keiser, R. A. Olmsted, L. A. Kopta, S. M. Swaney, S. M. Poppe, J. Morris, W. G. Tarpley and R. C. Thomas, *J. Med. Chem.*, 1998, **41**(20), 3793. The Boc group was inserted using the same procedure described in ref. 3*b* for **5a**.

7 Two independent molecules of **6b** were found in the asymmetric unit, both with crystallographic 2-fold imposed symmetry and both with similar conformations.

8 Compound **8a** presented crystallographic 2-fold imposed symmetry.