COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Hydroxy-substituted oligopyridine dicarboxamide helical foldamers

Ivan Huc,*[a] Victor Maurizot,[a] Heinz Gornitzka[b] and Jean-Michel Léger[c]

[a] *Institut Européen de Chimie et Biologie, 16 av. Pey Berland, 33607 Pessac Cedex, France. E-mail: i.huc@iecb-polytechnique.u-bordeaux.fr*

[b] *Laboratoire d'Hétérochimie Fondamentale et Appliquée, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex 4, France*

[c] *Laboratoire de Pharmacochimie, Université Victor Segalen Bordeaux II, 146 rue Léo Saignat, 33076 Bordeaux, France*

Received (in Cambridge, UK) 21st December 2001, Accepted 8th February 2002
First published as an Advance Article on the web 22nd February 2002

As shown by X-ray diffraction and NMR studies, short oligopyridine dicarboxamides bearing benzyloxy, hydroxy and hydroxylate moieties adopt very robust single helical conformations, even in water.

Aromatic oligoamides derived from 2,6-diaminopyridine and 2,6-pyridine dicarboxylic acids (AOA's) are a new class of foldamers[1] which adopt helical conformations stabilised by intramolecular hydrogen bonds (Fig. 1(*a*)).[2,3] Several features differentiate these helices from helices of α and β peptides: (i) the conjugation of π orbitals along the entire oligomer reduces conformational freedom, and provides favorable contacts between overlapping aromatic rings and amide bonds; (ii) hydrogen bonds occur between consecutive units in a non-cooperative fashion (*e.g.* a heptamer gives rise to six H-bonds, instead of 3 for the α helix of a α heptapeptide); (iii) H-bonds lay perpendicular to the helix axis in the helix hollow and are shielded from the solvent; and (iv) the helix can breath and extend like a spring with minor distortions of the H-bonds.

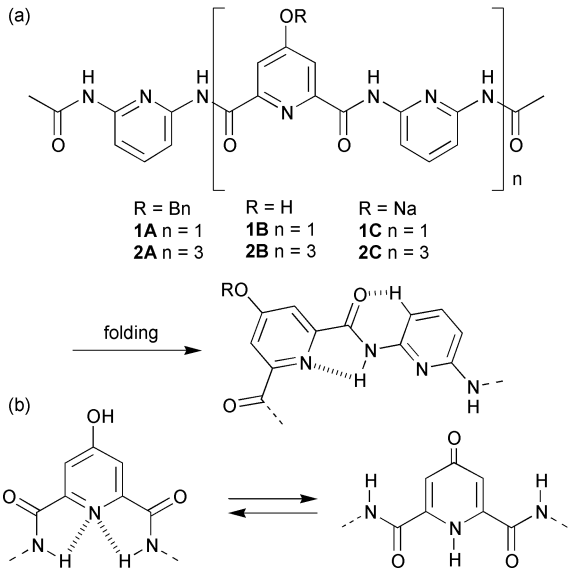

Fig. 1 (a) Structure and folding of the oligomers showing intramolecular hydrogen bonds; (b) tautomeric equilibrium for **1B** and **2B**.

Previous investigations on these compounds were performed in organic solvents (most often chlorinated or aromatic).[2] We now report that the helical pattern of short AOA's is robust enough to withstand competing factors such as tautomeric equilibria or the presence of water. Thus, helices of AOA's compare favorably with helices of short α and β peptides which do not fold readily in water without covalent/non-covalent stabilizations between side-chains, or unless a delicate balance in amino-acid composition is respected.[4] These results bode well for the design of stable tertiary structures using AOA's.

AOA's were functionalized with polar solubilizing groups in position 4 of the pyridine rings which diverge from the helix and point towards the solvent. Thus, trimer **1A** and heptamer **2A** (Fig. 1(*a*)) were prepared respectively in two and three steps from dimethyl 4-benzyloxypyridine-2,6-dicarboxylate[5] and 2,6-diaminopyridine using previously described procedures.[2b] The benzyl groups were hydrogenated using Pd/C in DMF to give hydroxypyridines **1B** and **2B**. These hydroxy functions are relatively acidic (a pK_a of 6.1 was measured for dimethyl 4-hydroxypyridine-2,6-dicarboxylate), and **1B** and **2B** were readily converted to their sodium salts **1C** and **2C** using $NaHCO_3$ (1 and 3 eq. respectively).

Several of these compounds yielded crystals suitable for X-ray analysis.† The two structures of heptamer **2A** (Fig. 2(*a*) and

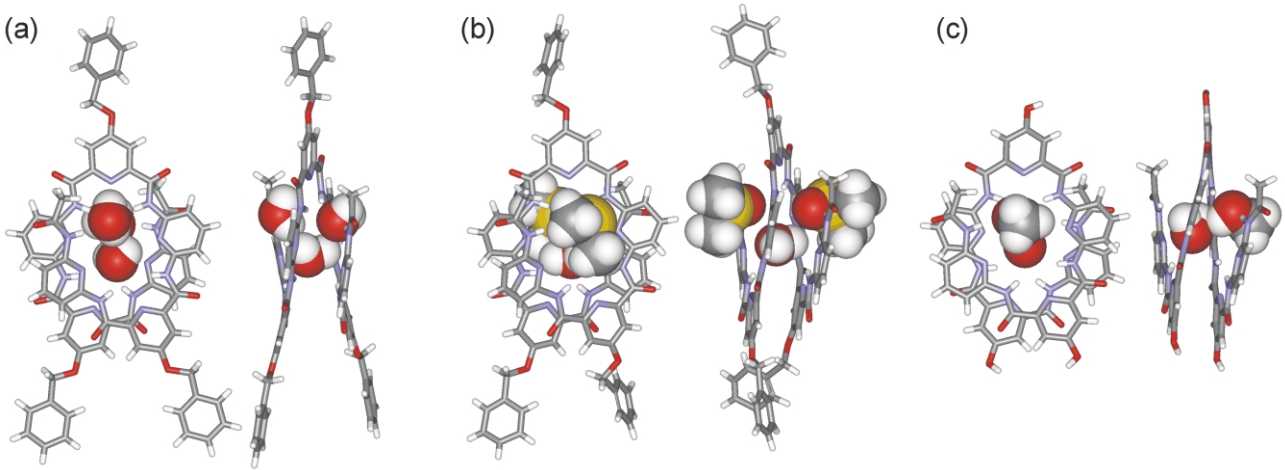

Fig. 2 Top view and side view of the crystal structures of (a) **2A** in crystals grown from nitrobenzene–heptane; (b) **2A** in crystals grown from DMSO–EtOH; and (c) **2B** in crystals grown from DMSO–EtOH. The helices are in stick representations. Solvent molecules included in the helices are in CPK representations; other solvent molecules are omitted for clarity. Hydrogens are at calculated positions.

DOI: 10.1039/b111612f

2(*b*)), and the structure of heptamer **2B** (Fig. 2(*c*)) all show single helical conformations extending to one and half turns. The 4-benzyloxy and the 4-hydroxy substituents affect the packing of the helices and of various solvent molecules included in the crystals. However, the shape of the helices remains highly conserved for these compounds, with a pitch of 3.5 Å, and about 4.5 pyridine rings per turn. The robustness of the helical pattern is evident for compounds **1B** (crystal structure not shown) and **2B**, where intramolecular hydrogen bonds between pyridine nitrogens and amide hydrogens stabilize the 4-hydroxypyridine forms despite the possibility of 4-pyridone tautomers (Fig. 1(*b*)).

Another feature of the helices is the presence of included solvent molecules in their polar cavities. The helix of **2A** in crystals grown from nitrobenzene–heptane contains a record high of three water molecules in its interior (Fig. 2(*a*)), supporting the idea of using longer version of these compounds as membrane channels.‡ In crystals grown from DMSO–EtOH, the two peripheral water molecules are replaced by two DMSO molecules, the oxygens of which occupy almost identical positions as the water oxygens in the first structure. The helix of **2B** contains one water and one methanol molecule.

In solution, single helical conformations are supported by (i) sharp ^{1}H NMR spectra; (ii) deshielding of those amide protons involved in intramolecular H-bonding to pyridine nitrogens and of aromatic protons ortho to amide nitrogens (Fig. 1(*a*)); and (iii) shielding of the protons belonging to the peripheral functions of the strand involved in helical overlap.[2,6]

Heptamer **2A** is soluble in chlorinated solvents. Its solution behaviour will not be detailed here as it is comparable to that reported for AOA's bearing no benzyloxy substituents. In particular, these compounds dimerize in solution to form double helical structures, illustrating the spring like extension of the helices. A dimerization constant of 50 L mol^{-1} was measured for **2A** in chloroform.§ The hydroxy derivatives **1B** and **2B** are soluble in chloroform doped with a few percent of MeOH or DMSO. Their NMR and UV spectra are similar to those of **1A** and **2A**, suggesting a folded structure involving the 4-hydroxypyridine tautomers observed in the solid. No double helices were observed in these solvent mixtures.

Compound **2C** is soluble in water. This may be surprising by itself for a compound bearing so many aromatic rings, and further supports the idea of a folded structure. Its ^{1}H NMR spectrum in H_2O–D_2O 9 : 1 is sharp and shows no evidence of dimerization (Fig. 3). Deshielded signals at 10–10.5 ppm are assigned to the six amide protons involved in intramolecular hydrogen bonds, and the signal at 9.1 ppm is assigned to the terminal amide protons which can only hydrogen bond to water. The signal of the methyl group is found shielded at 1.54 ppm in heptamer **2C**, whilst it is at 1.72 ppm in trimer **1C**. This difference indicates intramolecular overlap between peripheral groups in helical conformations of **2C**,[2] although its magnitude is lower than that observed between **2A** and **1A** in $CDCl_3$ (signals at 1.8 and 2.2 ppm, respectively). Most interestingly, the amide protons of **1C** show different susceptibilities towards chemical exchange with water. The signal at 9.1 ppm is broad at 25 °C (width at half height $\nu_{1/2}$ = 13 Hz), and coalesces at 45 °C. On the other hand, signals of amide protons involved in intramolecular H-bonding are sharp and do not coalesce below 80 °C ($\nu_{1/2}$ = 17 Hz). Despite the relative acidity of these protons and the basicity of the medium (pH > 8), exchange is slowed down by intramolecular hydrogen bonding and they are shielded from the solvent in the helical conformation, even at high temperatures. For longer AOA's than the heptamers described here, one can expect cooperative π–π stacking interactions to lead to an increasing stability of the helices.

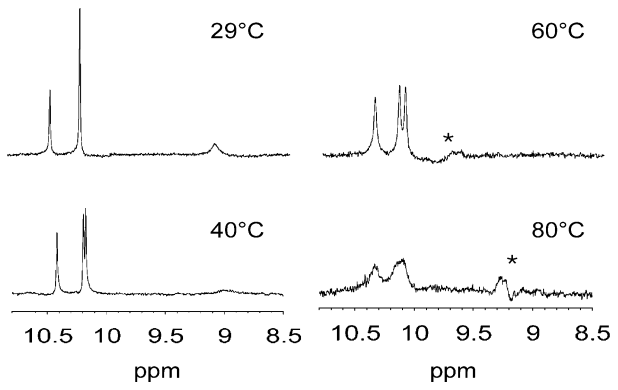

Fig. 3 400 MHz ^{1}H NMR spectra of **2C** in H_2O–D_6-DMSO 9 : 1 at various temperatures. The asterisks marks quadrature defects of the water signal.

This work was supported by the CNRS, the University of Bordeaux I, and by the Région Aquitaine (predoctoral fellowship to VM).

Notes and references

† *Crystal data*: **1B** $C_{23}H_{25}N_7O_6S$, M = 527.56, triclinic, a = 8.422(2), b = 10.165(3), c = 14.420(4) Å, α = 93.370(7), β = 91.761(5), γ = 91.344(7)°, V = 1231.3(6) Å^3, T = 173(2) K, space group $P\bar{1}$, Z = 2, μ(Mo-K$_\alpha$) = 0.186 mm^{-1}, 5591 reflections measured, 3507 unique (R_{int} = 0.0763). The final R indices were R_1 ($I > 2\sigma(I)$) = 0.0509, wR_2 (all data) = 0.1236. **2A** (from nitrobenzene–heptane) $C_{72}H_{64}N_{16}O_{16}$, M = 1409.39, monoclinic, a = 37.717(3), b = 13.171(1), c = 13.626(1) Å, β = 92.372(1)°, V = 6763.2(8) Å^3, T = 193(2) K, space group Cc, Z = 4, μ(Mo-K$_\alpha$) = 0.101 mm^{-1}, 17200 reflections measured, 9250 unique (R_{int} = 0.0583). The final R indices were R_1 ($I > 2\sigma(I)$) = 0.0547, wR_2 (all data) = 0.1384. **2A** (from DMSO–EtOH) $C_{142}H_{142}N_{30}O_{30}S_4$, M = 2528.59, triclinic, a = 13.429(3), b = 14.377(7), c = 19.518(2) Å, α = 87.66(1), β = 70.85(1), γ = 85.94(1)°, V = 3550.2(20) Å^3, T = 296(2) K, space group $P1$ (no. 1), Z = 1, μ(Cu-K$_\alpha$) = 0.951 mm^{-1}, 9165 reflections measured, 9165 unique. The final R indices were R_1 ($I > 2\sigma(I)$) = 0.1180, wR_2 (all data) = 0.3794. The poor quality of this structure is due to low diffraction intensity and crystal decomposition. A refinement in the space group $P\bar{1}$ was attempted but proved unsatisfactory. **2B** $C_{49}H_{53}N_{15}O_{16}$, M = 1108.06, monoclinic, a = 14.133(2), b = 25.805(3), c = 14.050(2) Å, β = 98.046(3)°, V = 5073.9(12) Å^3, T = 173(2) K, space group $P2_1/c$, Z = 4, μ(Mo-K$_\alpha$) = 0.111 mm^{-1}, 22683 reflections measured, 7312 unique (R_{int} = 0.0691). The final R indices were R_1 ($I > 2\sigma(I)$) = 0.0629, wR_2 (all data) = 0.1586. CCDC 176827–176830. See http://www.rsc.org/suppdata/cc/b1/b111612f/ for electronic files in .cif or other electronic format.

‡ Work in progress.

§ Compound **2A** may be compared to an analogous heptameric strand bearing no substituent in position 4 of the pyridine rings described in ref. 2a. In solution, both compounds undergo an equilibrium between single and double helices. In the solid, crystals grown from DMSO yielded single helices in both cases, but crystals grown from nitrobenzene yielded a single helix in the case of **2A** and a *double* helix for the latter compound.

1 S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; D. J. Hill, M. J. Mio, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893.

2 (*a*) V. Berl, I. Huc, R. Khoury, M. J. Krische and J.-M. Lehn, *Nature*, 2000, **407**, 720; (*b*) V. Berl, I. Huc, R. Khoury and J.-M. Lehn, *Chem. Eur. J.*, 2001, **7**, 2798; (*c*) V. Berl, I. Huc, R. Khoury and J.-M. Lehn, *Chem. Eur. J.*, 2001, **7**, 2810.

3 These foldamers have much in common with crescent oligoamides of isophthalic acid and 1,3-diaminobenzene: B. Gong, *Chem. Eur. J.*, 2001, **7**, 4337; and with anthranilic acid derivatives: Y. Hamuro, S. J. Geib and A. D. Hamilton, *J. Am. Chem. Soc.*, 1997, **119**, 10587.

4 For representative examples see: A. Jacobi and D. Seebach, *Helv. Chim. Acta*, 1999, **82**, 1150; C. E. Schafmeister, J. Po and G. L. Verdine, *J. Am. Chem. Soc.*, 2000, **122**, 5891; M. J. Keslo, H. N. Hoang, T. G. Appleton and D. P. Fairlie, *J. Am. Chem. Soc.*, 2000, **122**, 10488.

5 T. Braxmeier, M. Demarcus, T. Fessmann, S. McAteer and J. D. Kilburn, *Chem. Eur. J.*, 2001, **7**, 1889.

6 V. Berl, M. J. Krische, I. Huc, J.-M. Lehn and M. Schmutz, *Chem. Eur. J.*, 2000, **6**, 1938.